Київський національний університет імені Тараса Шевченка

Міністерство освіти і науки України

Київський національний університет імені Тараса Шевченка

Міністерство освіти і науки України

Кваліфікаційна наукова
праця на правах рукопису

МЕЛЬНИКОВ КОСТЯНТИН ПЕТРОВИЧ

УДК [547.51+(547.7+547.8):66.094.25]:546.16

ДИСЕРТАЦІЯ
«СИНТЕЗ ТА ФІЗИКО-ХІМІЧНІ ВЛАСТИВОСТІ ФУНКЦІОНАЛІЗОВАНИХ ФЛУОРОВМІСНИХ НАСИЧЕНИХ КАРБО- ТА ГЕТЕРОЦИКЛІВ»

02.00.03 – органічна хімія

Подається на здобуття наукового ступеня
доктора хімічних наук

Дисертація містить результати власних досліджень. Використання ідей, результатів і текстів інших авторів мають посилання на відповідне джерело
_____(К. П. Мельников)

Науковий консультант
ГРИГОРЕНКО ОЛЕКСАНДР ОЛЕГОВИЧ
доктор хімічних наук, професор

КИЇВ – 2025

АНОТАЦІЯ

Мельников К. П. **Синтез та фізико-хімічні властивості функціоналізованих флуоровмісних насичених карбо- та гетероциклів. –** Кваліфікаційна наукова праця, оформлена для наукової доповіді.

Дисертація на здобуття наукового ступеня доктора хімічних наук за спеціальністю 02.00.03 – органічна хімія. – Київський національний університет імені Тараса Шевченка МОН України, Київський національний університет імені Тараса Шевченка МОН України, Київ, 2025.

Дисертацію присвячено дослідженню флуоро- та флуороалкілвмісних насичених карбо- та гетероциклічних систем, а саме їх синтезу, застосуванню в хімічній практиці та вивченню фізико-хімічних властивостей.

Було проведено обробку та систематизацію масиву наявних даних щодо ролі флуорованих фрагментів у дизайні лікарських засобів, методах введення таких фрагментів, впливу на фізико-хімічні та біологічні властивості тощо. Було систематизовано різноманіття підходів синтезу флуорованих насичених карбо- та гетероциклічних сполук – від класичних методів прямого флуорування і до новітніх способів прямого введення флуороалкільних замісників.

Було запропоновано методи синтезу ряду простих карбо- та гетероциклічних будівельних блоків (на основі циклогептану, циклобутану, спіропентану, піролідину, піперидину) з флуоровмісними замісниками. Метод тандемної функціоналізації подвійного зв’язку з внутрішньомолекулярною циклізацією було адаптовано для багатограмового синтезу моно- та біфункціональних похідних біцикло[4.1.1]- та -[3.2.1]октану, біцикло[2.2.1]- та -[3.2.0]гептану, біцикло[3.1.0]гексану, а також біцикло[2.1.0]пентану (хаузану), зокрема, флуорованих амінів і карбонових кислот, амінокислот, монозаміщених діамінів та багатьох інших будівельних блоків для медичної хімії. Методом внутрішньомолекулярної циклізації було синтезовано похідні дифлуорооксетану та біциклічних аналогів піперидину та піролідину, а

методом бромофлуорування із послідовним нуклеофільним заміщенням – флуоровані циклічні похідні метанаміну.

Було проведено експериментально визначення фізико-хімічних параметрів досліджуваних сполук та їх модельних похідних. До цього списку величин віднситься кислотність/основність здатних до іонізації груп (pK_a), ліпофільність (Log$P$), , водорозчинність (S_w), мембранна проникність (PAMPA), метаболічна та хімічна стабільність, біологічна активність аналогів лікарських засобів тощо. Емпірично встановлено закономірності впливу структурних елементів (місткових атомів Карбону чи елементоорганічних замісників) на фізико-хімічні властивості. На основі даних щодо ліпофільності сполук та за допомогою квантово-хімічних розрахунків (зокрема, побудовою відображень електростатичного потенціалу молекул) було висловлено гіпотезу про опосередкований механізм впливу атомів Флуору як замісників на ліпофільність сполуки.

Було продемонстровано потенціал застосування флуорованих насичених карбо- та гетероциклічних похідних у якості вихідних сполук в органічному синтезі, зокрема і в умовах паралельного синтезу. Реакція рециклізації дифлуороциклопропанів (*N*-піразолільні похідні яких в свою чергу також було досліджено в рамках виконання дисертаційної роботи) з відповідними бінуклеофілами дозволила отримати флуоровані похідні піразолу та піримідину з додатковими функціоналізованими замісниками. Реакцію «видалення Нітрогену» за Левіним було відтворено, перевірено та адаптовано для синтезу бібліотек вторинних амінів в умовах паралельного синтезу та продемонстровано можливість ефективного застосування флуорованих будівельних блоків. Досліджено особливості реакції Мініші за використання циклоалканових похідних карбонових кислот та трифлуороборатів; статистично продемонстровано взаємну залежність результатів синтезу від природи джерела радикалів та гетероциклічного фрагменту. Висвітлено залежність активності в цій реакції флуорованих будівельних блоків від природи флуоровмісного замісника та проведено кореляції з експериментально визначеними електрохімічними параметрами цих сполук. Було синтезованно

флуороалкільовані похідні сульфоксімінів як нових гідрофільних ізостерів сульфонів для створення лікарських засобів.

Ключові слова: органічний синтез, насичені сполуки, карбоцикли, гетероцикли, будівельні блоки, Флуор, фізико-хімічні параметри, ліпофільність, паралельний синтез

SUMMARY

Melnykov K. P. **Synthesis and physicochemical properties of functionalised fluorinated saturated carbocycles and heterocycles** – thesis for scientific degree of Doctor of Chemical Sciences degree by speciality 02.00.03 – organic chemistry – Taras Shevchenko National University of Kyiv, Taras Shevchenko National University of Kyiv, Kyiv, 2025.

The thesis is devoted to fluorinated or fluoroalkylated saturated (hetero)cyclic systems, namely their synthesis, application and physicochemical properties.

The array of available data on the role of fluorinated fragments in drug design , methods of introducing such fragments, their influence on macroscopic parameters was processed and systematised. A generation of approaches to the synthesis of fluorinated compounds was systematised, ranging from classical methods of direct fluorination to the latest methods of direct introduction of fluoroalkyl substituents.

Approached for the synthesis of a number of simple carbocyclic and heterocyclic building blocks (based on cycloheptane, cyclobutane, spiropentane, pyrrolidine, piperidine) with fluorinated substituents were proposed. The method of tandem double bond functionalization with intramolecular cyclization was adapted for the multigram synthesis of mono- and bifunctional bicyclo[4.1.1]- and -[3.2.1]octane, bicyclo[2.2.1]- and -[3.2.0]heptane, bicyclo[3.1.0]hexane, and bicyclo[2.1.0]pentane (housane), including derivatives of fluorinated amines and carboxylic acids, amino acids, monosubstituted diamines, and many other building blocks for medicinal chemistry. Diphylluorooxetane derivatives were synthesised by intramolecular cyclization, and fluorinated methanamine derivatives were synthesised by bromofluorination with sequential nucleophilic substitution.

The physicochemical properties of the studied compounds and their model derivatives were experimentally determined. This list of these values includes the acidity/basicity of ionisable groups (pK_a), lipophilicity (Log*P*), water solubility (S_w), membrane permeability (PAMPA), metabolic and chemical stability, biological activity of modified drugs, etc. The regularities of the influence of structural elements (bridging carbon atoms or organometallic substituents) on physicochemical properties have been empirically established. On the basis of the obtained data on lipophilicity of compounds and using quantum chemical calculation (in particular, by calculation of the molecular electrostatic potentials), a hypothesis was made about the indirect mechanism of fluorine atoms influence on the lipophilicity of studied compound.

The potential of application of fluorinated compounds in organic synthesis, in particular, in parallel synthesis, was envisaged. The recyclization reaction of difluorocyclopropanes (*N*-pyrazolyl derivatives of which, in turn, were also studied as part of the proposed thesis) with the corresponding *bis*-nucleophiles allowed to obtain fluorinated pyrazole and pyrimidine derivatives with additional functionalized substituents. The Levin's nitrogen deletion reaction was adapted for the synthesis of libraries of secondary amines and the possibility of using fluorinated building blocks in this reaction was demonstrated. The peculiarities of the Minichi reaction of the cycloalkane derivatives (such as carboxylic acids and trifluoroborates) were investigated; the mutual dependence of the reactions outcomes on the nature of the radical source and the heterocyclic fragment was statistically demonstrated. The dependence of the activity in this reaction of fluorinated building blocks on the fluorination pattern is highlighted and correlations with experimentally determined electrochemical parameters of these compounds were made. The fluoroalkylated derivatives of sulfoxyimines were synthesised as new hydrophilic sulfone isosteres for the development of medicines.

Keywords: organic synthesis, saturated compounds, carbocycles, heterocycles, building blocks, Fluorine, physicochemical parameters, lipophilicity, parallel synthesis.

СПИСОК ПУБЛІКАЦІЙ ЗДОБУВАЧА

Статті в іноземних виданнях:

1. Grygorenko O. O.; **Melnykov K. P.**; Holovach S.; Demchuk O. Fluorinated cycloalkyl building blocks for drug discovery. *ChemMedChem* **2022**, *17*, e202200365. DOI: 10.1002/cmdc.202200365. [**Q1**]. *(Особистий внесок здобувача: аналіз літературних даних, участь у написанні статті).*

2. **Melnykov K. P.**; Nazar, K.; Smyrnov O.; Skreminskyi A.; Pavlenko S.; Klymenko-Ulianov O.; Shishkina S.; Volochnyuk D. M.; Grygorenko O. O. Mono- and difluorinated saturated heterocyclic amines for drug discovery: systematic study of their physicochemical properties. *Chem. Eur. J.* **2023**, *29* (47), e202301383. DOI: 10.1002/chem.202301383. [**Q1**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, участь у написанні статті).*

3. **Melnykov** K. P.; Tavlui O.; Skreminskiy A.; Kuchkovska Y. O.; Grygorenko O. O. Impact of fluoroalkyl substituents on physicochemical properties of saturated heterocyclic amines. *Chem. Eur. J.* **2022**, e202201601. DOI: 10.1002/chem.202201601. [**Q1**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, участь у написанні статті).*

4. Liashuk O. S.; Fedinchyk A.; **Melnykov K. P.**; Herasymchuk M.; Alieksieieva D.; Lesyk D.; Bas Y. P.; Keda T. Y.; Yatsymyrskiy A. V.; Holota Y.; Borysko P.; Yarmolchuk V. S.; Grygorenko O. O. 3,3-Difluorooxetane – a versatile functional group for bioisosteric replacements in drug discovery. *Chem. Eur. J.* **2024**, *30*(72), e202403277. DOI: 10.1002/chem.202403277. [**Q1**]. *(Особистий внесок здобувача: планування дослідження, участь у написанні статті).*

5. Semeno V. V.; Vasylchenko V. O.; Fesun I. M.; Ruzhylo L. Yu.; Kipriianov M. O.; **Melnykov K. P.**; Skreminskyi A.; Iminov R.; Mykhailiuk P.; Vashchenko B. V.; Grygorenko O. O. Bicyclo[m.n.k]alkane building blocks as promising

benzene and cycloalkane isosteres: multigram synthesis, physicochemical and structural characterization. *Chem. Eur. J.* **2024**, 30 (12), e202303859. DOI: 10.1002/chem.202303859. [**Q1**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних).*

6. **Melnykov K. P.**; Liashuk O. S.; Holovach S.; Shatnia V.; Horbenko A.; Lesyk D.; Melnyk V.; Skrypnik D.; Beshtynarska A.; Borysko P.; Viniichuk O.; Grygorenko O. O. Physicochemical and biological evaluation of *gem*-difluorinated saturated oxygen heterocycles as bioisosteres for drug discovery *Chem. Eur. J.* **2024**, e202404390. DOI: 10.1002/chem.202404390. [**Q1**]. *(Особистий внесок здобувача: планування дослідження, участь у написанні статті).*

7. Nosik P. S.; Poturai A. S.; Pashko M. O.; Melnykov K. P.; Ryabukhin S. V.; Volochnyuk D. M.; Grygorenko O. O. *N*-Difluorocyclopropyl-substituted pyrazoles: synthesis and reactivity. *Eur. J. Org. Chem.* **2019**, *27*, 4311–4319. [**Q1**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних).*

8. Holovach S.; **Melnykov K. P.**; Poroshyn I.; Iminov R. T.; Dudenko D.; Kondratov I. S.; Levin M.; Grygorenko O. O. C–C coupling through Nitrogen deletion: application to library synthesis. *Chem. Eur. J.* **2023**, *29*, e202203470. DOI: 10.1002/chem.202203470. [**Q1**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, участь у написанні статті).*

9. Holovach S.; Poroshyn I.; **Melnykov K. P.**; Liashuk O. L.; Pariiska O. O.; Kolotilov S. V.; Rozhenko A. B.; Volochnyuk D. M.; Grygorenko O. O. Parallel Minisci reaction of *gem*-difluorocycloalkyl building blocks. *ACS Org. Inorg. Au* **2024**, *4*(4), 424–431. DOI: 10.1021/acsorginorgau.4c00028. [**Q1**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, участь у написанні статті).*

10. Grygorenko O. O.; **Melnykov K. P.** Fluorinated building blocks in drug design: new pathways and targets. *Future Med. Chem.* **2024,** *16(14)*, 1375–1378. [**Q2**]. *(Особистий внесок здобувача: аналіз літературних даних, участь у написанні статті)*.

11. Herasymchuk M.; **Melnykov K. P.**; Yarmoliuk D. V.; Serhiichuk D.; Rotar V.; Pukhovoi T.; Kuchkovska Yu. O.; Holovach S.; Volochnyuk D. M.; Ryabukhin S. V.; Grygorenko O. O. Last of the *gem*-difluorocycloalkanes 2: synthesis of fluorinated cycloheptane building blocks. *Eur. J. Org. Chem.* **2021**, 6568–6576. DOI: 10.1002/ejoc.202001530. [**Q2**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, участь у написанні статті).*

12. Demchuk O. P.; Hryshchuk O. V.; Vashchenko B. V.; Trofymchuk S. A.; **Melnykov K. P.**; Skreminskiy A.; Volochnyuk D. M.; Grygorenko O. O. Fluoroalkyl-containing 1,2-disubstituted cyclobutanes: advanced building blocks for medicinal chemistry. *Eur. J. Org. Chem.* **2021**, 87–95. DOI: 10.1002/ejoc.202001345. [**Q2**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, участь у написанні статті).*

13. **K. P. Melnykov**, O. V. Voloshyna, B. V. Vashchenko, O. P. Demchuk, O. V. Hryshchuk, O. O. Grygorenko. 4,4-Difluorospiro[2.2]-pentan-1-yl – a fluorinated substituent to expand the synthetic and medicinal chemists' toolbox. *Eur. J. Org. Chem.* **2022**, e202200863. [**Q2**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, участь у написанні статті).*

14. Smyrnov O.; **Melnykov K. P.**; Semeno V.; Liashuk O. S.; Grygorenko O. O. α-CF_3-Substituted saturated bicyclic amines: advanced building blocks for medicinal chemistry. *Eur. J. Org. Chem.* **2024**, *27* (1), e202300935. DOI: 10.1002/ejoc.202300935. [**Q2**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих*

результатів, участь у написанні статті).

15. Fedinchyk A.; Herasymchuk M.; Smirnov O. V.; **Melnykov K. P.**; Yarmoliuk D. V.; Kyrylchuk A. A.; Grygorenko O. O. Fluorine-containing sp^3-enriched building blocks for the multigram synthesis of fluorinated pyrazoles and pyrimidines with (hetero)aliphatic substituents. *Eur. J. Org. Chem.* **2022**, e202200274. DOI: 10.1002/ejoc.202200274. [**Q2**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, участь у написанні статті).*

16. Pidvyshennyi O.; **Melnykov K. P.**; Liashuk O.; Lesyk D.; Holota Y.; Borysko P.; Grygorenko O. O. Acidity of saturated (hetero)cyclic *α*-fluoro carboxylic acids and lipophilicity of their amide derivatives. *J. Fluorine Chem.* **2024**, *278*, 110316. DOI: 10.1016/j.jfluchem.2024.110316. [**Q3**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, участь у написанні статті).*

17. **Melnykov** K. P.; Liashuk O. S.; Smyrnov O.; Lesyk D.; Holota Y.; Borysko P.; Yakubovskyi V.; Grygorenko O. O. Lipophilicity effects of monofluorination at the tertiary aliphatic carbon as a function of *α*-substituent. *J. Fluorine Chem*. **2025**, *281*, 110384. DOI: 10.1016/j.jfluchem.2024.110384. [**Q3**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, участь у написанні статті).*

18. Ryabukhin S.V.; **Melnykov K. P.** Synthesis of α-spirocyclic pyrrolidines. *Chem. Heterocycl. Compd*. **2020,** *56,* 1411–1413. [**Q4**]. *(Особистий внесок здобувача: аналіз літературних даних, участь у написанні статті).*

Статті у наукових фахових виданнях України:

19. Semeno, V. V., and **K. P. Melnykov**. Multigram Synthesis of *β*-Fluorinated Saturated Heterocyclic Methanamines. *Ukrainica Bioorganica Acta* **2023,** 18 (2), 16–21. DOI: 10.15407/bioorganica2023.02.016. *(Особистий внесок*

здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, написання статті).

20. **Мельников К.**, Підвишенний О., Смирнов О., Григоренко О. Флуоровані сульфоксіміни жирноароматичного ряду: масштабований синтез і вплив структурних елементів на ліпофільність. *ВІСНИК Київського національного університету імені Тараса Шевченка* **2024**, *1* (59), 1–5. DOI: 10.17721/1728-2209.2024.1(59). *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, участь у написанні статті).*

21. **Holovach** S. M.; **Melnykov**, **K. P.**; Poluektova M. S.; Rozhenko O. B.; Grygorenko O. O. Incorporation of *gem*-difluorocycloalkyl substituents into heterocycles via the Levin's "nitrogen deletion" strategy. *J. Org. Pharm. Chem.* **2023**, 21(3), 11–16. DOI: 10.24959/ophcj.23.278321. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, участь у написанні статті).*

ТЕЗИ КОНФЕРЕНЦІЙ

1. Герасимчук М.В., **Мельников** К.П., Рябухін С.В. Синтез білдінг-блоків на основі *гем*-дифлуорциклогептанів. *XX Міжнародна конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії»*, 15-17 травня **2019** р., м. Київ, с.103.

2. Олександр Григоренко, Костянтин **Мельников**, Сергій Головач, Олександр Демчук, Олександр Грищук, Антон Черних, Богдан Ващенко, Дмитро Волочнюк. Фізико-хімічні властивості насичених флуоровмісних карбо- та гетероциклів для потреб медичної хімії. *XIX наукова конференція «Львівські хімічні читання - 2023»*, 29-31 травня **2023** р., м. Львів, с.12

3. Бондарук А.А., **Мельников** К.П., Ляшук О.С., Григоренко О.О., Бас Ю.П., Кеда Т.Є. Нові пара-нітрофенольні естери пара-заміщених бензойних кислот як перспективні субстрати pNP-тесту. *XXV Міжнародна*

конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії», 15-17 травня **2024** р., м. Київ, с.39.

4. Федінчик А.В., Герасимчук М.В., **Мельников** К.П., Ляшук, О. С., Григоренко О.О. 3,3-Дифлуорооксетан-2-іл – перспективний флуоровмісний замісник для потреб медичної хімії. *XXV Міжнародна конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії»*, 15-17 травня **2024** р., м. Київ, с.124.

5. Шатня В.Ю., Горбенко А.Е., Головач С.М, **Мельников** К.П., Ляшук О.С., Григоренко О.О. Дослідження фізико-хімічних властивостей *гем*-дифлуорованих о-гетероциклів. *XXV Міжнародна конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії»*, 15-17 травня **2024** р., м. Київ, с.156

6. Волошина О.В., **Мельников** К.П., Шабликіна О.В., Григоренко О.О. Функціоналізовані похідні 4,4-дифлуороспіро[2.2]пентану. *XXIII Міжнародна конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії»*, 18-20 травня **2022** р., м. Київ, с.87.

7. Головач С., **Мельников** К., Порошин І., Григоренко О., Волочнюк Д., Роженко О. Впровадження методу утворення С-С зв’язку шляхом «видалення азоту» у комбінаторні хімію. *XIX наукова конференція «Львівські хімічні читання - 2023»,* 29-31 травня **2023** р., м. Львів, с.41.

8. Полуектова М., Головач С., **Мельников** К. П., Григоренко О. О. Введення *гем*-дифлуороциклоалкільних замісників у гетероцикли через стратегію «видалення нітрогену» Левіна. *XXIV Міжнародна конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії»*, 17-19 травня **2023** р., м. Київ, с.107.

9. Федінчик А.В, Герасимчук М.В., **Мельников** К.П., Григоренко О.О. Синтез флуорованих піразолів та піримідинів з фрагментами насичених гетероциклічних амінів. *XXIII Міжнародна конференція студентів,*

аспірантів та молодих вчених «Сучасні проблеми хімії», 18-20 травня **2022** р., м. Київ, с.64.

10. Підвишенний О.Р., Смирнов О.К., **Мельников** К.П., Григоренко О.О. Сульфоксіміни ароматичного ряду з флуоровмісними замісниками. *XXIII Міжнародна конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії»*, 18-20 травня 2022 р., м. Київ, с.81.

ЗМІСТ

АНОТАЦІЯ 2
SUMMARY 4
СПИСОК ПУБЛІКАЦІЙ ЗДОБУВАЧА 6
ПЕРЕЛІК УМОВНИХ СКОРОЧЕНЬ ТА ПОЗНАЧЕНЬ 14
ВСТУП 15
ОСНОВНІ РЕЗУЛЬТАТИ ДОСЛІДЖЕНЬ ТА ЇХ ОБГОВОРЕННЯ 28
Розділ 1 РОЛЬ ФЛУОРОВМІСНИХ НАСИЧЕНИХ СПОЛУК У РОЗРОБЦІ ЛІКАРСЬКИХ ЗАСОБІВ 28
Розділ 2 ФЛУОРОВАНІ ТА ФЛУОРОАЛКІЛЬНІ ПОХІДНІ ЦИКЛОАЛКАНІВ 35
Розділ 3 ФЛУОРОВАНІ ТА ФЛУОРОАЛКІЛЬНІ ПОХІДНІ НАСИЧЕНИХ ГЕТЕРОЦИКЛІВ 46
Розділ 4 НАСИЧЕНІ БІЦИКЛІЧНІ СПОЛУКИ ТА ЇХ ФЛУОРОВАНІ АНАЛОГИ – СИНТЕЗ ТА ДОСЛІДЖЕННЯ ВЛАСТИВОСТЕЙ 73
Розділ 5 МЕТОДИ ВВЕДЕННЯ ФЛУОРОВАНИХ ФРАГМЕНТІВ 87
ВИСНОВКИ 108
ДОДАТОК 1. СПИСОК ПУБЛІКАЦІЙ ЗДОБУВАЧА 111
ДОДАТОК 2. ОСНОВНІ ПУБЛІКАЦІЇ ЗА ТЕМОЮ ДИСЕРТАЦІЇ. КОПІЇ СТАТЕЙ 118
ДОДАТОК 3. ТЕЗИ ДОПОВІДЕЙ НАУКОВИХ КОНФЕРЕНЦІЙ ЗА ТЕМОЮ ДИСЕРТАЦІЇ 368

ПЕРЕЛІК УМОВНИХ СКОРОЧЕНЬ ТА ПОЗНАЧЕНЬ

F_{sp^3}	Вклад sp^3-гібридизованих атомів Карбону.
3,3-diFOx	3,3-дифлуороксетан
ADME	Абсорбція, розподілення, метаболізм, екскреція – фармакокінетичні параметри
DAST	Диетиламіносульфур трифлуорид
DPPA	Дифенілфосфорилазид
EDIEA	Електрофільна дифункціоналізація подвійного зв'язку з внутрішньомолекулярною реакцією алкілування єноляту
EVP	Exit vector plots; метод вихідних векторів
Log*P*	Показник ліпофільності
MAPK	Мітоген-активована протеїнкіназа
MEP	Молекулярний електростатичний потенціал
Morph-DAST	Морфоліносульфур трифлуорид
MsCl	Метилсульфонілхлорид
NBS	*N*-бромосукцинімід
NFSI	*N*-флуоробензенсульфонімід
PIDA	Фенілйододиацетат
pK_a	Показник кислотності
PROTAC	Proteolysis targeting chimera; Комбінована молекула вибіркового гідролізу білка
SelectFluor	1-флуор-4-хлорметил-1,4-діазоніабі-цикло[2.2.2]октану дитетрафлуороборат
S_w	Розчинність у воді
TMAF	Тетраметиламоній флуорид
XtalFluor-*E*	Диетиламінофлуоросульфін тетрафлуороборат
ВЕРХ	Високоефективна рідинна хроматографія
ГАМК	Гама-аміномасляна кислота
ПЕТ	Позитронна емісійна томографія
Реагент Тогні	1-трифлуорометил-1,2-бензйодоксол-3(1*H*)-он
РХ-МС	Тандем рідинна хроматографія з мас-спектроскопією

ВСТУП

Обґрунтування вибору теми дослідження. За останні роки флуоровані насичені циклічні фрагменти викликають жвавий інтерес серед розробників лікарських засобів та біологічно активних сполук.[1–9] Прикладами таких сполук можуть слугувати комерційно успішні препарати Маравірок (засіб для лікування ВІЛ), протиракові засоби Івосіденіб, Белзутіфан та Зосукідар, протидіабетичний препарат Госогліптин та інші[10–12] (Рисунок 1). Крім вищевказаних сполук, на різних стадіях розробки знаходиться ще ряд препаратів, зокрема інгібітор дуальної лейцинзіпер-кінази (DLK) GDC-0134, потенційно корисний для лікування бічного аміотрофічного склерозу,[13] або UNC0642, хімічний зонд для *in vivo* досліджень лізинметилтрансфераз G9a та GLP.[14] Найчастіше флуоровані циклоалкільні групи використовуються для заміни бензольних і нефлуорованих циклоалканових угрупувань;[15–17] також відомі приклади використання дифлуорометильного фрагменту CF_2 у циклі як біоізостера карбонільної[18] або сульфонової[19] функціональних груп.

Численні приклади широкого застосування таких структурних типів у медичній хімії є підґрунтям для розробки методів синтезу нових, раніше недосліджених насичених флуоровмісних карбо- та гетероциклічних сполук з метою збільшення їх доступності для фармацевтичної галузі та промотування їх подальшого використання як будівельних блоків для лікарських засобів.

Слід зазначити, що розроблені та успішно валідовані багатограмові методики синтезу будь-яких (флуорованих чи ні) будівельних блоків ще не є гарантією їх успішного застосування як фрагментів біологічно активної сполуки. За останні десятиліття розроблено ряд підходів до оцінки придатності тих чи інших будівельних блоків для застосування у дизайні лікарського засобу. Одним із найбільш розповсюджених є «правило двох», шо визначає граничні значення фізико-хімічних властивостей досліджуваних блоків і складається з двох частин.

Перша частина визначає молекулярну масу (*MW* < 200), ліпофільність (Log*P* < 2), кількість донорів ($H_{Don} \leq 2$) та акцепторів ($H_{Acc} \leq 4$) водневих зв'язків та кількість зв'язків, що здатні до вільного обертання (RotB ≤ 4).

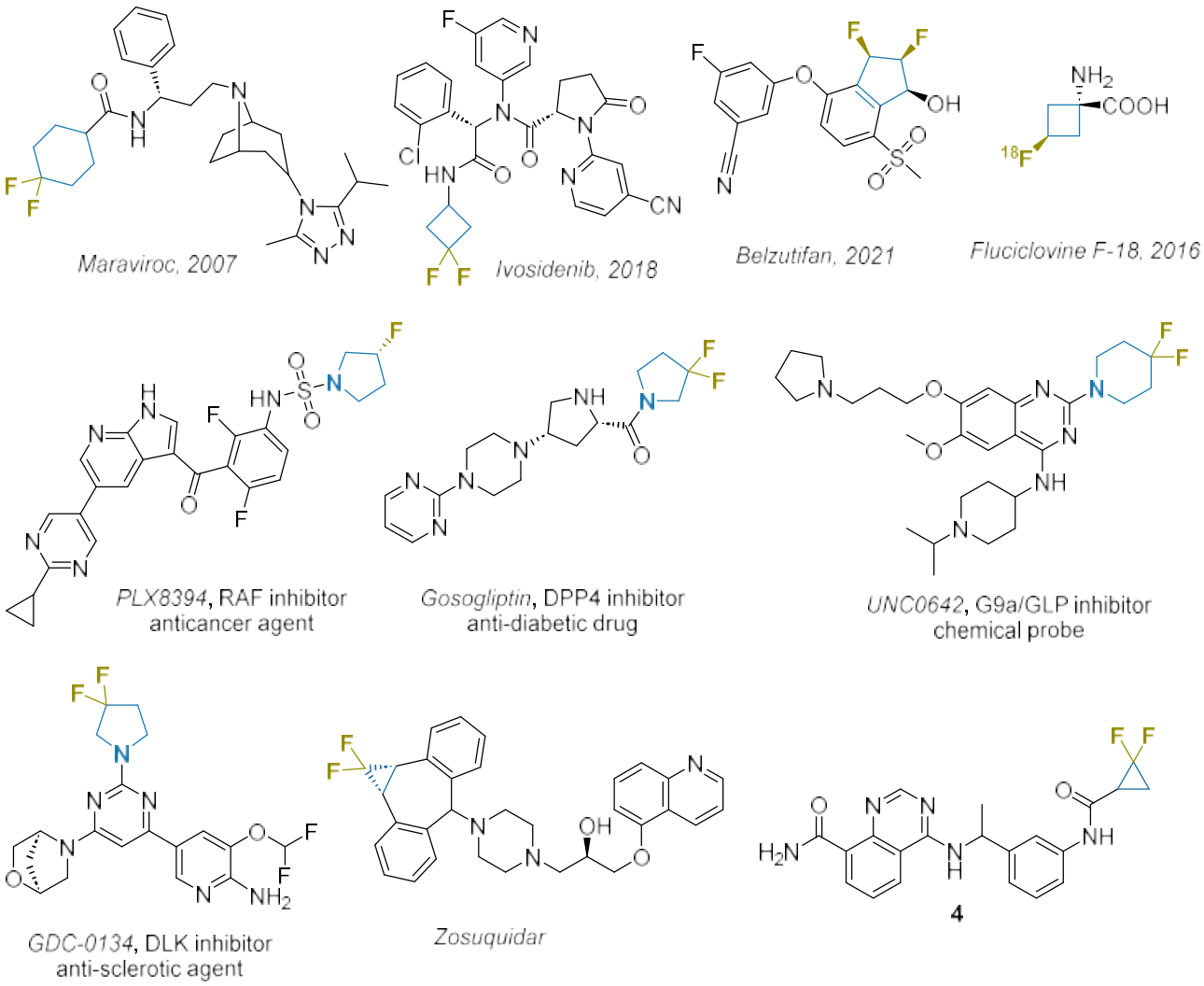


Рисунок 1. Приклади комерційно доступних лікарських засобів, що містять флуорований насичений карбо- та гетероциклічний фрагмент.

Друга частина описує тривимірність структури, оцінюючи вміст sp^3-гібридизованих атомів Карбону, надаючи перевагу або насиченим (F_{sp^3} = 0.8…1) або гетероароматичним (F_{sp^3} = 0.2…0.5) структурам. Використовуючи дані параметри, можна раціонально комбінувати фрагменти в одній молекулі, яка внаслідок такого дизайну буде знаходитись у рамках правил для лікарсько-подібних сполук (наприклад, правила Ліпінського) та з більшою ймовірністю зможе потрапити у перелік сполук-лідерів або навіть препаратів, що вийшли на ринок.

Таким чином, практичне вивчення фізико-хімічних параметрів перспективних будівельних блоків може стати ключем до раціонального дизайну бібліотек для ранніх етапів досліджень нових потенційно активних сполук або до передбачуваної ізостерної заміни різних фрагментів на етапі хіт-лід оптимізації. Саме тому однією із найважливіших частин даної роботи було визначено вимірювання та ґрунтовний аналіз ключових макроскопічних параметрів синтезованих та/або комерційно доступних речовин, зокрема таких, як кислотність/основність pK_a, ліпофільність Log$P$, розчинність у воді S_w та метаболічна стабільність.

Актуальність теми. Дизайн та розробка нових лікарських засобів є головною задачею органічної та медичної хімії. З плином еволюційного розвитку цього розділу хімічної науки виникло поняття ***будівельних блоків*** – невеликих за розміром моно- або поліфункціональних молекул, що шляхом добре досліджених та ефективних органічних перетворень можуть бути поєднані з іншими фрагментами з утворенням складної молекули власне біологічно активної сполуки або лікарського засобу. З одного боку, такий підхід дозволяє набагато простіше замінити один окремий фрагмент всієї структури без необхідності повністю синтезувати усю молекулу з самого початку. З іншого боку, це спрощує аналіз ключових взаємодій між лікарським засобом та його мішенню, дозволяє виокремити основні функціональні фрагменти, що відповідають за бажану фармакологічну дію і дозволяє раціонально планувати дизайн лікарського засобу без прямої необхідності перевірки активності усіх органічних молекул.

Таким чином, дизайн таких молекул (будівельних блоків) та вивчення фізико-хімічних властивостей відповідних фрагментів є актуальною задачею органічної хімії, що в разі комплексного і ретельного підходу дозволить суттєво спростити і пришвидшити створення нових ефективних лікарських засобів.

Останнім часом значної популярності набули два класи будівельних блоків – це насичені циклічні похідні та флуоровмісні сполуки. Розповсюдженість першого пояснюється відомою концепцією сучасної

медичної хімії, яка надає перевагу сполуками з підвищеним вмістом насичених атомів Карбону (параметр F_{sp^3}), що корелює з «тривимірністю» молекули. У той же час відомо, що наявність атомів Флуору значно підвищує метаболічну стабільність окремих фрагментів та суттєво впливає на ліпофільність всієї молекули, ефективно регулюючи фармакокінетичні параметри (абсорбція, розподіл, метаболізм, виведення та токсичність).

Саме тому двома основними напрямками даної роботи були розробка методів синтезу невідомих флуорованих насичених циклічних будівельних блоків та дослідження їх фізико-хімічних параметрів (кислотності/основності (pK_a), ліпофільності (Log$P$), водорозчинності (S_w), метаболічної стабільності тощо). Окрім того, після проведеної синтетичної та аналітичної частин роботи, було запропоновано ряд узагальнень, що безсумнівно будуть корисними для дизайну біологічно активних сполук.

Зв'язок роботи з науковими програмами, планами, темами. Робота виконувалася у рамках держбюджетної теми «Дизайн та розробка стратегій синтезу боро- та сульфурорганічних будівельних блоків, орієнтованих на пошук нових лікарських засобів» (2021–2023 р.р., 21БФ037-01М).

Мета і задачі дослідження. Метою даної роботи є розробка синтетичних підходів до невідомих будівельних блоків на основі флуорованих та флуоралкільованих карбо- та гетероциклів, в тому числі бі- та спіроциклічних, а також встановлення закономірностей їх фізико-хімічних параметрів, узагальнення та виведення певних емпіричних правил можливого використання таких фрагментів.

Для досягнення поставленої мети було необхідно вирішити наступні задачі:

- Розробка методів синтезу для кожного з обраних карбо- та гетероциклів – похідних циклопропану, циклобутану, спіро[2.2]пентану, циклогептану, їх Нітрогено- та Оксигеновмісних аналогів та відповідних біциклічних фрагментів;

- Встановлення оптимальних варіантів введення атомів Флуору у перелічені вище фрагменти та більш складні органічні молекули на їх основі;
- Проведення вимірів обраних фізико-хімічних параметрів (pK_a, Log$P$, водорозчинність, метаболічний кліренс тощо) для обраних представників одержаних сполук та встановлення закономірностей зв'язків «структура – властивість».

Об'єкт дослідження – флуоровмісні похідні циклопропану, циклобутану, циклогептану, азетидину, піролідину, піперидину, оксетану, тетрагідрофурану та тетрагідро-1*H*-пірану, їх біциклічні та гетероатомні аналоги..

Предмет дослідження – методи синтезу флуоровмісних похідних насичених карбо- та гетероциклів та їх фізико-хімічні властивості.

Методи дослідження – органічний синтез, ЯМР спектроскопія, елементний аналіз, мас-спектрометрія, хроматографія, рентгено-структурний аналіз, pH-метричне титрування, високоефективна рідинна хроматографія.

Наукова новизна одержаних результатів. Розроблено синтетичний підхід до всіх ізомерних *гем*-дифлуороциклогептанів, що містять додаткові функціональні групи, такі як аміно-, карбонільну та карбоксильну. Стратегія синтезу ґрунтувалася на методі розширення циклу за допомогою прекурсорів карбенів або на функціоналізації комерційно доступних похідних циклогептанону.

Запропоновано підхід до синтезу CF_3-, CHF_2- and CH_2F-вмісних похідних циклобутану, зокрема, 1,2-*транс*-дизаміщених аміно- та карбоксициклобутанів. Бажані сполуки були отримані шляхом класичних органічних перетворень виходячи із діестеру циклобутандикарбонової кислоти (яка у свою чергу була отримана за літературним методом починаючи із комерційно доступної адипінової кислоти). Флуоровмісні замісники вводились у досліджувані молекули шляхом деоксофлуорування (в автоклаві з використанням SF_4 чи без автоклаву з використанням Morph-DAST) або шляхом нуклеофільного

заміщення за допомогою джерела F^- (а саме, TMAF). Для синтезованих сполук було проведено дослідження фізико-хімічних властивостей (зокрема ліпофільності Log*P*, кислотності/основності pK_a та розчинності S_w) та встановлено закономірності впливу кількості та положення атомів Флуору на згадані показники.

Було запропоновано підхід до синтезу раніше невідомих дифлуорованого спіро[2.2]пентанового, біцикло[4.1.1]- та -[3.2.1]октанового, біцикло[2.2.1]- та -[3.2.0]гептанового, біцикло[3.1.0]гексанового, а також біцикло[2.1.0]пентанового скелетів та проведено ряд класичних хімічних перетворень, що дозволило отримати набір потенційно корисних будівельних блоків. З метою демонстрації потенціалу вказаних похідних одну із синтезованих сполук було проаналізовано за допомогою рентгеноструктурного аналізу і порівняно із моноциклічними аналогами методом вихідних векторів (EVP), за результатами якого показано значну тривимірність досліджуваного об'єкту.

Було проведено ґрунтовний аналіз фізико-хімічних параметрів (pK_a, Log*P* і розчинність у воді) для випадку *α*-монофлуорованих циклоалканкарбонових кислот (C_3-C_7), флуорованих насичених аза- (азетидину, піролідину та піперидину) та окса- (оксетану, тетрагідрофурану та тетрагідро-1*H*-пірану) гетероциклів, а також CF_3-, CHF_2- і CH_2F-вмісних похідних цих сполук. Крім того, було синтезовано і досліджено (флуоро)алкілзаміщені похідні арилсульфоксімінів. Було виявлено, що флуорування впливає на кислотність або основність досліджуваних сполук в основному за рахунок індуктивного ефекту атома Флуору і в загальному точно відтворює закономірності, які спостерігалися раніше для ациклічних аналогів. В той же час, варіативність ліпофільності була більш вираженою і непередбачуваною і залежала не тільки від положення флуорування, але також від розміру кільця і навіть природи функціональної групи. Встановлено, що зміни Δ Log*P* були різними для амідів відповідних карбонових кислот та первинних амінів і показано нелінійну залежність вказаних параметрів від кількості та властивостей флуорованих функціональних груп.

За результатами досліджень було запропоновано метод зображення хімічного простору в координатах pK_a – Log$P$ та продемонстровано з одного боку взаємозамінність, з іншого – взаємодоповнюваність синтезованих флуорованих насичених циклічних будівельних блоків при розробці нових лікарських засобів.

Розроблено підхід до синтезу *N*-дифлуороциклопропілзаміщених азолів із використанням уже відомих методів циклопропанування та показано обмежену застосовуваність реагенту Руперта–Пракаша для таких цілей. Показано значну стабільність дифлуорованих циклопропанів при проведенні ряду хімічних модифікацій піразольного кільця. Крім того, було показано синтетичний потенціал реакції дифлуороциклопропанування у випадку утворення хімічно активних дифлуороциклопропанів – таким чином було синтезовано ряд раніше невідомих флуорованих піразолів та піримідинів із циклоалкільними замісниками.

Було продемонстровано значний потенціал реакцій «видалення Нітрогену» за допомогою реагента Левіна та реакції Мініші у паралельному синтезі та розроблено методику його ефективного використання у такому варіанті. За результатами роботи було визначено критичні точки синтетичної послідовності та окреслено коло найбільш і найменш активних субстратів. На основі кількох баз даних молекул було показано значну унікальність згенерованого хімічного простору таким методом. Крім того, досліджено можливість введення у бажану молекулу флуорованого циклоалкільного фрагменту використовуючи такий підхід і показано значну його ефективність при виконанні ряду умов до вихідних сполук.

Практичне значення одержаних результатів. Синтезовано ряд нових будівельних блоків з перспективою використання у медичній хімії та проведено масштабування цих синтезів з метою підвищення їх синтетичної доступності. Зокрема, було запроновано підходи до *N*-заміщених дифлуороциклопропанів, 1,2-дизаміщених CF_3- та CHF_2-вмісних циклобутанів, похідних 4,4-дифлуороспіро[2.2]пентану, всіх ізомерних *гем*-дифлуорованих похідних

циклогептану та нітрогеновмісних біциклоалканів (зокрема 2-азабіцикло[2.1.1]гексану, -[2.2.1]гептану, -[3.2.1]октану, тощо), що містять α-CF_3 фрагмент біля вузлового атома Карбону. Стратегією послідовних реакцій функціоналізації подвійного зв'язку з внутрішньомолекулярним алкілуванням єноляту було отримано доступ до похідних біцикло[4.1.1]- та -[3.2.1]октану, біцикло[2.2.1]- та -[3.2.0]гептану, біцикло[3.1.0]гексану, а також біцикло-[2.1.0]пентану (хаузану).

Експериментально отримано ряд фізико-хімічних параметрів отриманих сполук та їх модельних похідних. Зокрема, було визначено кислотність/основність здатних до іонізації груп (pK_a), ліпофільність (у вигляді коефіцієнту розподілу 1-октанол – вода (Log$P$)), розчинність у воді S_w, хімічну та метаболічну стабільність тощо. Проведено порівняльний аналіз отриманих фізико-хімічних характеристик і запропоновано ряд емпіричних узагальнень по кореляціям між ними та структурою відповідних сполук для спрощення користування новою інформацією при дизайні бажаних молекул.

Впроваджено реакції видалення Нітрогену за Левіним та реакцію Мініші для синтезу бібліотек сполук в умовах паралельного синтезу. В результаті роботи розроблено дві бібліотеки потенційно біологічно активних речовин на основі нового методу одноатомного редагування молекул. На основі цього методу змодельовано хімічний простір нових сполук, що доступні за цим методом і показано надзвичайно високу унікальність (99%) цих сполук.

Особистий внесок здобувача є вирішальним на всіх етапах дослідження. Формування наукового напряму дисертаційної роботи, вибір об'єктів дослідження, генерування та обґрунтування ідей, систематизацію основної частини літературних даних, узагальнення та оформлення отриманих результатів було проведено автором самостійно. У постановці задач та обговоренні результатів дослідження, а також систематизації частини літературних даних брали участь науковий консультант д.х.н., проф. Григоренко О. О., д.х.н., проф. Волочнюк Д. М., д.х.н., проф. Рябухін С. В., на окремих етапах роботи к.х.н. Кондратов І. С., к.х.н. Імінов Р. Т., проф. Левін М. Синтез

сполук для проведення досліджень, аналіз результатів спектральних досліджень та встановлення будови одержаних сполук було проведено разом з PhD. Головачом С. М., PhD Ляшуком О. С., PhD Ващенком Б. В., PhD Смирновим О. К., Герасимчуком М. В., Порошиним І. Г. та іншими здобувачами освіти Київського національного університету імені Тараса Шевченка. Рентгеноструктурний аналіз здійснено у співробітництві з к.х.н. Русановим Е. Б. та д.х.н., проф. Шишкіною С.В. Квантовохімічні розрахунки проведено разом з PhD Ляшуком О. С. Визначення фізико-хімічних параметрів та біологічних властивостей окремих сполук було проведено у співпраці з к.б.н. Бориском П. О., Лесиком Д., к.б.н. Голотою Ю. О., Скремінським А., Коваленко О. та Болговою М.

Апробація результатів дисертації. Результати роботи доповідались і обговорювались на XX Міжнародній конференції студентів, аспірантів та молодих вчених «Сучасні проблеми хімії», 2019 р. (м. Київ), XXIII Міжнародній конференції студентів, аспірантів та молодих вчених «Сучасні проблеми хімії», 2022 р. (м. Київ), XXIV Міжнародній конференції студентів, аспірантів та молодих вчених «Сучасні проблеми хімії», 2023 р. (м. Київ), XIX науковій конференції «Львівські хімічні читання - 2023», 2023 р. (м. Львів) та XXV Міжнародній конференції студентів, аспірантів та молодих вчених «Сучасні проблеми хімії», 2024 р. (м. Київ).

Публікації. Результати дисертації відображені у 31 публікації: 18 статей у виданнях, проіндексованих в базі даних Scopus та/або Web of Science Core Collection (наукові журнали, в яких опубліковано результати дисертації, відповідно до класифікації SCImago Journal and Country Rank відносяться до першого квартилю (Q1) – 9 статей, до другого (Q2) – 6, до третього (Q3) – 3 статті та до четвертого (Q4) – 1 стаття), 3 статті, опубліковані у наукових фахових виданнях України та 10 тезах доповідей на конференціях, у т.ч. 8 міжнародних.

Структура та обсяг роботи. Дисертація викладена на 387 сторінках і складається зі вступу, п’яти розділів, висновків, переліку використаних джерел

(19 найменувань), містить 46 рисунків та 22 схеми. Перший розділ (літературний огляд) присвячено розгляду концепції флуорованих будівельних блоків та їх ролі в сучасній медичній хімії. У другому розділі обговорюються синтетичні підходи до раніше невідомих флуорованих/флуороалкільних похідних циклоалканів. Третій розділ присвячений послідовному дослідженню великого набору флуорованих насичених гетероциклічних систем та формулювання емпіричних правил на основі цих даних. У четвертому розділі описано методологію синтезу будівельних блоків на основі біциклічних сполук та їх флуорованих аналогів, а також дослідження їх фізико-хімічних характеристик.. П'ятий розділ присвячено прикладам новітнього застосування флуорованих будівельних блоків. У додатках розміщено копії наукових публікацій, на основі яких створено цю роботу.

Список використаних джерел

1. Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II–III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem*. *Rev*. **2016**, *116*, 422–518.

2. Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; Del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001-2011). *Chem*. *Rev*. **2014**, *114*, 2432–2506.

3. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in Medicinal Chemistry. *Chem*. *Soc*. *Rev*. **2008**, *37*, 320–330.

4. Isanbor, C.; O'Hagan, D. Fluorine in Medicinal Chemistry: A Review of Anti-Cancer Agents. *J. Fluor. Chem*. **2006**, *127*, 303–319.

5. Inoue, M.; Sumii, Y.; Shibata, N. Contribution of Organofluorine Compounds to Pharmaceuticals. *ACS Omega* **2020**, *5*, 10633–10640.

6. Yu, Y.; Liu, A.; Dhawan, G.; Mei, H.; Zhang, W.; Izawa, K.; Soloshonok, V. A.;

Han, J. Fluorine-Containing Pharmaceuticals Approved by the FDA in 2020: Synthesis and Biological Activity. *Chinese Chem. Lett*. **2021**, *32*, 3342–3354.

7. Mei, H.; Remete, A. M.; Zou, Y.; Moriwaki, H.; Fustero, S.; Kiss, L.; Soloshonok, V. A.; Han, J. Fluorine-Containing Drugs Approved by the FDA in 2019. *Chinese Chem. Lett*. **2020**, *31*, 2401–2413.

8. Mei, H.; Han, J.; Fustero, S.; Medio-Simon, M.; Sedgwick, D. M.; Santi, C.; Ruzziconi, R.; Soloshonok, V. A. Fluorine-Containing Drugs Approved by the FDA in 2018. *Chem. Eur. J*. **2019**, *25*, 11797–11819.

9. Emerging Fluorinated Motifs: Synthesis, Properties and Applications; Cahard, D., Ma, J.-A., Eds.; *Wiley-VCH*, **2020**.

10. Wishart, D. S.; Feunang, Y. D.; Guo, A. C.; Lo, E. J.; Marcu, A.; Grant, J. R.; Sajed, T.; Johnson, D.; Li, C.; Sayeeda, Z.; Assempour, N.; Iynkkaran, I.; Liu, Y.; MacIejewski, A.; Gale, N.; Wilson, A.; Chin, L.; Cummings, R.; Le, Di.; Pon, A.; Knox, C.; Wilson, M. DrugBank 5.0: A Major Update to the DrugBank Database for 2018. *Nucleic Acids Res*. **2018**, *46*, D1074–D1082.

11. Cripe, L. D.; Uno, H.; Paietta, E. M.; Litzow, M. R.; Ketterling, R. P.; Bennett, J. M.; Rowe, J. M.; Lazarus, H. M.; Luger, S.; Tallman, M. S. Zosuquidar, a Novel Modulator of P-Glycoprotein, Does Not Improve the Outcome of Older Patients with Newly Diagnosed Acute Myeloid Leukemia: A Randomized, Placebo-Controlled Trial of the Eastern Cooperative Oncology Group 3999. *Blood* **2010**, *116*, 4077–4085.

12. Alam, A.; Küng, R.; Kowal, J.; McLeod, R. A.; Tremp, N.; Broude, E. V.; Roninson, I. B.; Stahlberg, H.; Locher, K. P. Structure of a Zosuquidar and UIC2-Bound Human-Mouse Chimeric ABCB1. *Proc. Natl. Acad. Sci*. **2018**, *115*.

13. Katz, J. S.; Rothstein, J. D.; Cudkowicz, M. E.; Genge, A.; Oskarsson, B.; Hains, A. B.; Chen, C.; Galanter, J.; Burgess, B. L.; Cho, W.; Kerchner, G. A.; Yeh, F. L.; Ghosh, A. S.; Cheeti, S.; Brooks, L.; Honigberg, L.; Couch, J. A.; Rothenberg, M. E.; Brunstein, F.; Sharma, K. R.; van den Berg, L.; Berry, J. D.;

Glass, J. D. A Phase 1 Study of GDC-0134, a Dual Leucine Zipper Kinase Inhibitor, in ALS. *Ann. Clin. Transl. Neurol*. **2022**, *9*, 50–66.

14. Liu, F.; Barsyte-Lovejoy, D.; Li, F.; Xiong, Y.; Korboukh, V.; Huang, X. P.; Allali-Hassani, A.; Janzen, W. P.; Roth, B. L.; Frye, S. V.; Arrowsmith, C. H.; Brown, P. J.; Vedadi, M.; Jin, J. Discovery of an *in vivo* Chemical Probe of the Lysine Methyltransferases G9a and GLP. *J. Med. Chem*. **2013**, *56*, 8931–8942.

15. Sakai, H.; Inoue, H.; Murata, K.; Toba, T.; Shimmyo, Y.; Narii, N.; Ueno, S. ya; Igawa, Y.; Takemoto, N. Fibroblast Growth Factor Receptor Modulators Employing Diamines with Reduced Phospholipidosis-Inducing Potential. *Bioorg. Med. Chem*. **2020**, *28*, 115562.

16. Célanire, S.; Duvey, G.; Poli, S.; Rocher, J. P. MGluR2 Activators and MGluR5 Blockers Advancing in the Clinic for Major CNS Disorders. In *Annual Reports in Medicinal Chemistry*; Academic Press, **2012**; Vol. *47*, pp 71–88.

17. Xu, G.; Zhang, Y.; Wang, H.; Guo, Z.; Wang, X.; Li, X.; Chang, S.; Sun, T.; Yu, Z.; Xu, T.; Zhao, L.; Wang, Y.; Yu, W. Synthesis and Biological Evaluation of 4-(Pyridin-4-Oxy-3-(3,3-Difluorocyclobutyl.-Pyrazole Derivatives as Novel Potent Transforming Growth Factor-β Type 1 Receptor Inhibitors. *Eur. J. Med. Chem*. **2020**, *198*, 112354.

18. Bamborough, P.; Chung, C. wa; Demont, E. H.; Furze, R. C.; Bannister, A. J.; Che, K. H.; Diallo, H.; Douault, C.; Grandi, P.; Kouzarides, T.; Michon, A. M.; Mitchell, D. J.; Prinjha, R. K.; Rau, C.; Robson, S.; Sheppard, R. J.; Upton, R.; Watson, R. J. A Chemical Probe for the ATAD2 Bromodomain. *Angew. Chem. Int. Ed*. **2016**, *55*, 11382–11386.

19. Wityak, J.; McGee, K. F.; Conlon, M. P.; Song, R. H.; Duffy, B. C.; Clayton, B.; Lynch, M.; Wang, G.; Freeman, E.; Haber, J.; Kitchen, D. B.; Manning, D. D.; Ismail, J.; Khmelnitsky, Y.; Michels, P.; Webster, J.; Irigoyen, M.; Luche, M.; Hultman, M.; Bai, M.; Kuok, I. D.; Newell, R.; Lamers, M.; Leonard, P.; Yates, D.; Matthews, K.; Ongeri, L.; Clifton, S.; Mead, T.; Deupree, S.; Wheelan, P.; Lyons, K.; Wilson, C.; Kiselyov, A.; Toledo-Sherman, L.; Beconi, M.; Muñoz-

Sanjuan, I.; Bard, J.; Dominguez, C. Lead Optimization toward Proof-of-Concept Tools for Huntington's Disease within a 4-(1*H*-Pyrazol-4-yl)Pyrimidine Class of Pan-JNK Inhibitors. *J. Med. Chem*. **2015**, *58*, 2967–2987.

ОСНОВНІ РЕЗУЛЬТАТИ ДОСЛІДЖЕНЬ ТА ЇХ ОБГОВОРЕННЯ

Розділ 1 РОЛЬ ФЛУОРОВМІСНИХ НАСИЧЕНИХ СПОЛУК У РОЗРОБЦІ ЛІКАРСЬКИХ ЗАСОБІВ

Важливість флуоровмісних сполук в сучасній медичній науці важко переоцінити. Так, за останні десятиліття були роки, коли до 50% препаратів, схвалених Адміністрацією харчових продуктів та ліків (FDA) США, були флуороорганічними сполуками, а 12 з них були виведені на ринок у 2023 році.

З метою узагальнення знань про роль флуоровмісних будівельних блоків в створенні лікарських засобів у межах виконання дисертаційної роботи було опубліковано оглядову роботу, присвячену флуорованим насиченим циклоалканам [**1.1**]. В огляді було розглянуто моно-, ди- та поліфлуоровані аліциклічні (C_3–C_7) будівельні блоки з різними флуорованими замісниками (зокрема, *гем*- та *вік*-дифлуоровані, *α–δ* заміщені флуороциклоалкани та ін.) (Рисунок 1.1).

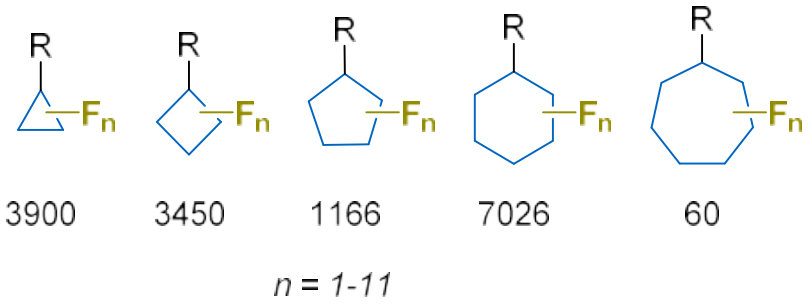


Рисунок 1.1. Кількість публікацій, де згадуються вказані флуоровані фрагменти.

У першій частині огляду було перераховано основні стратегії синтезу досліджуваних сполук. Серед найбільш розповсюджених можна виокремити нуклеофільне заміщення флуорид-аніоном, електрофільне α-флуорування, радикальне флуорування, циклоприєднання або циклізації флуоро-вмісних проміжних сполук, приєднання до кратних зв’язків та перетворення уже готових флуорованих циклоалканів.

Наступна частина огляду була присвячена розгляду стереохімічних особливостей флуорованих циклоалканів, зокрема вплив стеричних факторів (1,3-діаксіального відштовхування), ефекту мінімізації диполя, гіперкон'югації та слабких міжмолекулярних взаємодій на заселеність конформацій для різних циклів. Крім того, було зроблене узагальнення впливу атомів Флуору на фізико-хімічні параметри, такі як кислотність та основність pK_a, ліпофільність Log$P$ і метаболічну стабільність.

В кінці огляду значну увагу було приділено застосуванню досліджуваних сполук у розробці новітніх лікарських засобів. Для більш зручної класифікації, розглянуті сполуки були розподілені по мішені, на яку вони діють, як от інгібітори ензимів, ліганди G-протеїнозв'язаних рецепторів, ліганди кіназ, ліганди йонних каналів, комбіновані молекули вибіркового протеолізу (PROTACs) та багато інших (Рисунок 1.2).

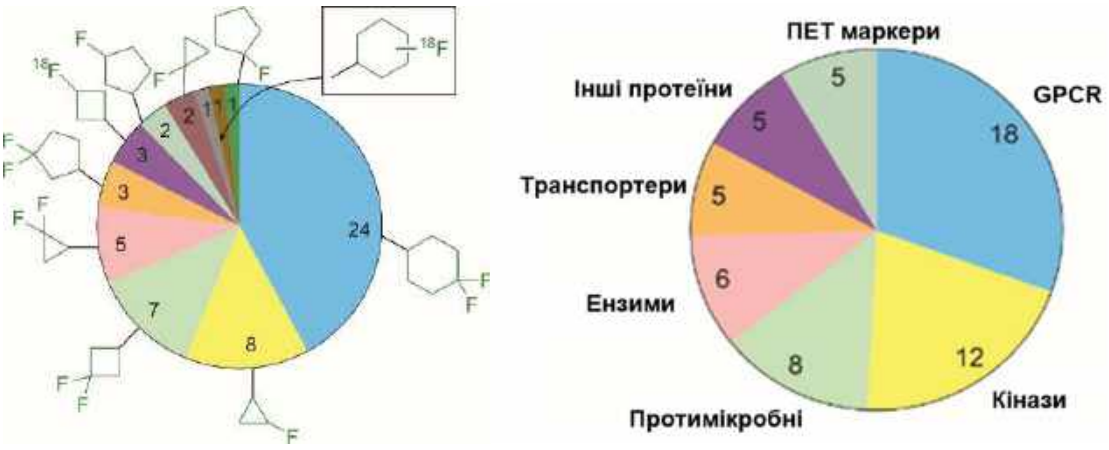


Рисунок 1.2. Основні флуоровані циклічні фрагменти, що уже застосовуються в лікарських засобах на різних стадіях досліджень (зліва) та сфери застосування або біологічні мішені цих сполук (справа).

Такий значний перелік сфер застосування однозначно вказує на актуальність синтезу нових невідомих флуорованих циклічних будівельних блоків, розробки ефективних методів їх мультиграмового синтезу та дослідження їх фізико-хімічних параметрів.

Хоча переважна більшість нещодавно схвалених флуорованих лікарських засобів досі містять групи F або CF_3, приєднані до бензольного або іншого ароматичного кільця, спостерігається чітка тенденція до більш широкого

представлення інших флуорованих хемотипів, особливо на пізніх етапах відкриття та розробки. До них відносяться флуоро-, *гем*-дифлуоро- (розглянуті вище), віцинальні та «пропущені» («skipped») ди/поліфлуоро- чи флуоралкіл- (особливо CF_3- та CHF_2-) заміщені аліфатичні сполуки, зокрема, карбо- та гетероцикли; сполуки з флуоралкокси- (переважно OCF_3), *N*-флуоралкіл- (переважно NCF_3), флуорований сульфоксимін, CF_2Cl/OCF_2Cl, SF_5-групи тощо. (Рисунок 1.3).

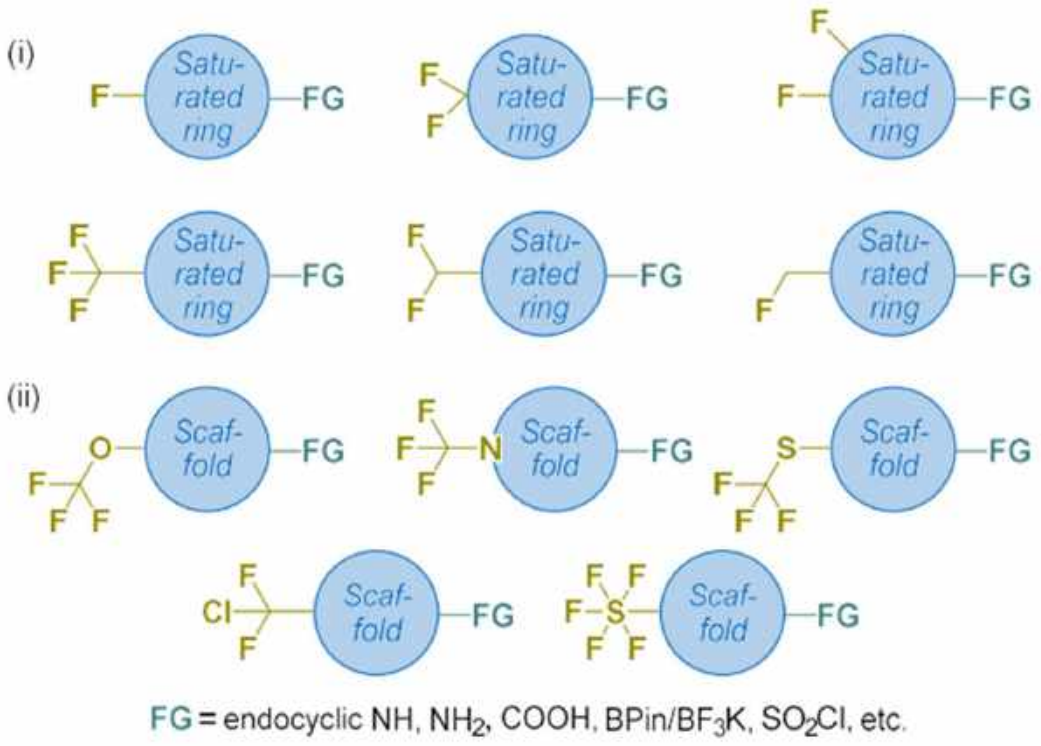


Рисунок 1.3. Обрані флуоровані хемотипи, що дедалі частіше використовуються в розробці лікарських засобів.

Продовжуючи думку переважання застосування флуорованих будівельних блоків над прямими методами введення флуору для створення складних молекул, в цій частині роботи було проведено систематизацію поточних методів створення флуоровмісних функціоналізованих сполук.[**1.2**]

Один з них базується на прямому радикальному або каталізованому перехідними металами C–H-флуоруванні, -флуороалкілуванні, -флуороалкоксилуванні тощо (Рисунок 1.4, *A*). Як правило, (гетеро)ароматичні субстрати є сумісними з вищезазначеними методами, однак в цьому випадку такі стратегії або вимагають присутності направляючих груп, або потенційно можуть

страждати від проблем регіоселективності. Ще одне помітне обмеження стратегії в її нинішньому стані пов'язане з сумісністю з бічними функціональними групами цільових блоків; досить часто важко передбачити ефекти заміщення на селективність чи загальний вихід перетворення.

Стратегія флуородекарбоксилювання – ще одна відносно нова методологія, яку можна використовувати для введення флуоровмісних замісників у цільові молекули (Рисунок 1.4, *B*). Завдяки високій доступності різних функціоналізованих карбонових кислот ця стратегія може бути відносно легко реалізована для синтезу будівельних блоків. Також варто відзначити застосовність методу до sp^3-збагачених, насичених циклічних систем. Через радикальну природу цього перетворення очікувана низька стереоселективність стає важливим недоліком вищевказаної стратегії. Наприклад, нещодавно цей метод було використано для одержання 2-флуороциклобутанкарбонової кислоти у вигляді суміші діастереомерів, які в подальшому було розділено дериватизацією із подальшим хроматографічним розділенням.

Електрофільне приєднання флуоровмісної групи та (замаскованої) функціональної групи до зв'язків C=C (або C≡C) є класичним підходом до синтезу флуорорганічних сполук, проте останнім часом було запропоновано ряд його радикальних та каталізованих перехідними металами модифікацій (Рисунок 1.4, *C*). Важливою ілюстрацією цієї стратегії є флуоро- або флуороалкілборилювання подвійного зв’язку. Хоча повний потенціал цих новітніх методів синтезу флуорованих будівельних блоків ще тільки належить оцінити, їх сумісність з низькомолекулярними насиченими циклічними системами, та, особливо, висока спостережувана регіо- та стереоселективність є багатообіцяючими з точки зору подальшого розвитку стратегії. Як цікавий приклад такого розвитку, можна згадати асиметричне Pd-каталізоване амінофлуорування неактивованих алкенів, що дає можливість отримати хіральні 3-флуоропіперидини та їх спіроциклічні аналоги.

Серед інших важливих методів, що отримали увагу останнім часом, можна назвати перетворення *гем*-дифлуорованих алкенів (Рисунок 1.4, *D*),

гомологізацію флуорованими фрагментами (*E*), реакції вивільнення деформаційного напруження з флуоровмісними перехоплювачами (*F*), а також реакції на основі кремнійорганічних дифлуорокарбенових реагентів ($TMSCF_2X$), зокрема, реакції *гем*-дифлуороциклопропанування (*G*). Важливим варіантом останнього підходу є використання систем на основі CF_3SiMe_3 (реагент Рупперта-Пракаша). Важливим аспектом обговорюваного напрямку досліджень є отримання хіральних флуоровмісних будівельних блоків. Серед методів, впроваджених останнім часом з цією метою, можна назвати хемоферментативний синтез флуорорганічних сполук або нуклеофільне приєднання до хіральних флуоралкілзаміщених сульфінімідів.

Хоча важливість наведених вище стратегій не викликає сумнівів, більшість останніх робіт з синтезу нових флуорованих будівельних блоків (за деякими винятками, подібними до наведених вище) ґрунтуються на класичних перетвореннях флуорорганічної хімії. Так, більшість моно- та *гем*-дифлуорованих, а також флуоралкілзаміщених насичених карбо- та гетероциклічних сполук було отримано за допомогою нуклеофільного флуорування спиртів чи їх активованих похідних, або карбонільних сполук (за допомогою досить типового переліку реагентів: KF, DAST, Morph-DAST, XtalFluor-*E* та ін.) (Рисунок 1.5, *A*). У той час як той же підхід був задіяний для синтезу насичених аліциклічних та гетероциклічних будівельних блоків з віцинальним та «пропущеним» розташуванням атомів Флуору (включаючи відомі циклоалкани О'Хагана), інші методи включали реакції нуклеофільного розкриття оксиранового циклу (напр., за допомогою Et_3N-3HF) або електрофільне флуорування (наприклад, NFSI або SelectFluor) (Рисунок 1.5, *Б*). Слід зазначити, що багато зусиль було докладено для оцінки фізико-хімічних, конформаційних та фізико-хімічних властивостей вищезгаданих хемотипів (зокрема, кислотність/основність та ліпофільність) та відповідні ефекти флуоровмісних замісників. Через незвичайну природу відповідних хемотипів були розроблені спеціальні синтетичні методики для отримання $OCHF_2$-/OCF_3-, NCF_3-,SF_5 -заміщених та інших споріднених будівельних блоків (Рисунок 1.5, *B*).

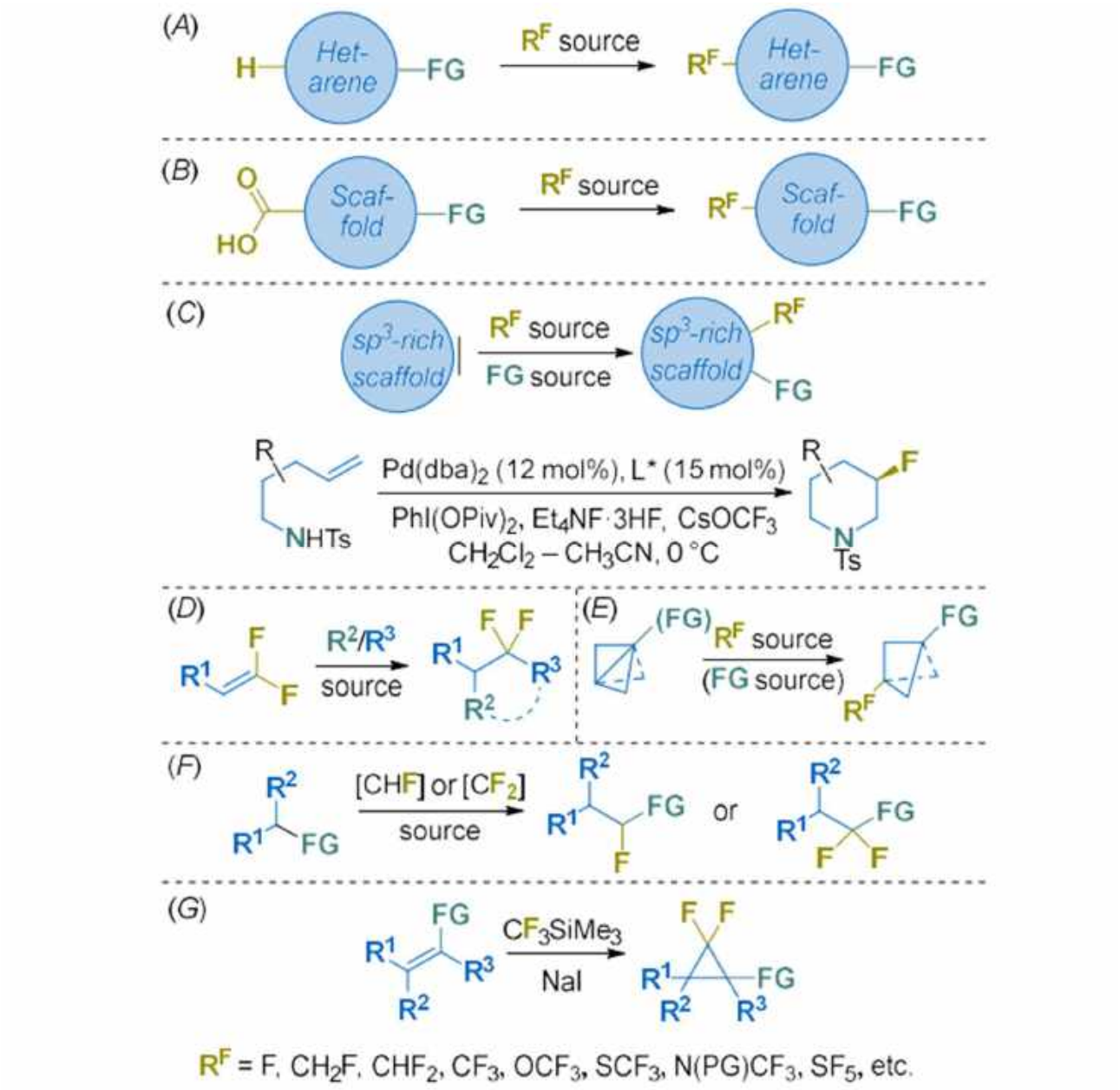


Рисунок 1.4. Нові стратегії синтезу флуоровмісних будівельних блоків.

Наприклад, нещодавно описаний багатокілограмовий синтез ди- і трифлуорометоксизаміщених похідних проліну, що базується на каталізованому перехідними металами ди- або трифлуорометилюванні 4-гідроксипроліну. Для синтезу *N*-трифлуорметильних гетероциклічних будівельних блоків, як правило, застосовують алкілування основами за допомогою CF_2Br_2 з наступною реакцією з $AgBF_4$, а також електрофільне *N*-трифлуорметилювання з використанням реагентів Тогні. Хлорування в присутності KF (з утворенням Cl-заміщених похідних SF_4) з наступним нуклеофільним заміщенням на AgF або $AgBF_4$ є

найбільш прямим методом отримання ароматичних SF_5-заміщених будівельних блоків.

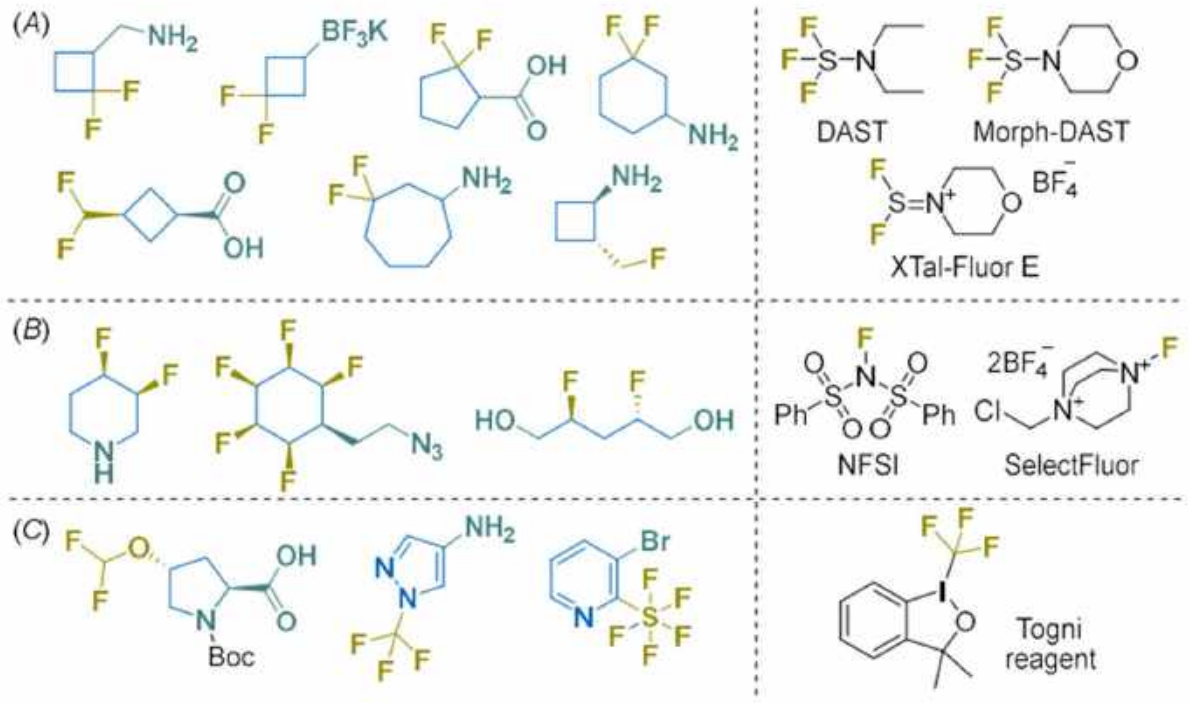


Рисунок 1.5. Приклади новітніх флуорованих будівельних блоків та методи їх введення: (*A* та *B*) Класичні підходи; (*C*) З використанням спеціалізованих підходів.

Таким чином, в цьому розділі було проведено узагальнення відомих на сьогодні сфер застосування, методів синтезу та окремих макроскопічних характеристик флуорованих будівельних блоків. Розгляд основних хемотипів, описаних в літературі дозволив чітко виокремити ідею важливості флуорованих будівельних блоків та необхідності їх всебічної характеризації з метою практичного застосування в майбутньому.

Основні публікації за розділом:

1.1. Grygorenko, O. O.; Melnykov, K. P.; Holovach, S.; Demchuk, O. Fluorinated cycloalkyl building blocks for drug discovery. *ChemMedChem* **2022**, *17*, e202200365. DOI: 10.1002/cmdc.202200365.

1.2. Grygorenko, O. O.; Melnykov, K. P. Fluorinated building blocks in drug design: new pathways and targets. *Future Med. Chem.* **2024,** *16(14)*, 1375–1378. DOI 10.1080/17568919.2024.2379229.

Розділ 2 ФЛУОРОВАНІ ТА ФЛУОРОАЛКІЛЬНІ ПОХІДНІ ЦИКЛОАЛКАНІВ

Пошук у базі даних Reaxys показує, що на відміну від флуорованих похідних малих і середніх циклів, синтез і застосування вищих гомологів – *гем*-дифлуорованих похідних циклогептану – залишаються недостатньо вивченими як у статтях, так і в патентах. Слід зазначити, що згадані вище флуоровані фрагменти циклогептану є не лише черговими представниками гомологічного ряду *гем*-дифлуороциклоалканів – нещодавно було показано, що семичленні кільця забезпечують унікальне тривимірне розташування приєднаних функціональних груп, чого нелегко досягти нижчими гомологами. Таким чином, було визначено мету в розробці методів синтезу усіх трьох ізомерів дифлуороциклогептанів **2.1–2.9** із найпоширенішими функціональними фрагментами – карбоксильною, аміно- та карбонільною групами (Рисунок 2.1).[**2**.**1**]

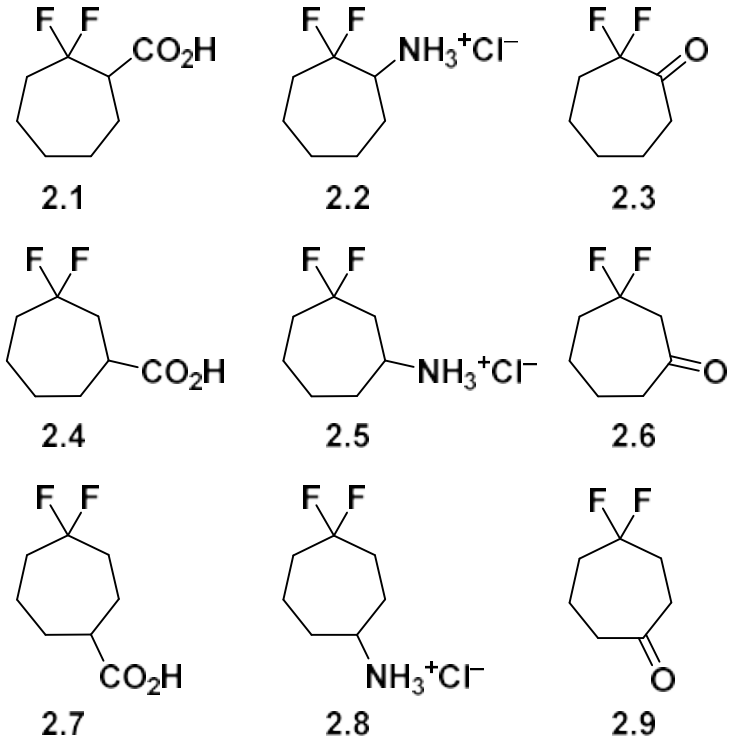


Рисунок 2.1. Набір ізомерних *гем*-дифлуорованих циклогептанів, запропонованих до синтезу в даній роботі.

Перетворення циклогексанону **2.10** у 2,2-дифлуорозаміщений циклогептанон **2.3** (Схема 2.1) було описано Амі та його колегами за участі $BrCF_2CO_2Na$ при нагріванні до 150 °C. У даній роботі було запропоновано застосування системи $TMSCF_3$ – NaI для утворення дифлуоркарбену в більш м'яких умовах, що дозволило отримати до 150 г продукту **2.3** за один синтетичний підхід (вихід 60% з **2.10**). Подальше відновне амінування з наступною обробкою 4 М HCl в діоксані дозволило отримати бажаний амін **2.2** з виходом 45%. Олефінування циклогептанону **2.3** за Віттігом з наступним гідроборуванням – окисненням дало спирт **2.12** (вихід 64% на 3 стадії), який після окиснення за допомогою системи $RuCl_3$–$NaIO_4$ було перетворено у кислоту **2.1** з високим (97%) виходом.

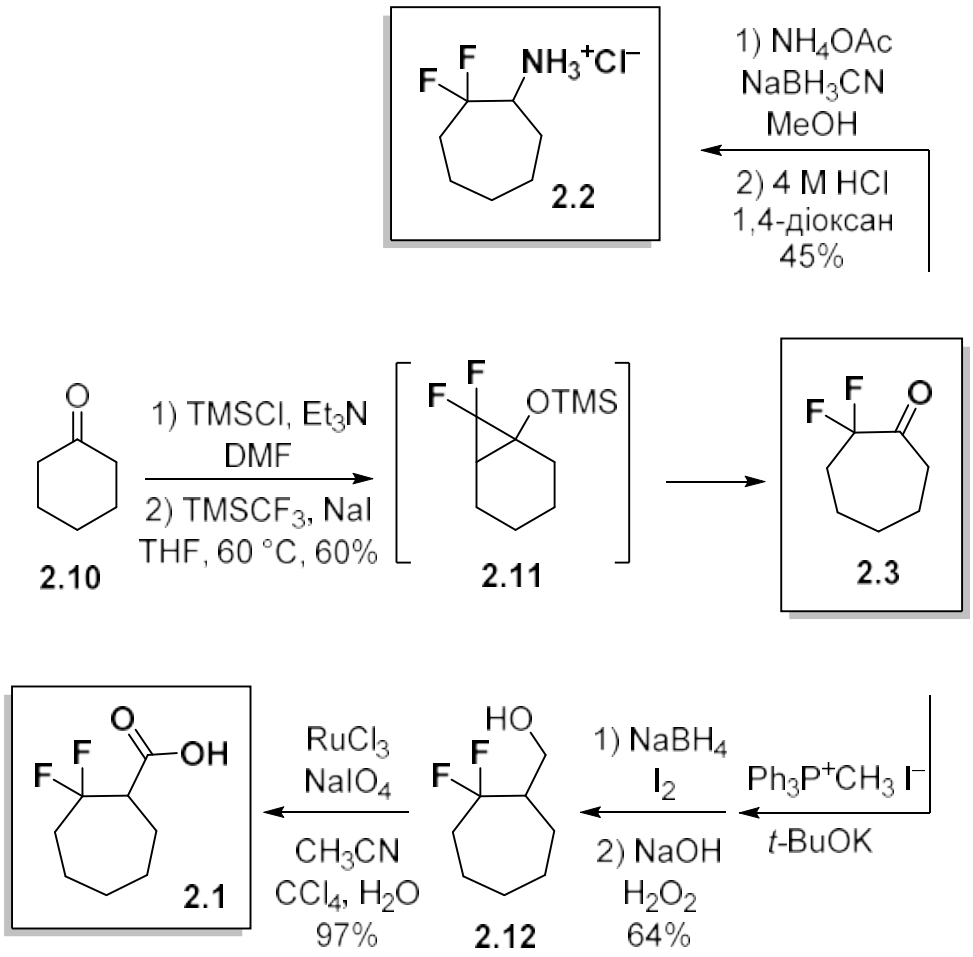


Схема 2.1. Синтез α-заміщених дифлуороциклогептанів.

Використання циклогепт-2-енону **2.13** як вихідної речовини дозволило отримати карбонову кислоту **2.4** лише за три стадії (Схема 2.2). Послідовне гідроціанування, деоксофлуорування **2.14** за допомогою DAST та лужний

гідроліз дав цільову сполуку **2.4** з виходом 48% на 3 стадії. Гідрохлорид аміну **5** було отримано шляхом модифікованого перегрупування Курціуса із подальшим зняттям захисної групи із загальним виходом 75%.

За схожою схемою було отримано спирт **2.18**, після окиснення якого за допомогою піридинхлорохромату (PCC) було отримано кетон **2.6** із сумарним виходом 30%.

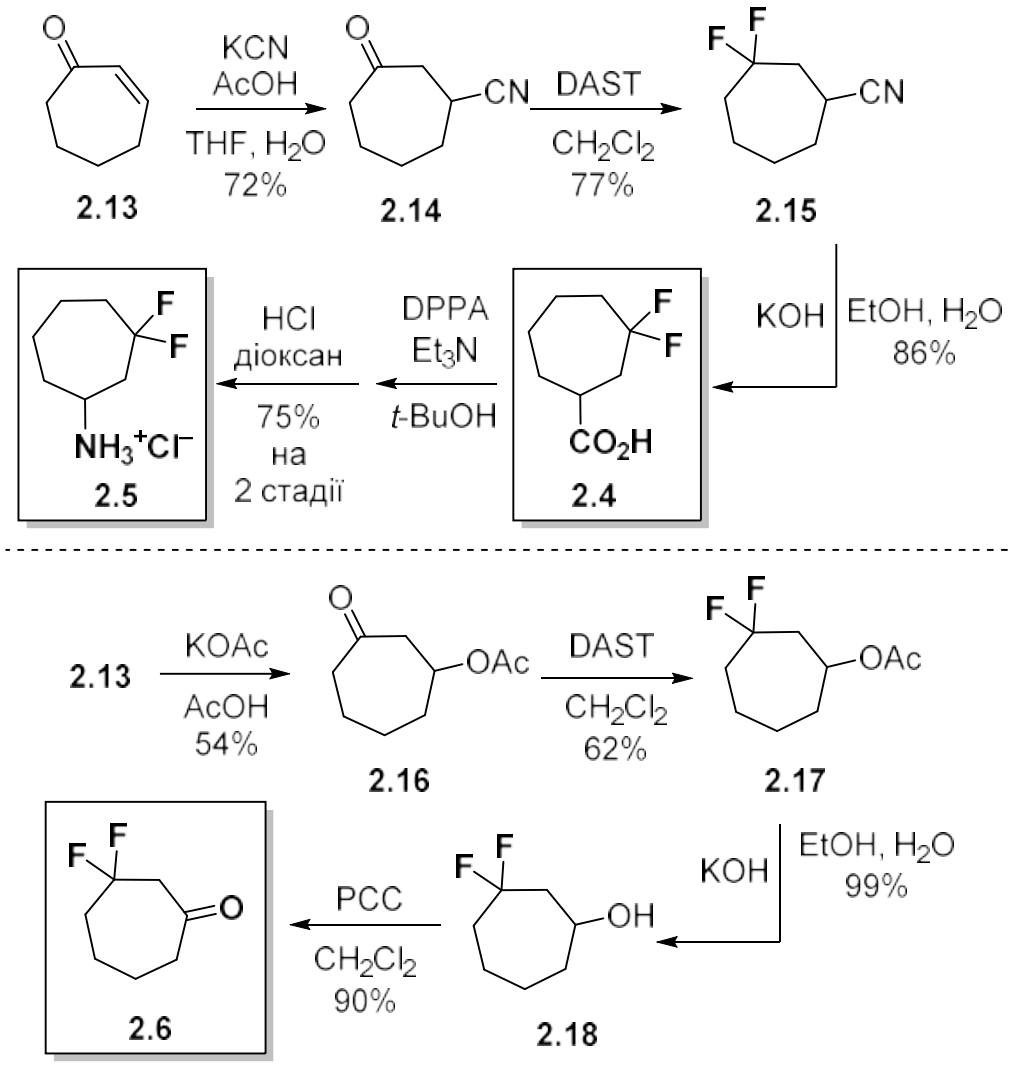


Схема 2.2. Синтез *β*-заміщених дифлуороциклогептанів.

Нарешті, *γ*-заміщені похідні *гем*-дифлуороциклогептану **2.7–9** були отримані з циклогексанонового субстрату **2.19** або **2.21** шляхом розширення циклогексанового циклу з використанням етилдіазоацетату (Схема 2.3). Обробка 4,4-дифлуороциклогексанону (**2.19**) етилдіазоацетатом з наступним кислотним гідролізом і декарбоксилюванням дала 4,4-дифлуороциклогептанон

2.9 (67% за дві стадії). Подальше відновне амінування кетону **2.9** та обробка 4 М розчином HCl в 1,4-діоксані дали цільовий амін **2.8** з виходом 57%.

Для отримання семичленної γ-дифлуоркарбонової кислоти **2.7** було проведено розширення циклу етил-4-оксоциклогексанкарбоксилату **2.21** з наступним гідролізом діестеру, декарбоксилюванням в лужних умовах та естерифікацією. (Схема 3). Після деоксофлуорування з використанням DAST (63%) та лужного гідролізу отриманого проміжного продукту **2.23** цільова карбонова кислота **2.7** була отримана з виходом 69%.

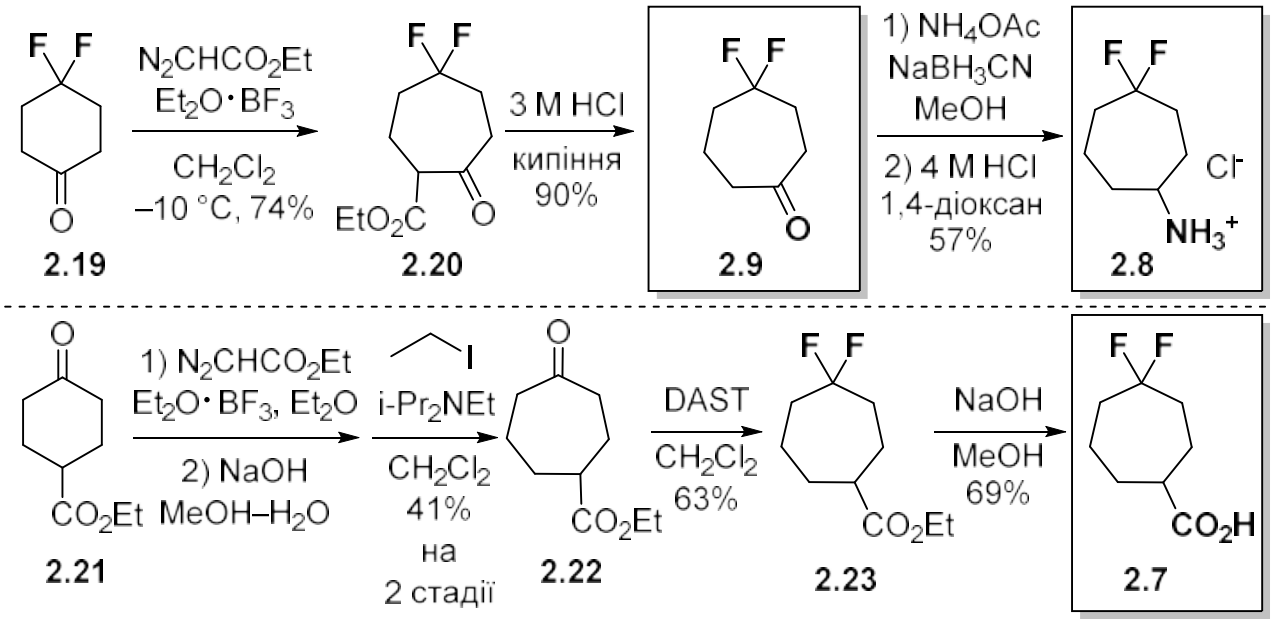


Схема 2.3. Синтез γ-заміщених дифлуороциклогептанів.

Варто зазначити, що запропоновані синтетичні схеми є економними з точки зору ресурсів, використовують широко доступні комерційні реагенти та дозволяють отримати бажані семичленні флуоровані будівельні блоки у багатограмових кількостях (до 133 г).

Продовженням дослідження флуоровмісних насичених аліциклів є синтез та вивчення циклобутанів та їх похідних. Актуальність такого дослідження підтверджується рядом уже впроваджених CF_3-, CHF_2- and CH_2F-вмісних похідних циклобутану, зокрема агентів для ПЕТ, таких як флуцикловін (FACBC) або його гомолог FMACBC (**2.24**), конформаційно обмежені аналоги γ-аміномасляної кислоти (ГАМК) (**2.25** або серину (**2.26**) та інші (Рисунок 2.2).

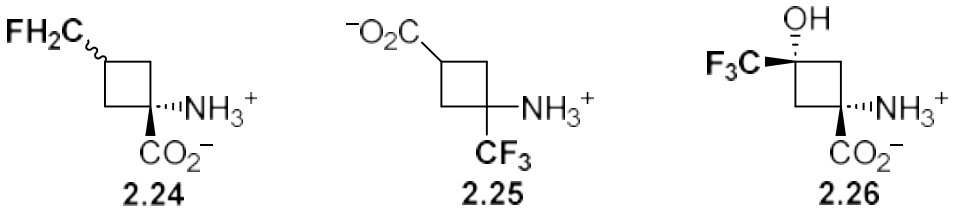


Рисунок 2.2. Приклади біологічно активних флуоровмісних циклобутанів.

Переважна більшість флуорованих будівельних блоків представлена 1,3-дизаміщеними циклобутанами, в той же час 1,2-дизаміщені похідні циклобутанів є практично невідомими. Маючи на меті ефективно заповнити хімічний простір флуорованих будівельних блоків, було запропоновано ефективні синтетичні схеми до цільових сполук **2.27–2.32** виходячи із комерційно доступних реагентів (Рисунок 2.3).[**2.2**]

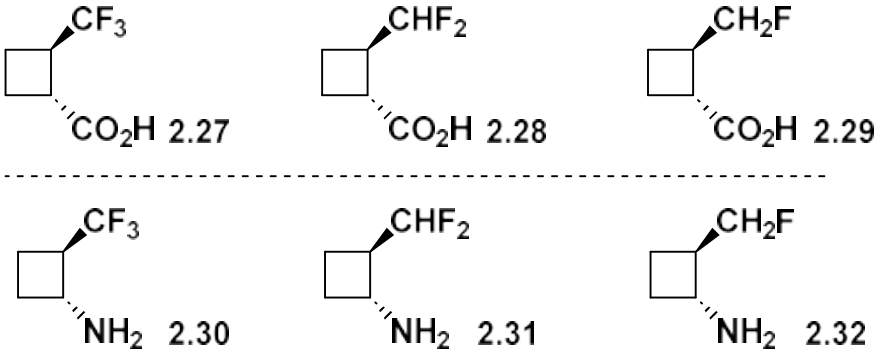


Рисунок 2.3. 1,2-дизаміщені похідні циклобутану, заплановані до синтезу в ході роботи.

Передбачалося, що цільові молекули **2.27–2.32** можуть бути отримані з *trans*-циклобутан-1,2-дикарбоксилату **2.33** шляхом простих органічних перетворень та деоксофлуоруванням (для CF_3/CHF_2) або нуклеофільним заміщенням (для CH_2F) як ключовими етапами (Схема 2.4). Основний проміжний продукт **2.33** було отримано у вісім стадій (в той же час варто зазначити, що багато з них проводилися в одноколбовому форматі без виділення проміжних сполук) згідно з літературними протоколами, починаючи з адипінової кислоти.

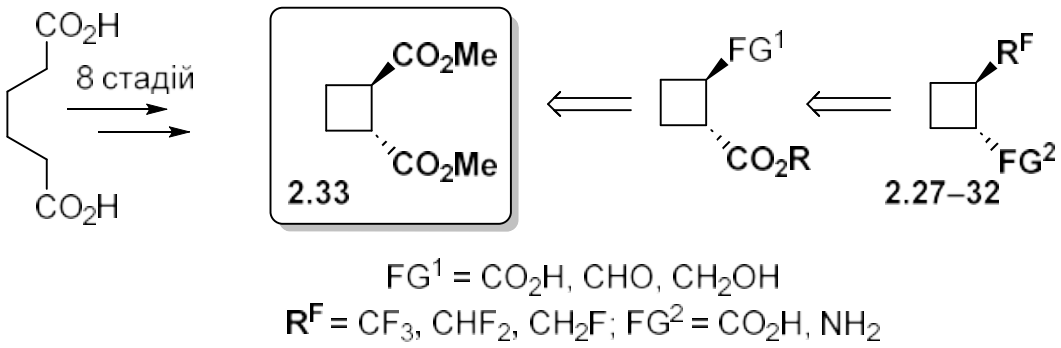


Схема 2.4. Ретросинтетичний підхід до цільових циклобутанів.

Послідовність реакцій, запропонована в цій роботі, починалася з хемоселективного гідролізу діестеру **2.33** у відповідний моноестер **2.34** з виходом 66% (Схема 2.5)**.** Деоксофлуорування **2.34** з використанням SF_4 в автоклаві Hastelloy з подальшим лужним гідролізом естерної групи забезпечило цільовий продукт **2.27** з виходом 67% на 2 стадії. Перегрупування Курціуса за модифікованою процедурою (за допомогою DPPA) у присутності Et_3N у *t*-BuOH дала *N*-Boc-захищений амін **2.35** (вихід 88%), який після обробки 4 M HCl у Et_2O було перетворено у гідрохлорид **2.30** із 85% виходом. Встановлення *трет*-бутильного захисту на кислоту **2.34** дозволило отримати несиметричний диестер **2.36**, який було послідовно гідролізовано та відновлено диметилсульфідним комплексом борану з утворенням спирту **2.37** з виходом 79%. Окиснення гідроксильної групи за Сверном, деоксофлуорування проміжного альдегіду за допомогою Morph-DAST та зняття захисної групи дозволило отримати кислоту **2.28** з виходом 63%. Знову ж таки, перегрупування Курціуса за модифікованою процедурою (за допомогою DPPA) у присутності Et_3N у *t*-BuOH дала *N*-Boc-захищений амін, який після обробки 4 M HCl у Et_2O було перетворено у гідрохлорид **2.31** із 71% виходом.

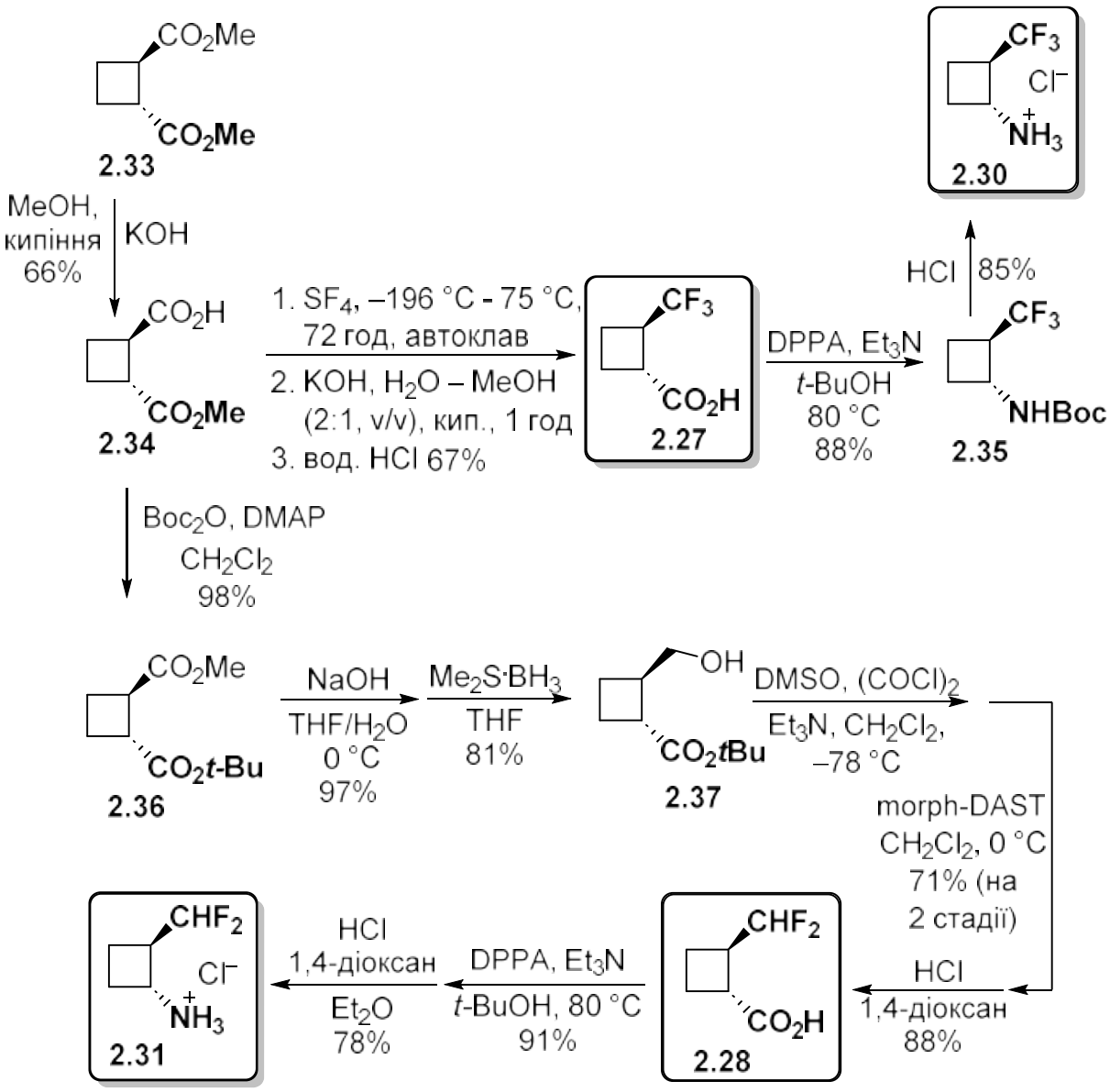


Схема 2.5. Синтез цільових CF_3- та CHF_2-вмісних циклобутанів.

Для отримання CH_2F-заміщених будівельних блоків **2.29** і **2.32** було використано проміжний гідроксиестер **2.37** (Схема 2.6)**.** Так, цю сполуку було перетворено у відповідний мезилат **2.38** (94% вихід), який потім дією тетраметиламмонійфлуориду (TMAF) було перетворено на 2-(флуорометил)циклобутанкарбоксилат **2.39** із 69% виходом. Естер **2.39** легко перетворюється на цільову циклобутанкарбонову кислоту **2.29** при обробці сухим HCl (вихід 87%). Модифіковане перегрупування Курціуса у *t*-BuOH дало *N*-Boc-захищений амін **2.40** (вихід 91%), який після обробки 4 M HCl у Et_2O було перетворено у гідрохлорид **2.32** із 76% виходом.

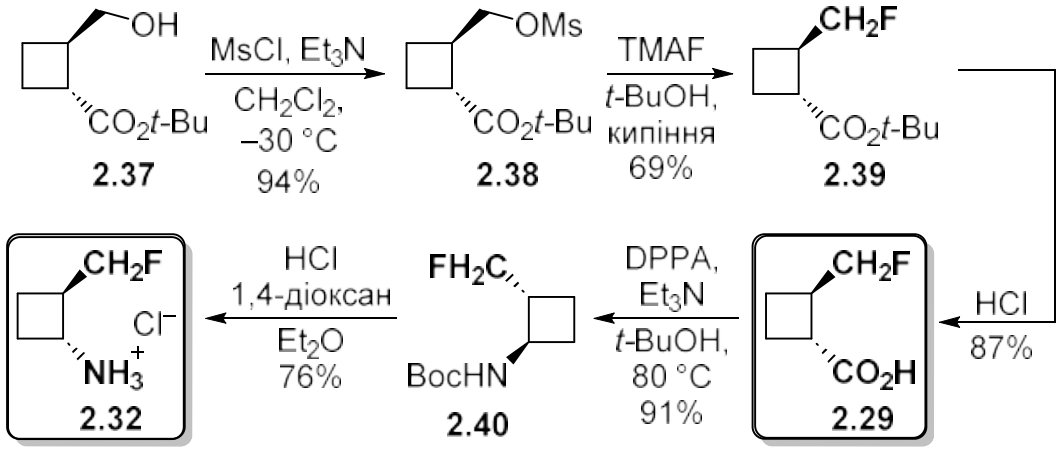


Схема 2.6. Синтез цільових CH_2F-вмісних циклобутанів

Щоб оцінити вплив флуоралкільного фрагмента на фізико-хімічні властивості карбоксильної або аміногрупи в циклобутановому ядрі, були виміряні відповідні значення pK_a для сполук **2.27–2.32** (Рисунок 2.4). Встановлено, що в межах досліджуваного ряду значення кислотності здатних до дисоціації груп змінювалися очікуваним чином. Так, введення флуорметильної групи в циклобутанкарбонову кислоту, і подальше додавання атомів Флуору підвищували кислотність на 0,11 (**2.29**), 0,12 (**2.28**) і 0,39 (**2.27**) одиниць pK_a відповідно. Для відповідних амінів максимальна різниця в 1,03 одиниці pK_a спостерігалася для **2.31** і **2.32**, і спостережувані значення відповідали загальному правилу: введення атомів Флуору в γ-положення аліфатичного аміну призводить до зниження pK_a приблизно 0,7 одиниць на кожен атом.

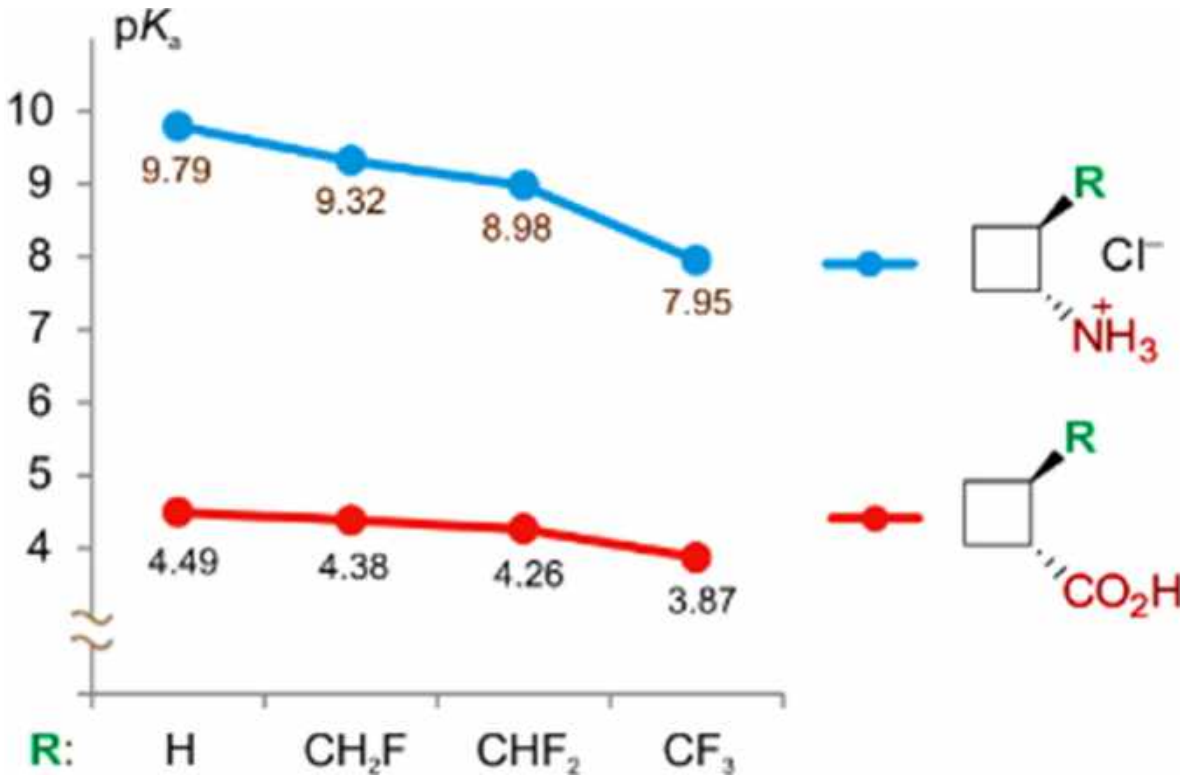


Рисунок 2.4. Порівняння виміряних значень кислотності та основності отриманих сполук.

Для оцінки впливу флуоралкільних замісників на ліпофільність сполуки **2.27–2.32** перетворили у відповідні аміди (Рисунок 2.52). У серії сполук **2.41–2.46** виміряні значення Log*P* дотримувалися тенденції, описаної в літературі для ациклічних флуорованих похідних, що містять F-атоми в положенні C-3: $CH_2F \leq CHF_2 << CF_3$, з ΔLog*P* 0,11 для **2.41** і **2.42** і 0,66 для **2.42** і **2.43**. Цікаво, що введення групи CH_2F або CHF_2 замість атома Гідрогену дещо зменшило ліпофільність сполук у цих рядах, навіть незважаючи на збільшення кількості атомів Карбону. Ізомерні аміди **2.44–2.46**, отримані з відповідних циклобутиламінів, продемонстрували подібну поведінку з дещо нижчими значеннями Log*P* порівняно з **2.41–2.43**.

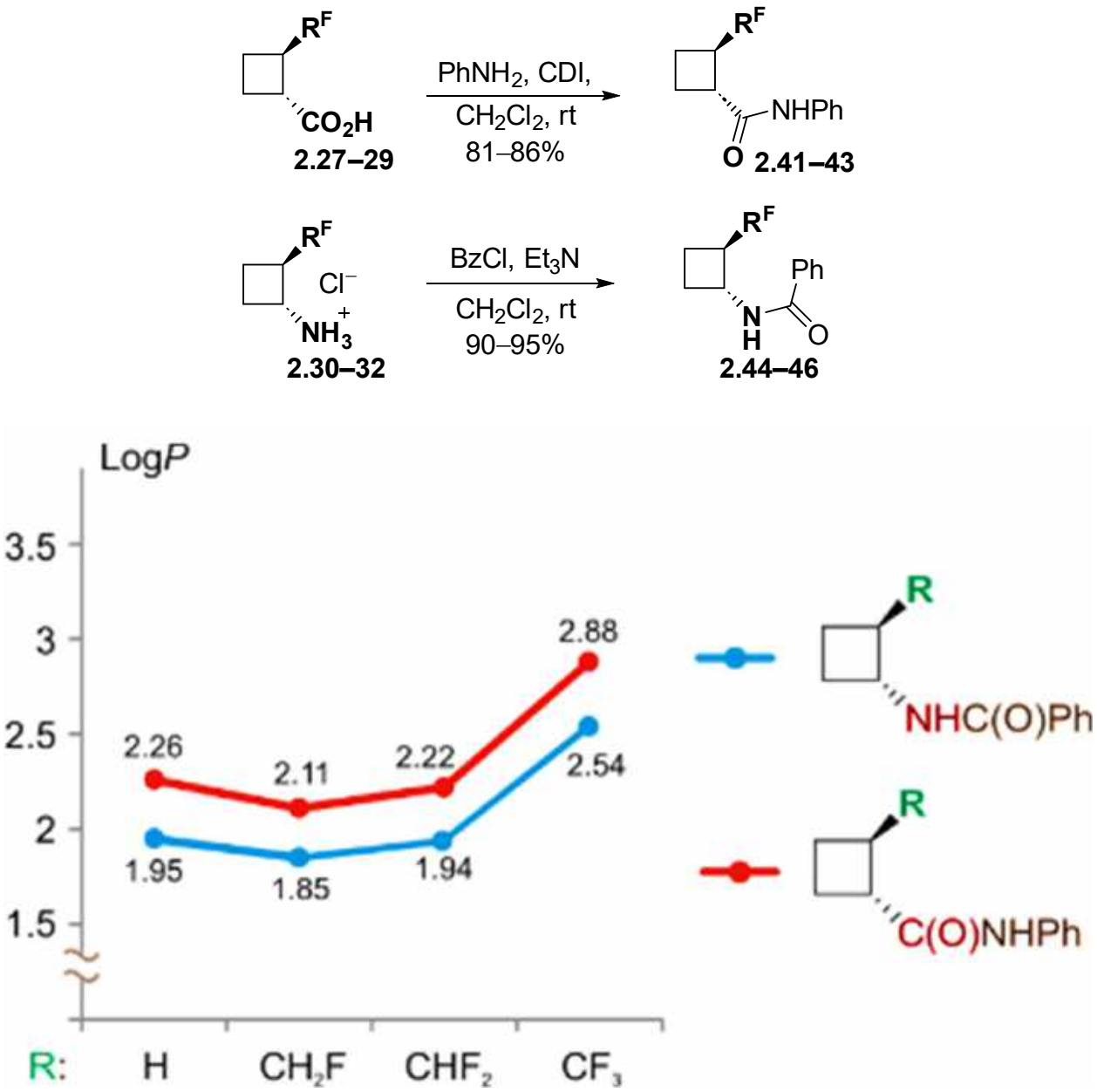


Рисунок 2.52. Синтез та порівняння виміряних значень ліпофільності Log*P* отриманих будівельних блоків.

Нарешті, розчинність у воді (S_w) сполук **2.41–2.46** змінювалася симбатно із ліпофільністю, причому CF_3-заміщені похідні були найменш розчинними (Рисунок 2.6).

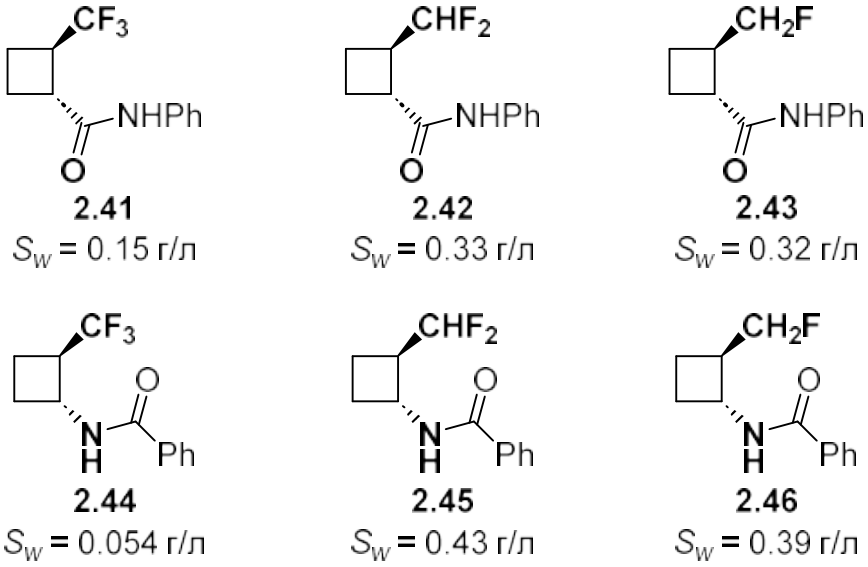


Рисунок 2.6. Порівняння виміряних значень водорозчинності отриманих сполук.

Основні публікації до розділу:

2.1. Herasymchuk, M.; **Melnykov**, K. P.; Yarmoliuk, D. V.; Serhiichuk, D.; Rotar, V.; Pukhovoi, T.; Kuchkovska, Yu. O.; Holovach, S.; Volochnyuk, D. M.; Ryabukhin, S. V.; Grygorenko, O. O. Last of the *gem*-difluorocycloalkanes 2: synthesis of fluorinated cycloheptane building blocks. *Eur. J. Org. Chem.* **2021**, 6568–6576. DOI: 10.1002/ejoc.202001530.

2.2. Demchuk, O. P.; Hryshchuk, O. V.; Vashchenko, B. V.; Trofymchuk, S. A.; **Melnykov**, K. P.; Skreminskiy, A.; Volochnyuk, D. M.; Grygorenko, O. O. Fluoroalkyl-containing 1,2-disubstituted cyclobutanes: advanced building blocks for medicinal chemistry. *Eur. J. Org. Chem.* **2021**, 87–95. DOI: 10.1002/ejoc.202001345.

Тези конференцій

1. Герасимчук М.В., **Мельников** К.П., Рябухін С.В. Синтез білдінг-блоків на основі *гем*-дифлуорциклогептанів. *XX Міжнародна конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії»*, 15-17 травня 2019 р., м. Київ, с.103.

Розділ 3 ФЛУОРОВАНІ ТА ФЛУОРОАЛКІЛЬНІ ПОХІДНІ НАСИЧЕНИХ ГЕТЕРОЦИКЛІВ

Наступна частина даної роботи розширює коло флуорованих циклічних систем, зміщуючи увагу на флуоровані насичені аза-гетероцикли – азетидин, піролідин та піперидин.

До розгляду та досліджень було обрано ряд моно- та дифлуорованих похідних, вказаних на Рисунок 3.1 [**3.1**].

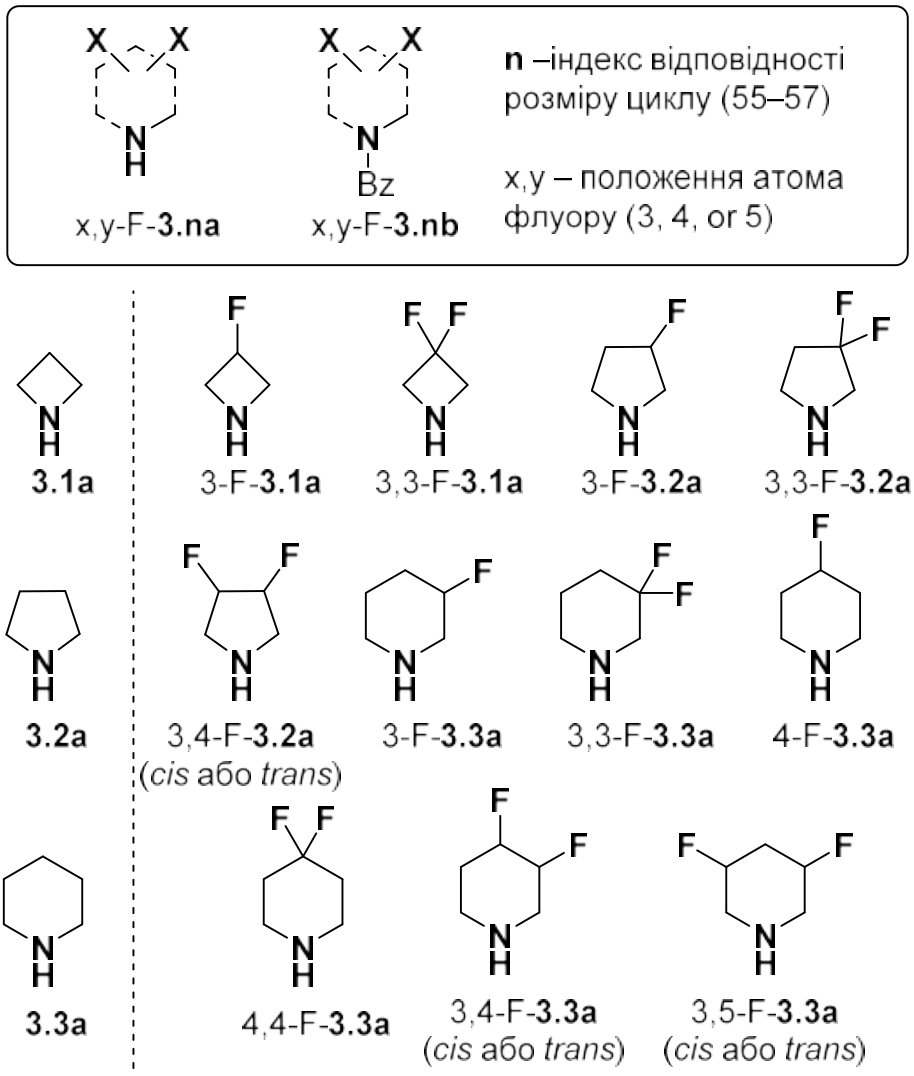


Рисунок 3.1. Флуоровані аза-циклоалкани, що досліджуються в цій роботі.

Перш за все, було проведено синтез комерційно недоступних дифлуорованих амінів *цис*-3,4-F-**3.3a**, *транс*-3,4-F-**3.3a** та *транс*-3,5-F-**3.3a**

шляхом деоксофлуорування спиртів як ключової стадіїв, використовуючи такі відомі реагенти $Et_3N{\cdot}3HF$, Morph-DAST або Deoxofluor® (Схема 3.1).

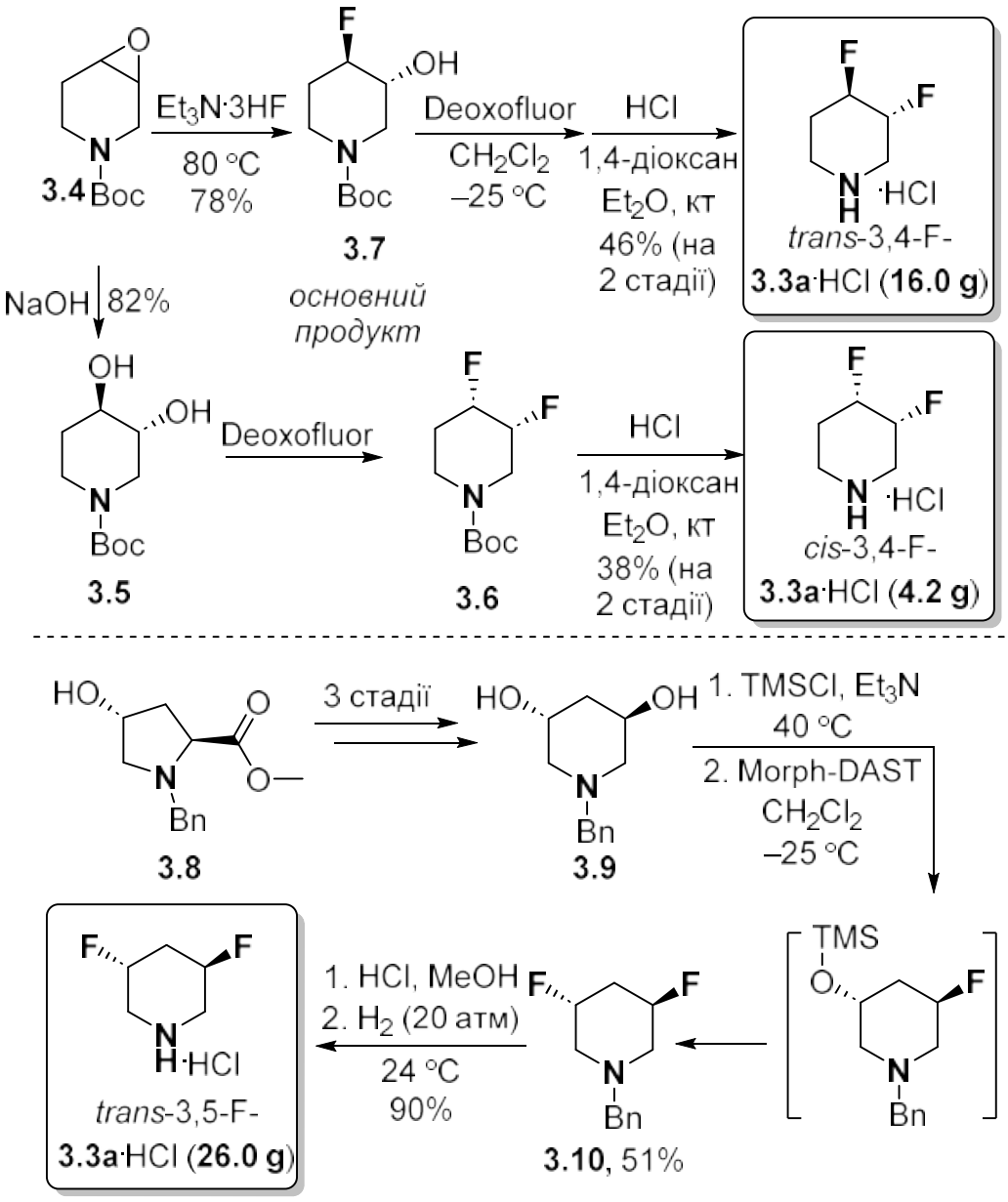


Схема 3.1. Шлях до раніше невідомих дифлуоропіперидинів *цис*-3,4-F-**3.3a**, *транс*-3,4-F-**3.3a** та *транс*-3,5-F-**3.3a**.

Кислотність/основність. У повному узгодженні з результатами попередніх досліджень розмір кільця мав незначний вплив на значення pK_a, отримані для моно- та *гем*-дифлуорованих похідних; найбільш визначальним було число атомів Флуору та відстань до місця флуорування через обидва доступні шляхи зв'язку (Рисунок 3.2). Дійсно, флуорування за положенням С-3 азетидину призвело до найбільш значного зниження pK_a (на 2,5 і 2,1 одиниці для першого і другого атомів Флуору відповідно). Для похідних піролідину

відповідні значення становили 2,3 і 2,1. У серії піперидину вони становили 2,4 і 1,8 для С-3-флуорованих ізомерів, а також 2,0 і 1,2 – для С-4-флуорованих. Слід зазначити, що додавання першого атома Флуору мало більший вплив на основність порівняно з другим, особливо для 4-флуорованих похідних піперидину.

Обидва 3,4-дифлуоровані піролідини, *цис*- і *транс*-3,4-F-**3.2a**, виявилися дещо більш основними (pK_a = 7,1), ніж 3,3-дифлуорований аналог 3,3-F-**3.2a** (pK_a = 6,8). Ці результати є ще однією ілюстрацією того факту, що прості адитивні моделі для індуктивного ефекту атома(ів) Флуору, можуть забезпечити лише приблизну оцінку основності сполуки.

Подібна ситуація спостерігалася для 3,4-дифлуорованих піперидинів: як *цис*-, так і *транс*-3,4-F-**3.3a** мали pK_a = 7,0 (ΔpK_a = –2,0 відносно 4-F-**3.3a**). Той самий результат (ΔpK_a = –2,0 відносно 3 F-**3.3a**) було отримано для *цис*-3,5-F-**3.3a**.

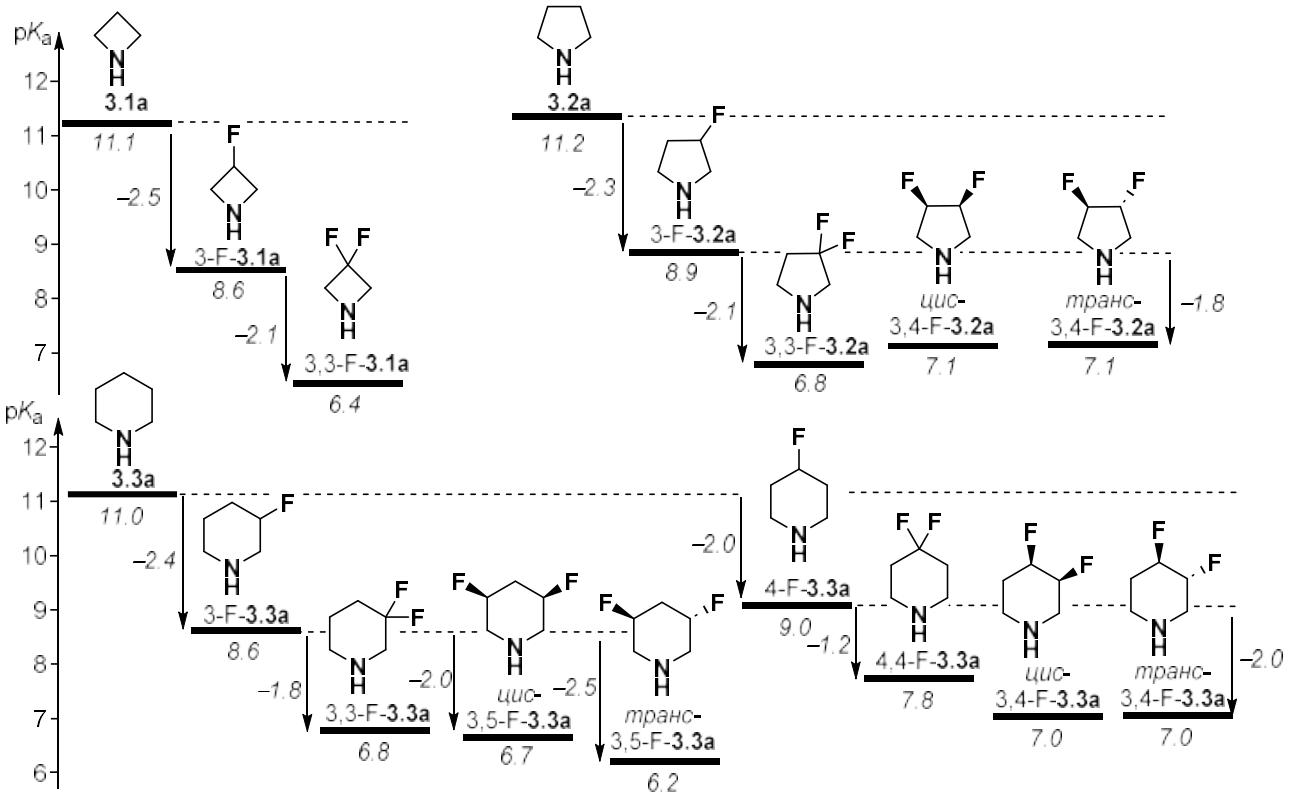


Рисунок 3.2. Порівняння виміряних значень основності сполук, що досліджуються в даній роботі.

Ліпофільність. Спостережувані зміни в Log*P* можна здебільшого пояснити за допомогою якісного аналізу дипольних моментів зв'язків C–F і амідних фрагментів.

Розмір кільця. Встановлено, що 3-моно- та 3,3-дифлуоровані похідні азетидину та піролідину мають приблизно однакову ліпофільність (Рисунок 3.3). Це може бути частково пояснено нижчою симетрією 3-флуорованого піролідинового кільця, яке врівноважує ефект додаткової групи CH_2. Для відповідного ряду 3-флуорованих піперидинів значення Log*P* були приблизно на 0,3 одиниці вище, що можна очікувати для наступного гомолога.

Флуорування за одним положенням. Для ліпофільності в досліджуваних серіях спостерігалася така тенденція:

гем-дифлуорований > нефлуорований > монофлуорований.

Для монофлуорованих похідних зниження Log*P* становило приблизно 0,1–0,3 од. Імовірно, цей результат можна пояснити поляризацією як C–F, так і сусідніх C–H зв'язків (що також узгоджується з висновками, зробленими вище). Примітно, що *гем*-дифлуорування насичених гетероциклічних амідів, досліджених у цій роботі, збільшило їх Log*P* приблизно на 0,2 од. Це суперечить результатам роботи щодо серії циклоалканів, де CF_2 зазвичай знижувала ліпофільність сполуки. Однією з причин цього може бути те, що в молекулах цієї частини дослідження наявна інша функціональна група (тобто третинний проти вторинного аміду).

Флуорування за двома різними положеннях. У більшості випадків 3,4- та 3,5-дифлуоровані насичені гетероциклічні бензаміди мали проміжну ліпофільність між їх моно- та *гем*-дифлуорованими аналогами. Таким чином, *цис*-3,4-**3.12b** і *цис*-3,4-**3.13b** були на 0,18–0,24 одиниць менш ліпофільними, ніж нефлуоровані аналоги, що корелює з ідеєю часткової компенсації дипольних моментів. Водночас *транс*-3,4-**3.12b**, *транс*-3,4-**3.13b** і *транс*-3,5-**3.13b** мали лише трохи нижчу ліпофільність порівняно з вихідними сполуками

3.12a і **3.13a** відповідно (на 0,04–0,11 одиниць Log*P*) , що знову ж таки можна пояснити протилежною орієнтацією відповідних диполів.

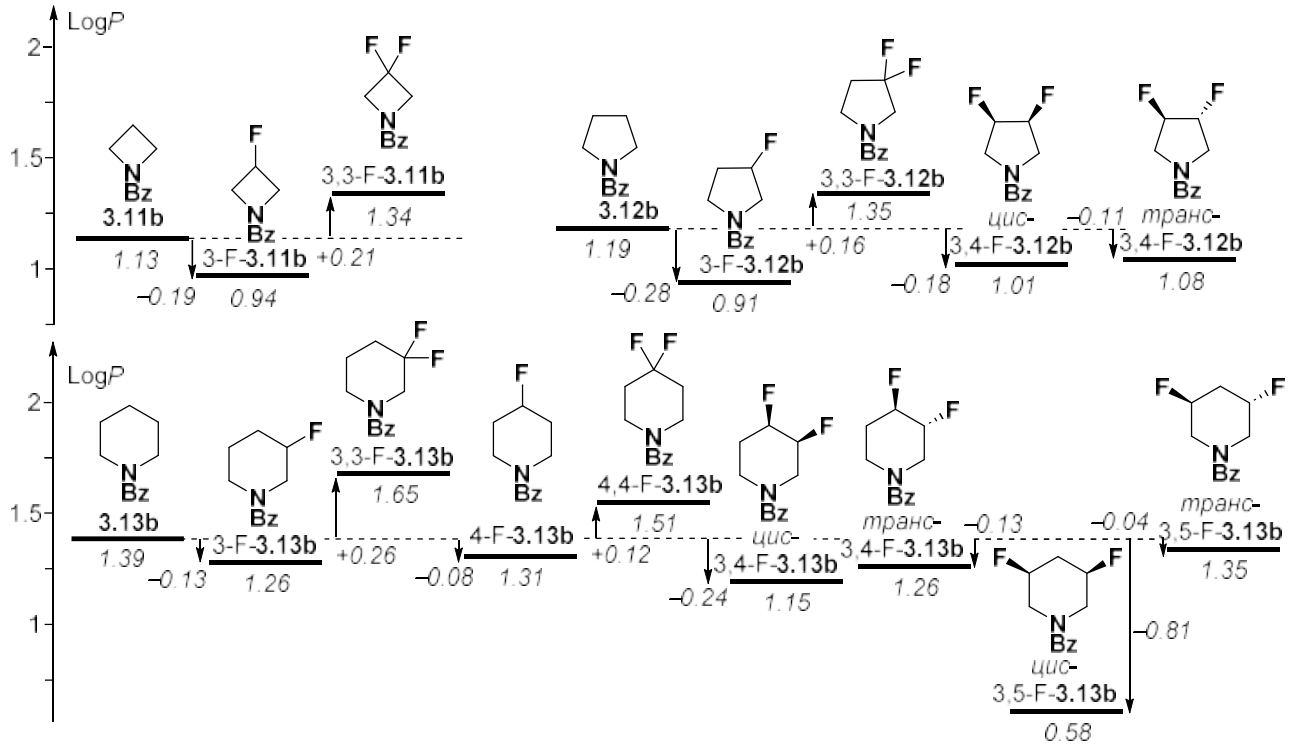


Рисунок 3.3. Порівняння виміряних значень ліпофільності сполук, що досліджуються в даній роботі.

Під час оптимізації потенційних лікарських препаратів перевагу може мати одночасне, комбіноване модулювання ключових фізико-хімічних параметрів сполук замість поступової зміни окремих властивостей. З цієї точки зору діаграма pK_a – Log*P* (що подібна до класичних діаграм Крейга) для сполук, досліджених у цій роботі, може бути корисною для раціонального підходу до пошуку ізостерних замін у серії насичених гетероциклічних амінів.

Як і можна було очікувати, сполуки, що обговорюються у цій частині роботи, природним чином згруповані у три серії, що відповідають не-, моно- та дифлуорованим насиченим гетероциклічним амінам (з однією випадаючою точкою, що відповідає 4,4-дифлуоропіперидину), що визначається в основному їх значенням pK_a – близько 11, 9 і 7 одиниць відповідно (Рисунок 3.4). За кількома винятками варіація значень Log*P* для відповідної серії амідів не була значною. Більшість точок даних знаходяться в межах інтервалу ±0,3 навколо середнього значення 1,0. Найбільшу зміну Log*P* (1,07 одиниць) було знайдено

для дифлуорованих похідних, що пов'язано зі специфічними властивостями *цис*-3,5-дифлуоропіперидину.

З іншого боку, найбільш заселена ділянка обговорюваних флуорованих сполук знаходиться в діапазоні 7,8–10,5 одиниць pK_a і 1,4–2,5 одиниць Log*P*, що дозволяє використовувати ці будівельні блоки взаємозамінно для тонкого «налаштування» фізико-хімічних властивостей сполуки. Крім того, одержані дані можуть стати корисними, коли потрібна оптимізація перелічених фізико-хімічних властивостей, але є необхідність мінімізувати зміну інших (зокрема, структурних) параметрів.

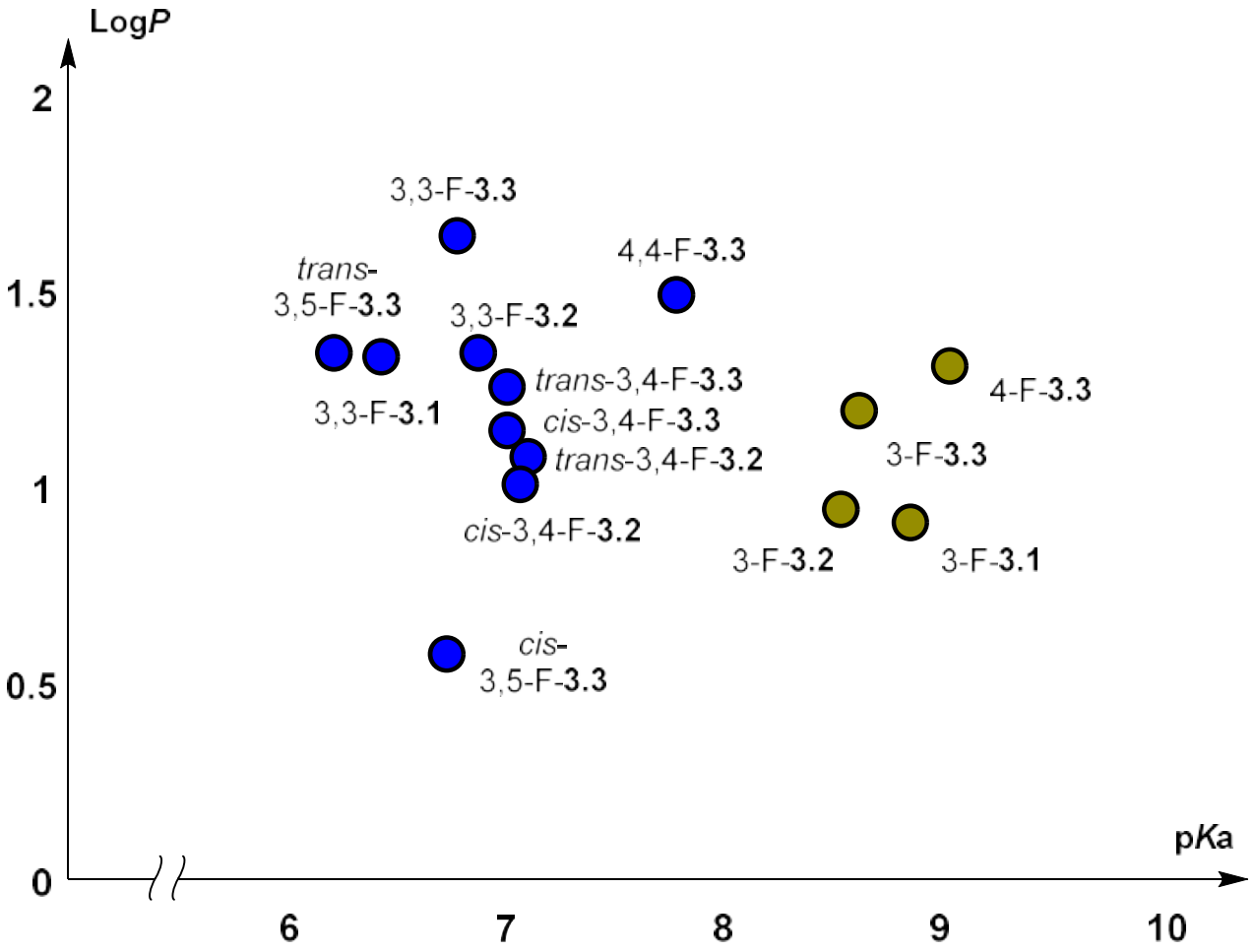


Рисунок 3.4. Візуалізація отриманих результатів у координатах pK_a– Log*P*.

Як логічне продовження попередніх результатів було проведено аналіз впливу флуороалкільних замісників (а саме CF_3-, CHF_2- та CH_2F-) на насичені аза-гетероцикли та прості лінійні аліфатичні аміни (Рисунок 3.5) [**3.2**].

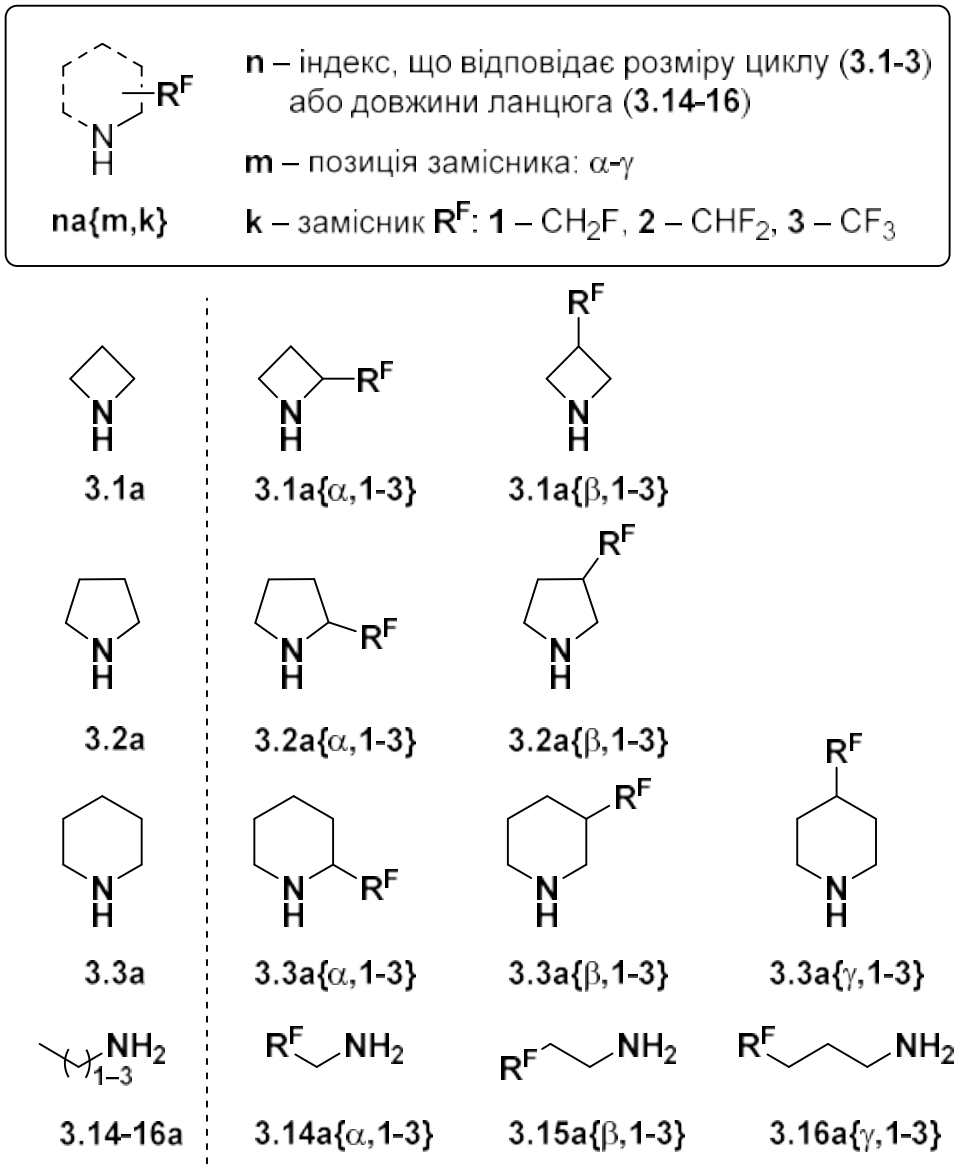


Рисунок 3.5. Флуоровані аза(цикло)алкани, що досліджуються в цій роботі.

Вплив розміру кільця. Виміряні значення pK_a для циклічних амінів із різними розмірами кілець, які несуть R^F-групу в тому самому положенні та з однаковою кількістю атомів Флуору, були дуже подібними (зазвичай у діапазоні одиниць 0,1–0,2 pK_a) для більшості похідних, крім α-CF_3 заміщених (**3.1a–3.3a**{*α*,3}) (Рисунок 3.6). Тому розмір кільця зазвичай незначно впливає на основність сполуки. Причини такої аномальної поведінки сполук **3.1a–3.3a**{*α*,3} не ясні, однак конформаційні ефекти можуть впливати на отримані результати.

Вплив флуорованого замісника. З сукупності отриманих даних було отримано наступне емпіричне правило, засноване на положенні R^F і кількості

атомів Флуору: коли R^F вводиться в аміни **3.1a–3.3a**, значення pK_a зменшується на

$$\Delta pK_a = (1{,}68 \pm 0{,}10) \times k \text{ для } \alpha\text{-}R^F \text{ заміщених похідних;}$$

$$\Delta pK_a = (0{,}86 \pm 0{,}16) \times k \text{ для } \beta\text{-}R^F \text{ заміщених похідних;}$$

$$\Delta pK_a = (0{,}54 \pm 0{,}10) \times k \text{ для } \gamma\text{-}R^F \text{ заміщених похідних;}$$

де k відповідає числу атомів Флуору у групі R^F.

Ці спостереження узгоджуються з раніше запропонованим емпіричним правилом для ациклічних амінів типу **3.14a–3.16a**{*α–β*,1–3}. Зокрема, раніше було показано, що pK_a зменшується на 1,7 і 0,7 одиниць на атом Флуору для лінійних амінів, які містять групи CH_xF_y в положеннях α і *β* відповідно. Однак для циклічних амінів **3.1a–3.3a**{*γ*,1–3} зміна становить 0,54 одиниці, що трохи вище, ніж повідомляється для їхніх ациклічних аналогів (на 0,3 одиниці).

Вплив конформаційного обмеження. Зменшення pK_a має однакові тенденції у серії α-, *β*- та *γ*-заміщених похідних як для циклічних (**3.1a–3.3a**{*γ*,1–3}), так і для лінійних (**3.14a–3.16a**{*α–γ*,1–3}) сполук. Значення pK_a для циклічних амінів, які несуть групу α-R^F, були на 0,61 одиниці (в середньому) вищими, ніж у α-R^F заміщених похідних метиламіну **3.14a**{*α*,1–3}). Спостережувана різниця у значеннях pK_a відповідає очікуваній вищій основності вторинних порівняно з первинними.

Натомість середня різниця основності циклічних і лінійних амінів у ряду похідних *β*-R^F і *γ*-R^F була нижчою (0,27 і 0,13 одиниць відповідно). Таким чином, очікується, що введення конформаційного обмеження у пропільний і бутильний замісники шляхом замикання їх у 4–6-членні цикли матиме незначний вплив на основність аміну, але, можливо, модулюватиме біологічну афінність.

Наведені вище дані показують, що наявність циклічного фрагменту має суттєвий вплив на основність досліджуваного ряду сполук, і цей ефект протилежний збільшенню pK_a, що пов’язане з переходом від первинного до

вторинного аміну при замиканні циклу. Іншими словами, введення флуороалкільної групи в *β*- або *γ*-положення циклічних амінів має більший вплив на основність порівняно з ациклічними.

Ліпофільність. *Вплив розміру кільця*. Розмір гетероциклічного кільця **3.1–3.3b** по-різному впливав на ліпофільність у ряді α- та *β*-заміщених сполук. Зокрема, очевидне збільшення Log*P* спостерігалося в серії α-R^F-заміщених похідних (**3.1b**{*α*,1–3} < **3.2b**{*α*,1–3} < **3.3b**{*α*,1–3}), що можна віднести лише до приросту ліпофільності за рахунок додаткових ланок CH_2. Проте незалежно від розміру кільця, ліпофільність *β*-CH_2F-піролідину **3.2b**{*β*,1} наближалася до ліпофільності *β*-CH_2F-піперидину **3.3b**{*β*,1}. Ще одним прикладом є ліпофільність *β*-CHF_2-азетидину **3.1b**{*β*,1}, що була такою ж, як і для *β*-CHF_2-піролідину **3.2b**{*β*,1}.

Вплив флуорованого замісника. Як і можна було очікувати, ліпофільність зростала в серії H < CH_2F ≤ CHF_2 < CF_3 майже для всіх досліджених гетероциклічних систем. Як правило, CH_2F- та CHF_2-заміщені похідні з однаковим розміром кільця та позицією R^F мали близькі значення Log*P*, тоді як їхній CF_3-заміщений аналог був набагато більш ліпофільним. Винятком з обох закономірностей було *β*-CH_2F-заміщене похідне азетидину **3.1b**{*β*,1}, для якого Log*P* несподівано знизився на 0,2 одиниці порівняно з незаміщеним *N*-бензоїлазетидином **3.1b**.

Було відзначено, що положення замісника мало більш виражений вплив на Log*P*, ніж розмір кільця у серії сполук, що містять ту ж групу R^F. Зокрема, для CH_2F- та CHF_2-заміщених амідів введення групи R^F у α-положення призвело до значного збільшення ліпофільності (ΔLog*P*), яке було вище середнього значення для кожної із серій. Навпаки, зміна ліпофільності для сполук **3.1b–3.3b**{*β*,1} та **3.1b–3.3b**{*β*,2}, що містять групи *β*-R^F, була нижчою за середню. Однак інший тренд спостерігався для CF_3-заміщеної серії. У цьому випадку більший вплив групи CF_3 на значення ΔLog*P* було відзначено для α-CF_3-піролідину **3.2b**{*α*,3} та всіх CF_3-заміщених піперидинів **3.3b**{*α–γ*,3}.

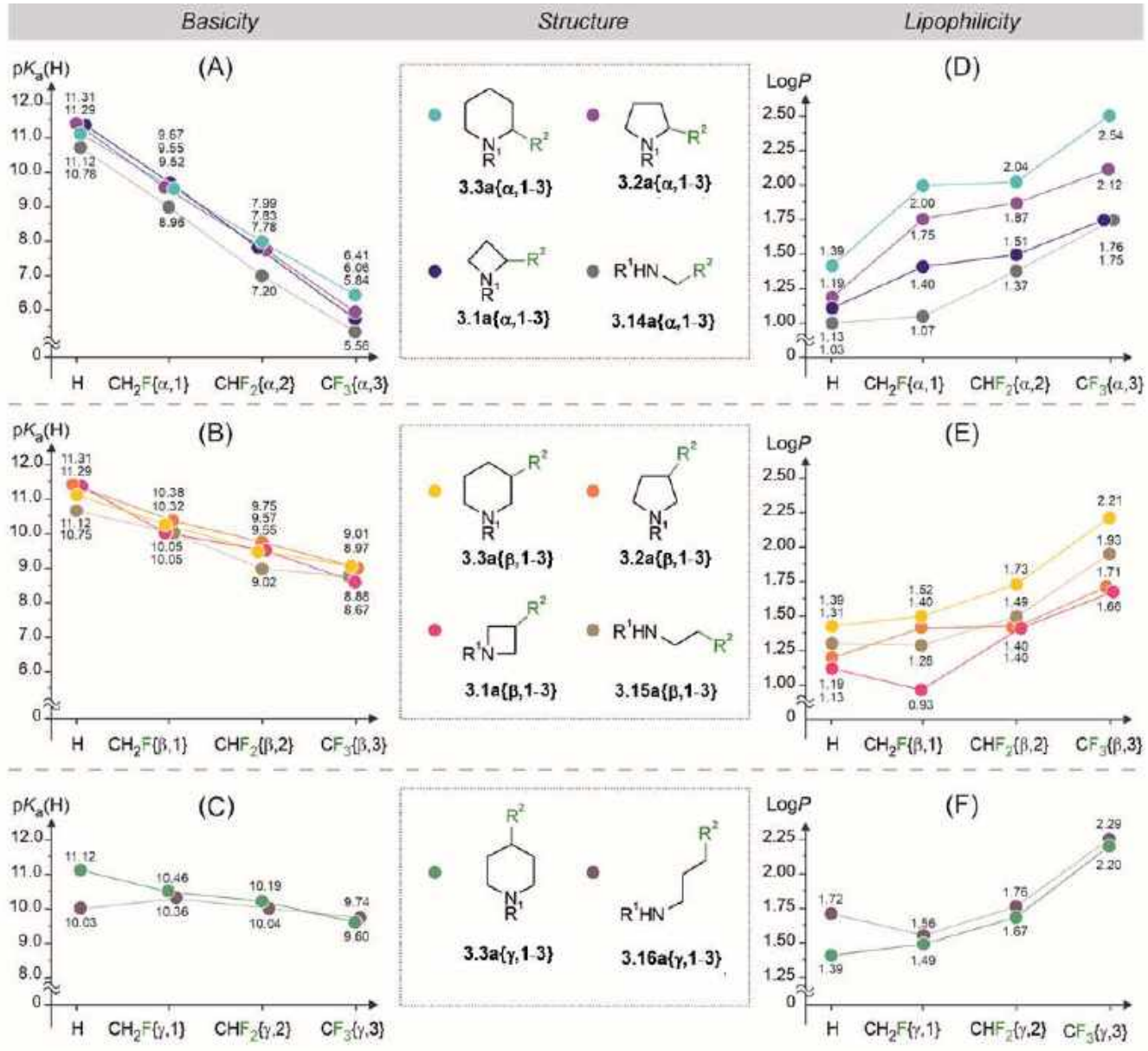


Рисунок 3.6. Порівняння виміряних значень основності та ліпофільності сполук, що досліджуються в даній роботі.

Загалом, ліпофільність досліджуваних серій змінювалася немонотонно, узагальнити варіативність Log*P* і вивести емпіричне правило, подібне до аналогічного для pK_a виявилось неможливим. Тим не менш, отримані дані все ще корисні як для аналізу змін ліпофільності в серіях, а також як довідкові.

Аналогічно до попередніх робіт, було побудовано діаграму pK_a – Log*P* для більш наочного відображення результатів дослідження (Рисунок 3.7). На цьому графіку було виділено чотири окремі області відповідно до флуоровмісної групи R^F (CH_2F, CHF_2, CF_3 або жодної).

Графік показує щільне покриття значень pK_a в діапазоні від приблизно 7,8 до 10,5 одиниць, а також три випадаючих точки **3.1–3a**{α,3} зі зменшенням основності приблизно на шість порядків величини. З іншого боку, значення Log$P$ змінюються від 1,4 до 2,5, причому єдина точка (**3.1b**{β,1}) має Log$P$ = 0,93.

Цікаво відмітити, що існує значне перекриття фізико-хімічних властивостей CH_2F- і CHF_2-заміщених будівельних блоків. Двома чудовими прикладами є пара α-CH_2F-азетидину (**3.1**{α,1}) і β-CHF_2-піролідину (**3.2**{β,2}), та пара α-CH_2F-піролідину (**3.2**{α,1}) і β-CHF_2-піперидин (**3.3**{β,2}) мають попарно майже однакові значення pK_a і Log$P$. Це спостереження підкреслює, як два будівельних блоки з різними за розміром циклами, різними флуорованими групами та їх положеннями можуть бути взаємозамінними, зберігаючи фізико-хімічні властивості, але модулюючи інші характеристики (наприклад, конформаційні властивості або афінітет з біологічною мішенню).

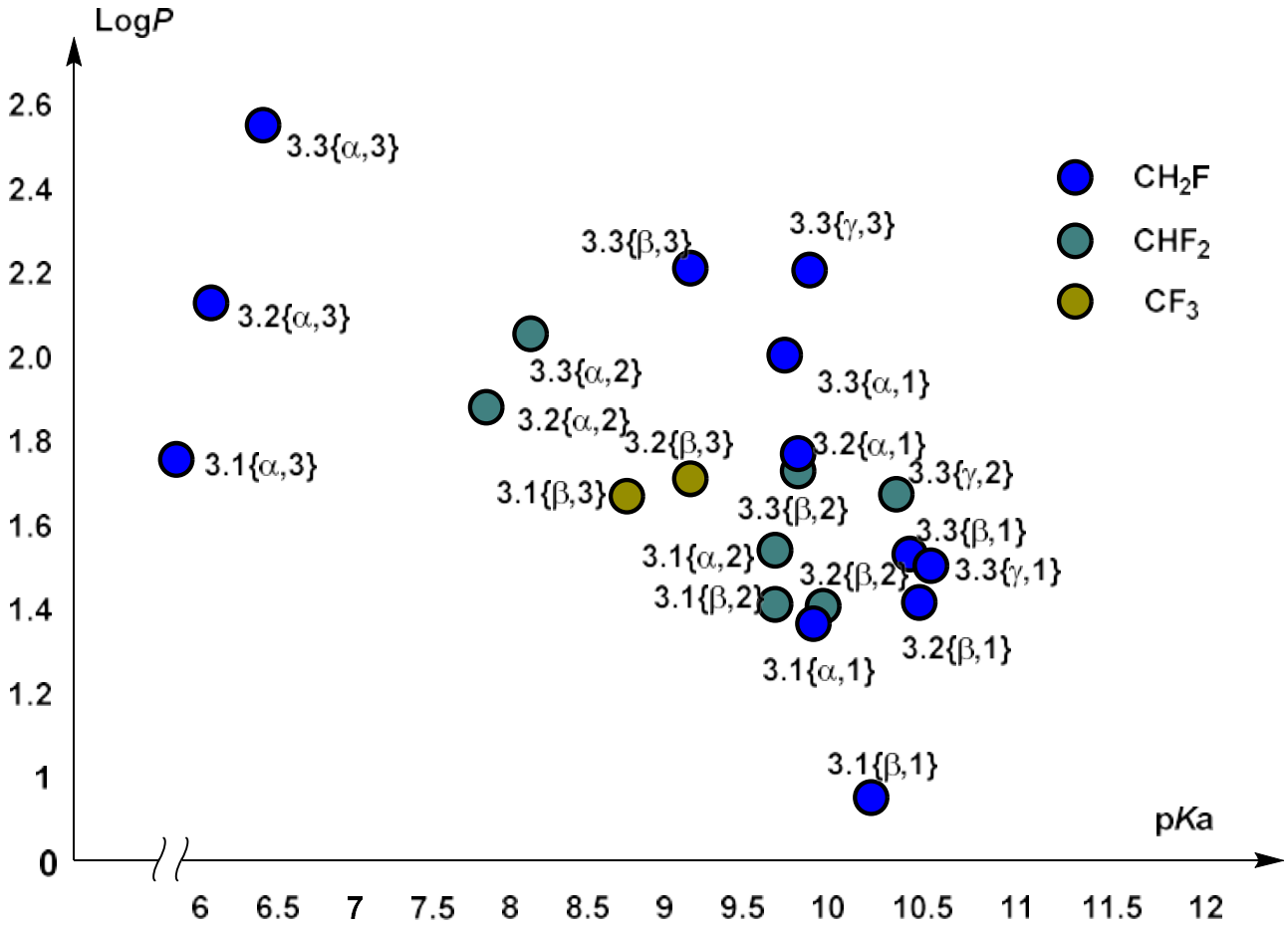


Рисунок 3.7. Візуалізація отриманих результатів у координатах pK_a – Log$P$.

З широким розповсюдженням методу біоізостерних замін у медичній хімії значно зріс попит на нові функціональні групи, що дозволяють тонко регулювати бажані властивості потенційних лікарських засобів. У наступній частині роботи запропоновано 3,3-дифлуороксетан-2-іл (3,3-diFOx) як перспективний флуорований замісник і некласичний ізостер численних функціональних груп [**3.3**]. Було показано, що функціоналізовані похідні (ароматичні та аліциклічні) з 3,3-дифлуороксетановим фрагментом можуть бути отримані в багатограмових кількостях (до 64 г продукту за один підхід).

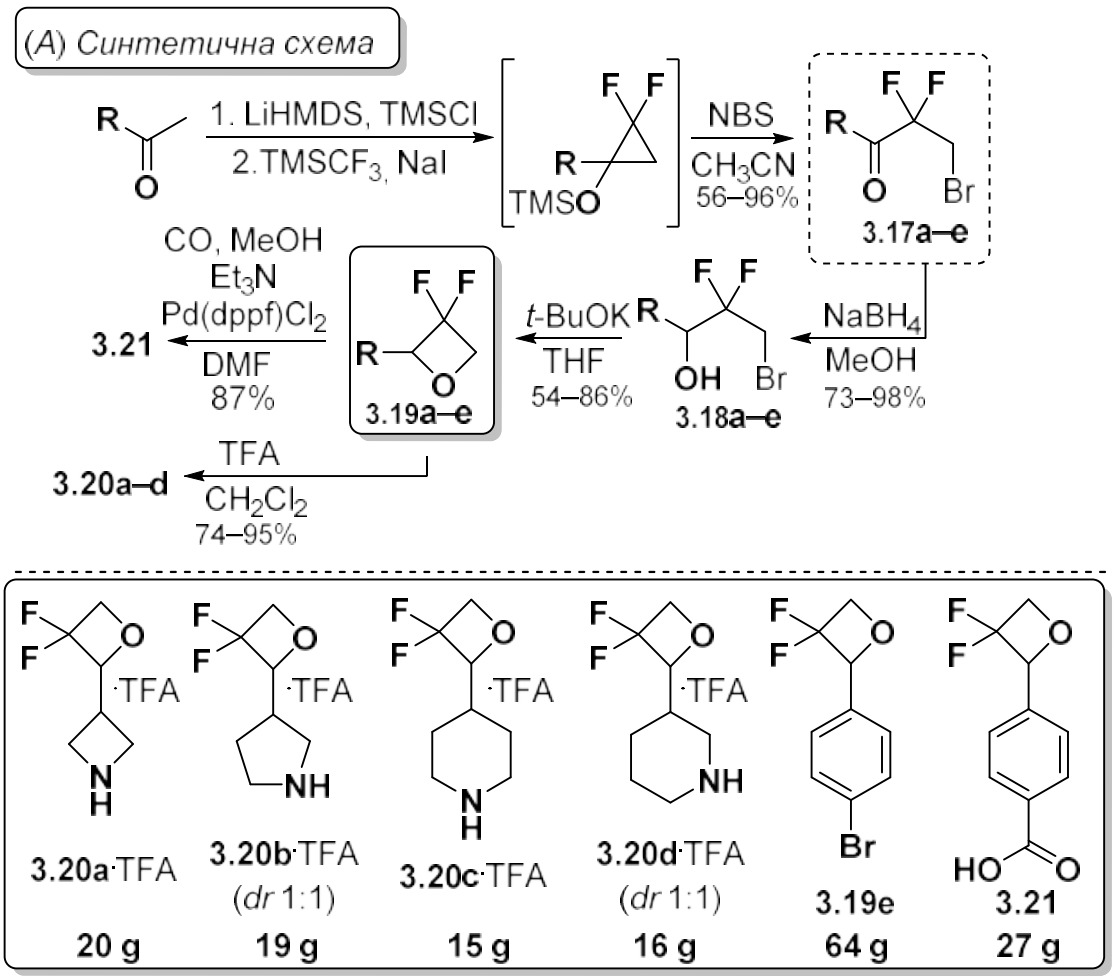


Схема 3.2. Синтез будівельних блоків **3.19e**, **3.20a**–**d**, і **3.21** з вмістом 3,3-дифлуороксетанового фрагменту.

Вимірювання значень pK_a для модельних похідних показало, що фрагмент 3,3-diFOx є слабким акцептором, який можна використовувати для тонкого регулювання кислотності/основності шляхом заміни або донорних алкільних груп, або сильніших акцепторів, таких як CF_3, CO_2Me або $C(O)NH_2$. Це корелювало з експериментально визначеними значеннями констант Гамета для цього фрагменту як замісника бензойної кислоти (σ = 0,24), найближче порівнюване з відновідним значенням для атома Хлору (σ = 0,29).

Вимірювання ліпофільності для ряду модельних похідних показало, що фрагмент 3,3-дифлуороксетан-2-ілу дещо підвищує ліпофільність сполуки при введенні його у вихідну молекулу (ΔLog$P$ = +0,5). Знову ж таки, цей ефект є проміжним між впливом (цикло)алкільних груп та полярних фрагментів, таких

як амід, естер, 1,3-діоксолан або нефлуорований оксетан, що свідчить про потенціал ізостерних замін обох цих типів фрагментів.

З точки зору тривимірної структури, фрагмент 3,3-diFOx показав проміжну між оксетаном і циклобутаном/*гем*-дифлуороциклобутаном неплощинність циклу і був другим за розміром серед цих фрагментів (Рисунок 3.8, *A*). Карта молекулярного електростатичного потенціалу (MEP) групи 3,3-diFOx мала X-подібну форму з протилежними знаками потенціалу на діагональних атомах кільця (Рисунок 3.8, *B*). В результаті загальний дипольний момент 3,3-дифлуороксетану виявився відносно низьким (0,39 D), що свідчить про те, що запропонований фрагмент може бути кращим імітатором (цикло)алкільних груп, ніж простіші *гем*-дифлуоровані або оксигеновмісні аналоги (Рисунок 3.8, *C*).

Нарешті, 3,3-дифлуороксетановий фрагмент показав достатню стійкість до звичайних хімічних реагентів, відмінну стабільність при зберіганні (понад 5 років) і хорошу метаболічну стабільність. Останній факт було підтверджено введенням досліджуваного фрагменту 3,3-diFOx замість *трет*-бутильної групи в молекулу Теновіну-6, відомого інгібітора сіртуїну. Ця модифікація зберегла значну частину біологічної активності сполуки, підвищила гідрофільність і знизила спорідненість до Р-глікопротеїнів. Ці дані підтверджують можливість біоізостерного заміщення 3,3-дифлуороксетанового фрагмента для конкретного досліджуваного випадку та потенціал для використання аналогічних підходів у майбутньому.

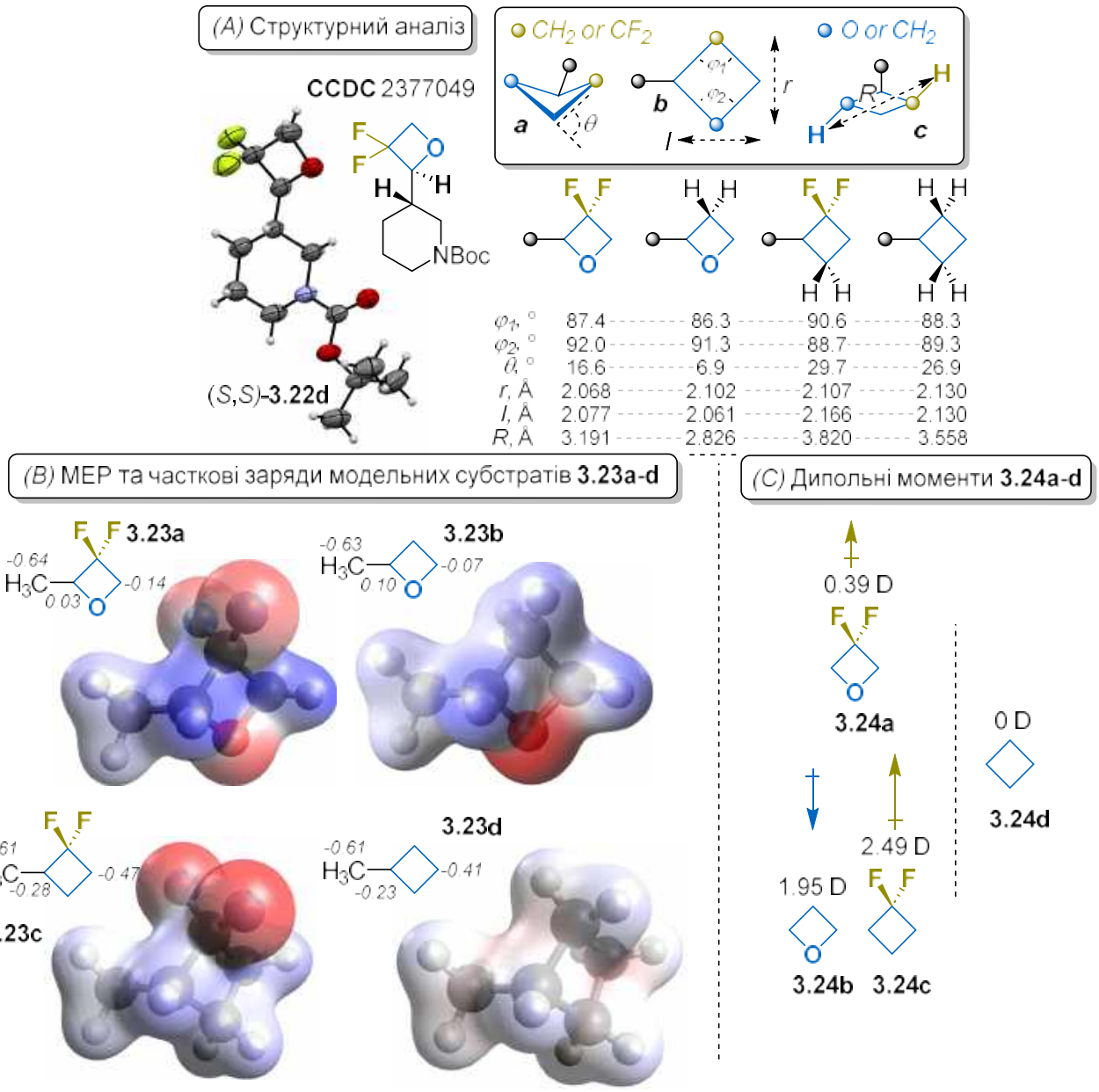


Рисунок 3.8. Визначення структурних та електронних параметрів 3,3-дифлуороксетанового фрагменту.

Після одержання обговорених вище результатів сферу дослідження фізико-хімічних та біологічних властивостей було розширено на інші флуоровані насичені оксигеновмісні гетероциклічні будівельні блоки (а саме, карбонові кислоти і первинні аміни) у порівнянні з нефлуорованими і карбоциклічними аналогами [**3.4**].

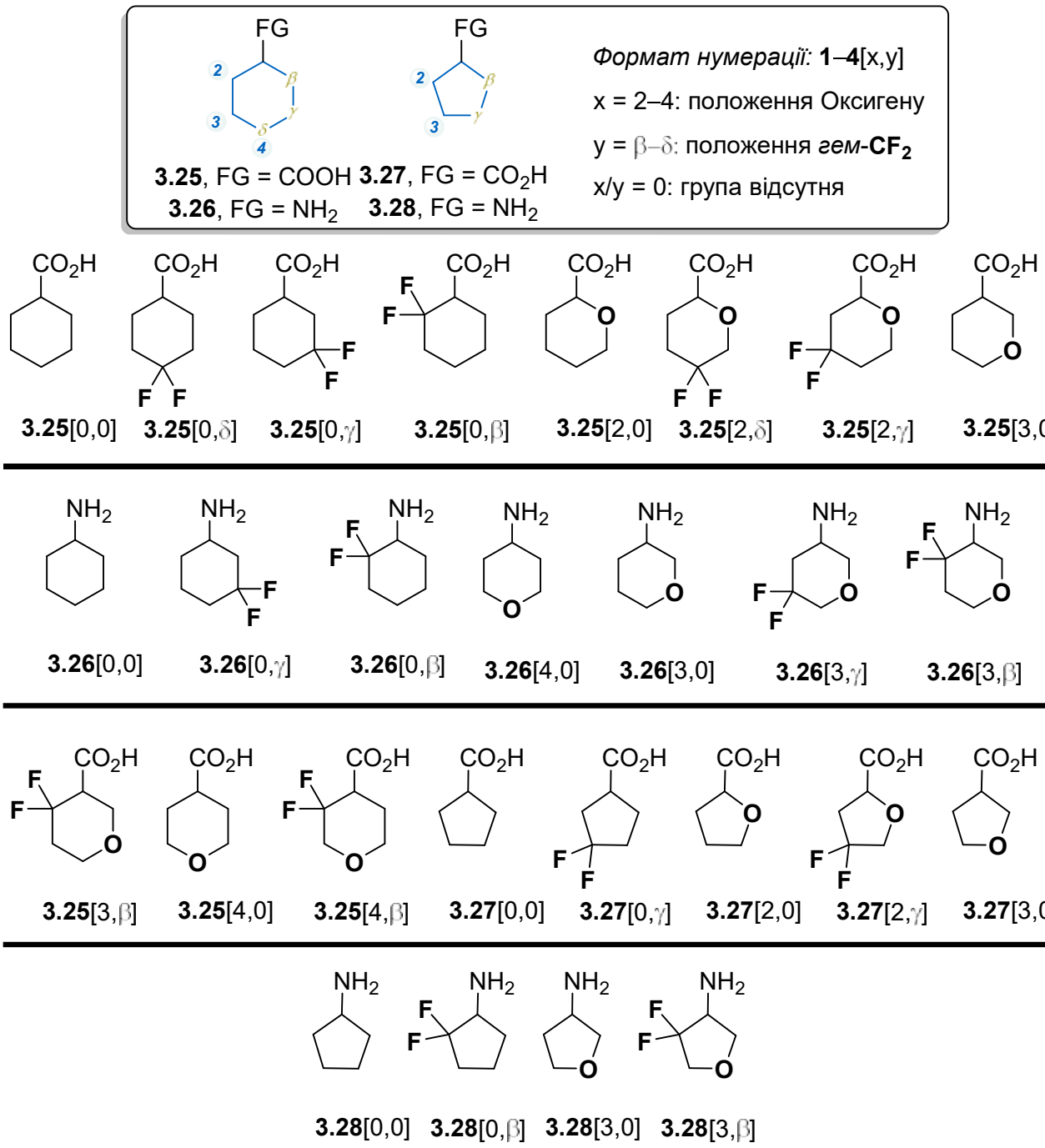


Рисунок 3.9. Оксигеновмісні гетероцикли – об’єкти дослідження цієї частини роботи.

Для глибшого розуміння природи впливу замісників O/CF_2 на ліпофільність сполук досліджуваного ряду було розраховано середні значення ΔpK_a та Δ*Log*P для відповідних пар сполук (тобто з/без O або CF_2-групи) для кожного положення п'яти- та шестичленних кільцевих систем (2, 3 або 4 для O, та β, γ або δ для CF_2). Наприклад, щоб оцінити вплив введення атома Оксигену в положення 2 шестичленного кільця на кислотність COOH-групи, значення pK_a всіх доступних тетрагідропіран-3-карбонових кислот порівнювали зі

значеннями pK_a відповідних циклогексанових аналогів і визначали середнє значення ΔpK_a в межах цієї підмножини. Отримані прирости ΔpK_a та ΔLog$P$ наведено на малюнку нижче (Рисунок 3.10).

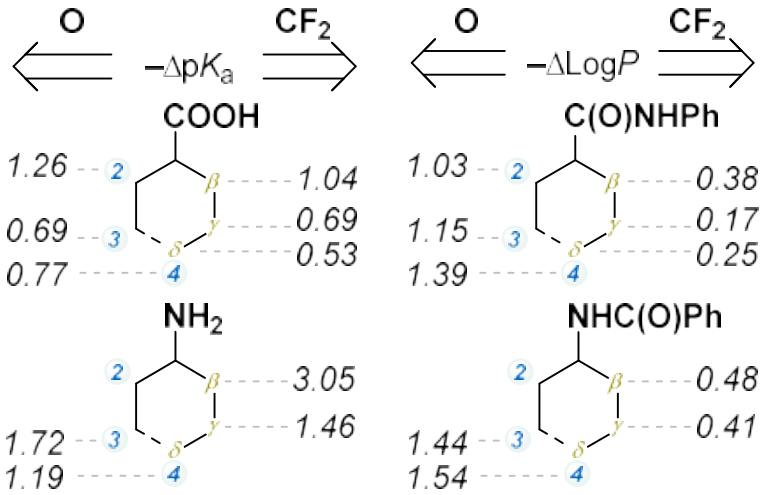


Рисунок 3.10. Усереднені значення інкрементів кислотності та ліпофільності для O- та CF_2-заміщених аліциклічних сполук.

Крім того, було оцінено, чи можуть вищезгадані інкременти бути використані для прогнозування ΔpK_a та ΔLog$P$ *гем*-дифлуоровмісних *O*-гетероциклічних сполук відносно вихідних нефлуорованих циклоалканів (Рисунок 3.11). Для значень ΔpK_a адитивність було підтверджено: відповідна похибка передбачення (ΔΔpK_a = –0,08±0,56) була в межах довірчого інтервалу 3σ, що корелює з літературними даними. Для значень ΔLog$P$ передбачення мало значно більші похибки (ΔΔLog$P$=0,56±0,79) і були систематично вищими за відповідні експериментальні значення. Іншими словами, зменшення ліпофільності від одночасної дії як *O*-, так і CF_2-фрагментів було меншим, ніж можна було очікувати від окремих інкрементів, визначених цими фрагментами. Цікаво, що вищі похибки передбачення спостерігалися для амінів та відповідних їм бензамідів, аніж для карбонових кислот та анілідів.

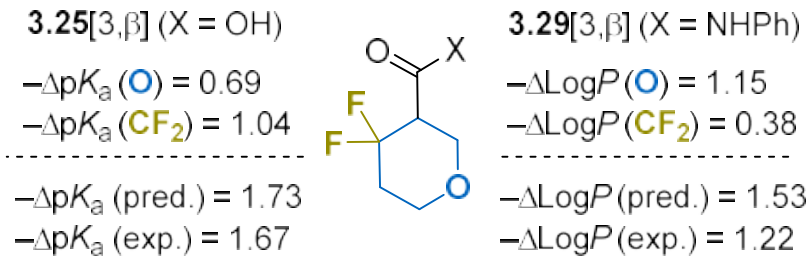


Рисунок 3.11. Порівняння адитивності інкрементів кислотності та ліпофільності для O- та CF_2-заміщених аліциклічних сполук.

Ці результати показують, що при обговоренні ефектів як оксигеновмісного, так і *гем*-CF_2 фрагментів слід враховувати їх взаємний вплив. Цікаво, що похибка передбачення (ΔΔLog*P*) простої адитивної моделі була вищою для сполук з вищими значеннями ΔpK_a. Оскільки ΔpK_a корелює зі змінами електронного розподілу в молекулах відповідних будівельних блоків (а отже, частково – їхніх модельних похідних), цей результат показує, що властивості амідної функціональної групи, приєднаної до насиченого кільця, також можуть бути важливими для визначення ліпофільності сполуки в цілому.

Нарешті, у межах цієї частини дослідження було продемонстровано потенціал флуорованих *O*-гетероциклічних замісників для біоізостерних замін шляхом синтезу та оцінки синтезу інгібіторів p38 *α*-MAPK – аналогів клінічного кандидата R-1487 компанії Roche. Синтезовані флуоровані міметики зберігали наномолярну ефективність проти біологічної мішені, мали дещо вищу ліпофільність та нижчу розчинність у воді, але покращену метаболічну стабільність.

Систематичний опис фізико-хімічних параметрів часто вимагає дизайну та одержання серій сполук, які не були раніше синтетично доступними. Вище було описано експериментальні дослідження третинних флуоропохідних карбонових кислот; у цій частині роботи описано ефективний багатограмовий синтез *β*-флуоровмісних насичених гетероциклічних метанамінів, що доповнюють відповідні їм α-флуоровані карбонові кислоти [**3.5**].

Запропонований метод ґрунтується на літературному підході, описаному для найпростіших *N*-гетероциклічних похідних (тобто олефінування за Віттігом

відповідного гетероциклічного кетону, бромфлуорування за допомогою комбінації $Et_3N{\cdot}3HF$ – NBS, реакція нуклеофільного заміщення NaN_3 та відновлення азидів), але передбачає декілька важливих модифікацій, необхідних для успішного масштабування (Схема 3.3). Зокрема, олефінування летких кисневмісних гетероциклічних кетонів за Віттігом проводили за допомогою NaH в ДМСО, що дозволило виділити відповідні алкени дистиляцією. Крім того, було встановлено, що в даному випадку відновлення азидів в умовах реакції Штаудінгера (Ph_3P-H_2O) є ефективнішим за каталітичне відновлення.

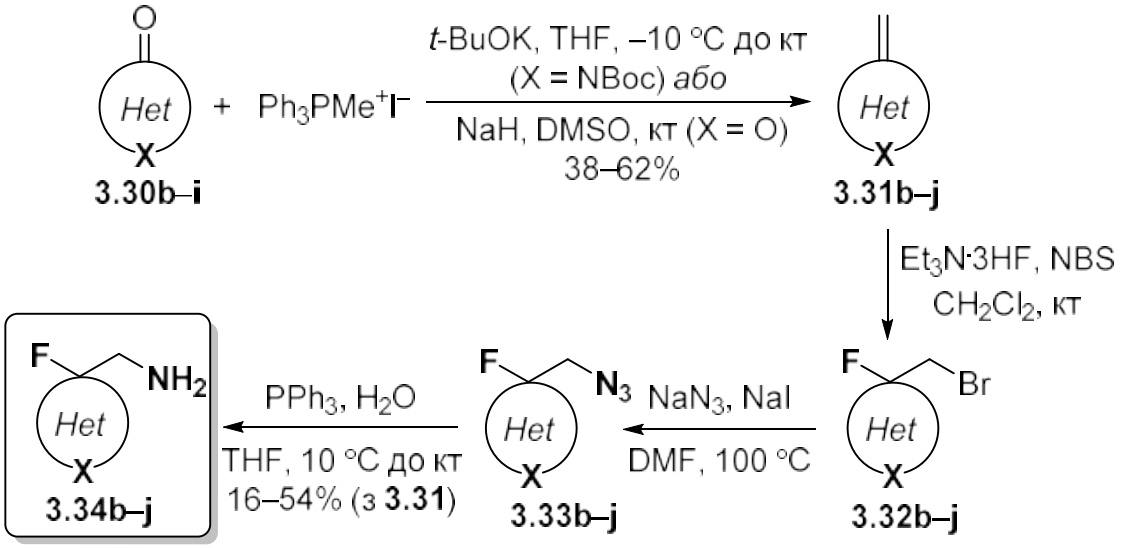


Схема 3.3. Схема синтезу цільових сполук.

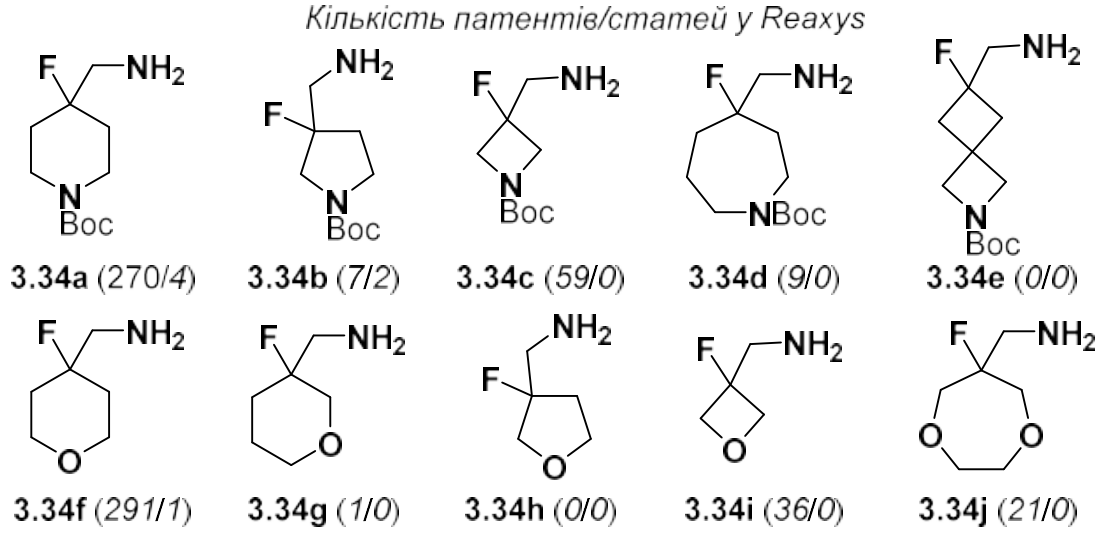


Рисунок 3.12. Сполуки, що було синтезовано в рамках дослідження реакції амінофлуорування подвійного зв’язку.

Оптимізований протокол було успішно застосовано для синтезу дев'яти цільових насичених *N*- або O-вмісних 4–7-членних гетероциклічних амінів масою до 77 г (Рисунок 3.12).

Описані вище сполуки мають одну спільну рису – функціональні групи та флуоровані замісники рознесені між собою як мінімум одним зв’язком С–С. З метою встановлення взаємних ефектів функціональних груп та флуоровмісних замісників в цій частині дисертаційної роботи увагу було приділено α-заміщеним похідним карбонових кислот [**3**.**6**]. Очікувано, що α-заміщення атомом Флуору призводить до значного зменшення значень pK_a для всіх досліджених сполук **3.35a**–**i** (ΔpK_a = 1,33...2,41 од.) (Рисунок 3.13). Цікаво, що кислотність флуорзаміщених карбонових кислот **3.35a**–**i** знаходиться у вужчому діапазоні порівняно з нефлуорованими сполуками **3.36a**–**i** – різниця між найвищим та найнижчим значеннями pK_a в межах кожної серії становить 0,52 та 1,50 одиниць, відповідно. Зокрема, загальна тенденція до зростання pK_a в гомологічних рядах, яка чітко простежується для не флуорованих сполук (карбонових кислот **3.36c**–**f**), була менш помітною після α-заміщення (ΔpK_a = 0,58 і 0,16 одиниць для пар **3.35c**/**3.35f** і **3.36c**/**3.36f** відповідно). Нарешті, введення атома Оксигену в карбоциклічне кільце мало більш незначний вплив на значення pK_a порівняно з введенням атома Флуору, і зновув більш вираженим для нефлуорованих сполук. Ці результати показують, що інкременти pK_a атомів Флуору і Оксигену не є адитивними в досліджуваних серіях сполук.

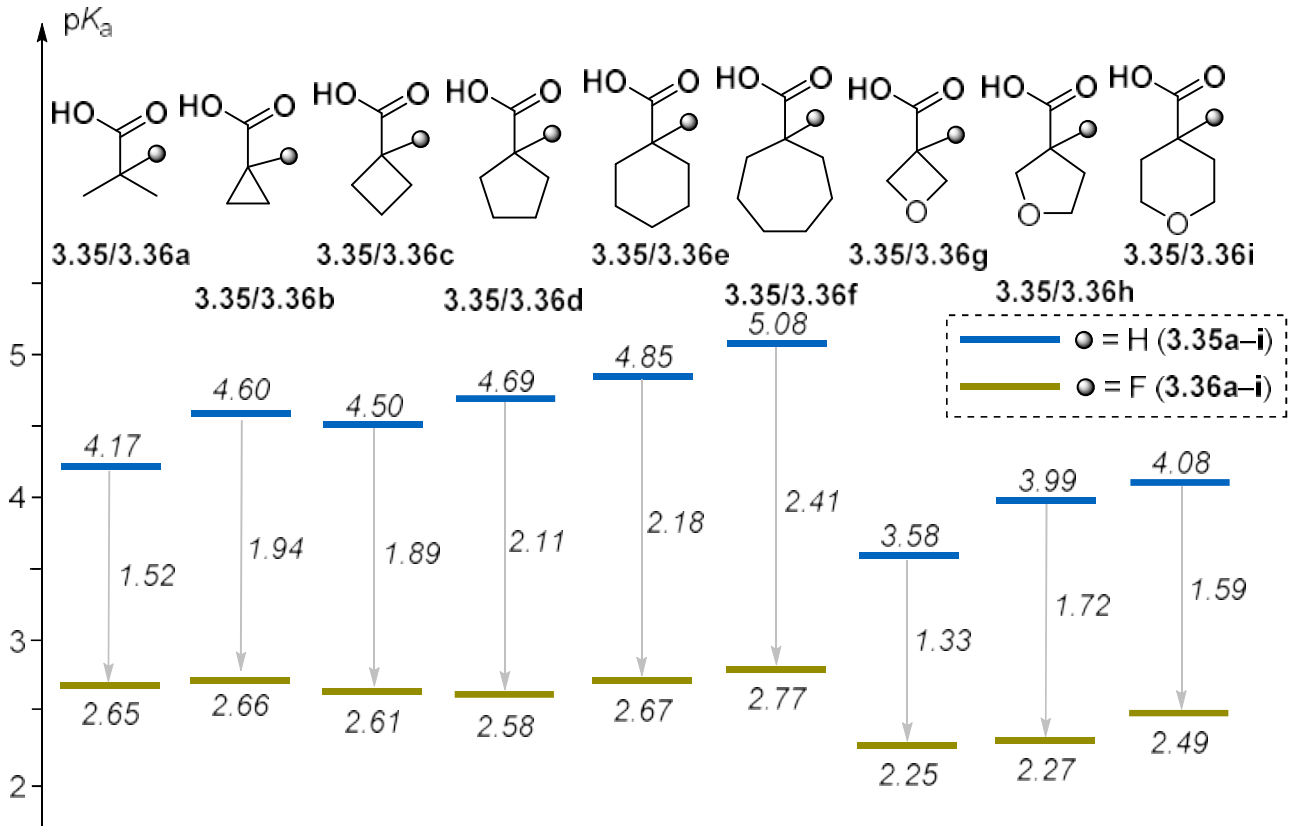


Рисунок 3.13. Значення pK_a для сполук **3.35** та **3.36** (21 °C).

На відміну від розглянутого раніше випадку з pK_a, вплив α-заміщення атома Гідрогену флуором на ліпофільність сполук виявився значно менш помітним (Рисунок 3.14). Дійсно, різниця між значеннями Log*P* для анілідів **3.37** і **3.38** (–0,04...0,12, в середньому близько 0,08 одиниць) чітко демонструє, що атом Флуору має незначний вплив на їх ліпофільність. Цей факт дещо суперечить попереднім даним щодо інших монофлуорованих похідних, які є значно більш гідрофільними, ніж відповідні не флуоровані аналоги.

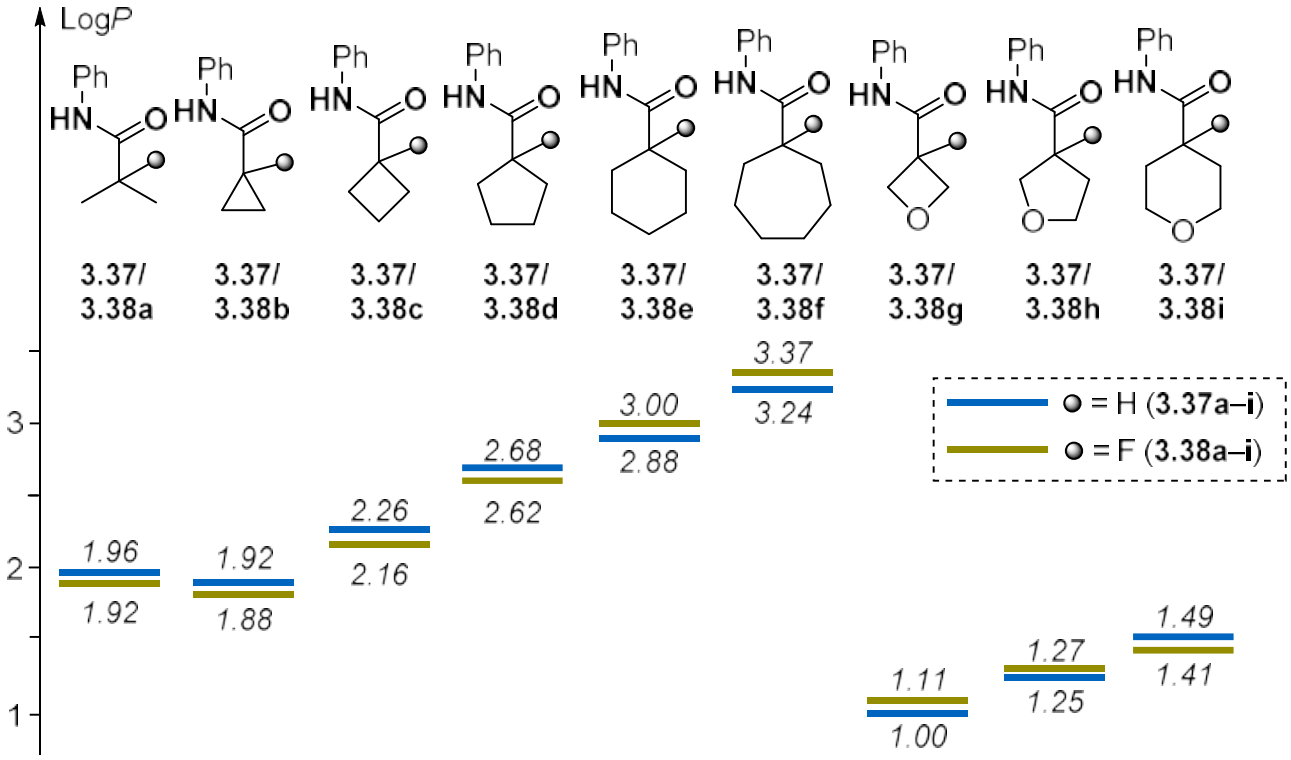
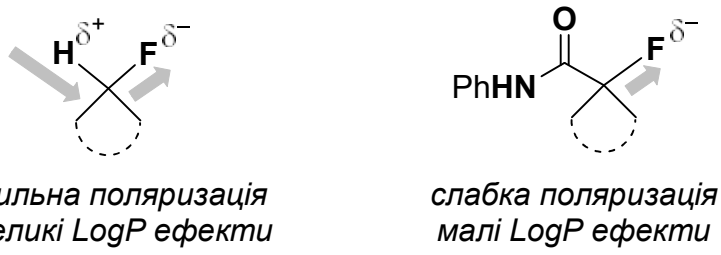


Рисунок 3.14. Значення Log*P* для сполук **3.37** і **3.38** (21 °C).

Порівнюючи із попередніми даними, ці результати можна пов'язати з відсутністю у досліджуваних сполуках сусіднього до функціональної групи C-H зв'язку. Очевидно, вплив заміщення атома(ів) Флуору на значення Log*P*, що спостерігався в попередніх роботах, сильно залежить від поляризації сусіднього C-H зв'язку, спричиненої атомом Флуору, тоді як поляризація самого C-F зв'язку є несуттєвою з точки зору впливу на макроскопічні параметри (Рисунок 3.15). Більше того, в деяких випадках (наприклад, **3.37e**–**h**) заміна атома Гідрогену флуором навіть призводить до незначного збільшення ліпофільності .



сильна поляризація
великі LogP ефекти

слабка поляризація
малі LogP ефекти

Рисунок 3.15. Можливе пояснення відсутності значного впливу флуорування на Log*P* у циклічних бензамідах.

Таким чином, у цьому розділі представлені результати роботи щодо заповнення малодослідженого хімічного простору найпростіших флуоровмісних аліциклічних будівельних блоків (а саме, похідних циклогептану та циклобутану). Всебічна фізико-хімічна характеризація флуорованих похідних циклоалканів (як уже відомих, так і запропонованих в даній частині роботи) дозволила виділити певні тенденції впливу флуорованих замісників на фізико-хімічні параметри речовин. На основі цих емпіричних правил було висловлено гіпотезу про непрямий вплив флуорування на ліпофільність; додаткові експерименти, описані у наступних розділах дозволять до певної міри підтвердити цю гіпотезу.

У численних дослідженнях було показано, що монофлуорування призводить до зниження ліпофільності сполуки. Слід зазначити, однак, що майже у всіх вищезгаданих роботах атом Флуору вводився в первинне або вторинне положення. Вище було оцінено ліпофільність ряду α-розгалужених карбоксамідів і виявлено, що α-флуорування біля третинного атома Карбону лише незначно впливає на значення Log*P*. Було висловлено припущення, що додаткова поляризація сусідніх C-H зв'язків може бути основним фактором, відповідальним за зниження ліпофільності аліфатичних монофлуорованих сполук. Натомість, коли цей фактор усувається (через відсутність відповідних C-H зв'язків), ефект флуорування повинен бути зведений до мінімуму. У цій частині роботи було перевірено цю гіпотезу, шляхом дослідження ряду сполук, флуорованих у третинному положенні, та порівнявши їх з відповідними нефлуорованими аналогами [**3**.**7**]. Як модельні об’єкти було обрано *N*-бензоїльовані 4-заміщені піперидини **3.41** та **3.42** як модельні субстрати для цього дослідження (Рисунок 3.16, *ліворуч*). У положенні C-4 було перевірено наступні вісім замісників R, що відрізняються за електронними властивостями:

CN (**a**), F (**b**), CF_3 (**c**), Ph (**d**), H (**e**), CH_2F (**f**), CH_2OMe (**g**) і Me (**h**).

Було виявлено, що у випадку сильних електроноакцепторних замісників α-флуорування призводить до збільшення ліпофільності, тоді як для слабких акцепторів і донорів спостерігається зменшення величини Log*P*. При пошуку

імовірних кореляцій значень ΔLog*P* (між флуорованими та нефлуорованим сполуками) з константою Гаммета та іншими подібними константами було виявлено, що модифікований параметр ефекту поля Свейна-Луптона *F* дає задовільні результати (R^2 = 0,78) (Рисунок 3.16, зправа). Також помітно, що замісники з атомами Гідрогену (CH_2F, CH_2OMe і особливо CH_3) демонструють менші від'ємні значення ΔLog*P*. Якщо групу CH_3 виключити як відхилення, то спостерігається ще краща кореляція (R^2 = 0,83). Примітно, що середнє значення ΔLog*P* для серії α-флуорованих анілідів, описаних вище, дуже добре відповідає цій кореляції (використовували значення параметру *F* для групи $C(O)NH_2$).

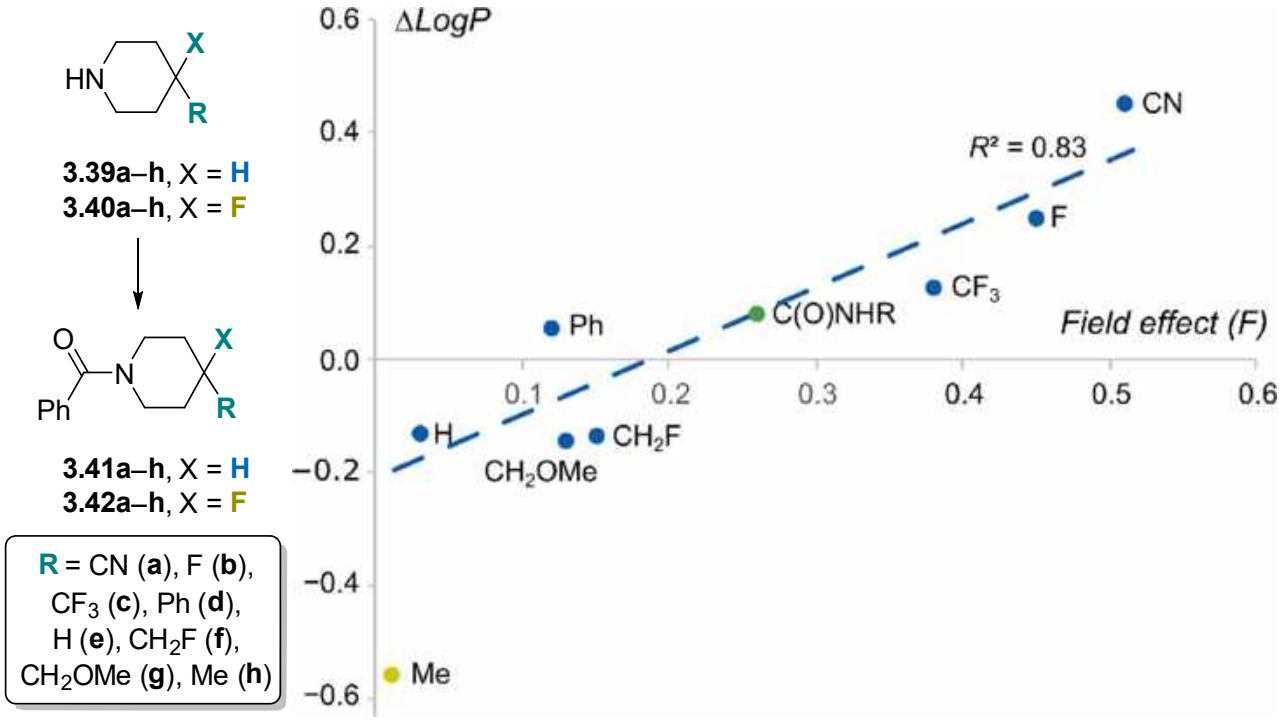


Рисунок 3.16. (*Ліворуч*) Сполуки, що досліджувались в даній роботі; (*Праворуч*) Залежність ΔLog*P* (при введенні атома Флуору у третинне положення) від ефекту поля *F*.

Виходячи з цих результатів, можна констатувати, що поява атома Флуору саме по собі не є визначальною для ліпофільності сполуки; натомість, ефект флуорування виражається через модуляцію електронного розподілу на сусідніх атомах (переважно Гідрогену). Дійсно, найбільш значне зниження ліпофільності (ΔLog*P* = −0.56) спостерігається для пари **3.41h**/**3.42h** (вісім атомів Гідрогену у віцинальному положенні до місця флуорування). Для інших похідних з близьким розташуванням атомів Гідрогену в замісник (**3.41e**/**3.42e**,

3.41f/**3.42f**, **3.41g**/**3.42g**) цей ефект був менш вираженим (ΔLog*P* = −0.13...−0.14). Електронозбіднені замісники (CN, CF_3, F або Ph) зменшували ефект поляризації атомів Гідрогену, спричинений флуоруванням; з іншого боку, їхня власна поляризація також зменшувалася, що призводило до збільшення ліпофільності.

В даному розділі було всебічно досліджено флуоровані похідні лінійних аліфатичних амінів, піролідину, піперидину, оксетану, тетрагідрофурану та тетрагідро-2*H*-пірану. Електрофільною дифункціоналізацією подвійного зв'язку було досягнуто синтез ряду похідних метанаміну з третинним флуорованим замісником, які можна розглядати як доповнюючий набір до α-флуорованих карбонових кислот при дослідженні фізико-хімічних параметрів. Результати цієї частини роботи є надзвичайно важливими з точки зору розуміння механізмів впливу атома Флуору на молекулярному рівні. Так, було отримано ряд даних, що підтверджують раніше запропоновану гіпотезу про опосередкований механізм впливу флуорування на ліпофільність, підтверджено основний механізм впливу на кислотність здатних до іонізації груп (за індуктивним ефектом) та встановлено факт взаємного врівноважуючого впливу трьох функціональних груп (власне, атому Оксигену, флуорованого фрагменту та амідного) при формуванні результуючої ліпофільності речовини.

Основні публікації за розділом

3.1. **Melnykov**, K. P.; Nazar, K.; Smyrnov, O.; Skreminskyi, A.; Pavlenko, S.; Klymenko-Ulianov, O.; Shishkina, S.; Volochnyuk, D. M.; Grygorenko, O. O. Mono- and difluorinated saturated heterocyclic amines for drug discovery: systematic study of their physicochemical properties. *Chem. Eur. J.* **2023**, *29* (47), e202301383. DOI: 10.1002/chem.202301383.

3.2. **Melnykov**, K. P.; Tavlui, O.; Skreminskiy, A.; Kuchkovska, Y. O.; Grygorenko, O. O. Impact of fluoroalkyl substituents on physicochemical properties of saturated heterocyclic amines. *Chem. Eur. J.* **2022**, e202201601. DOI: 10.1002/chem.202201601.

3.3. Liashuk, O. S.; Fedinchyk, A.; **Melnykov**, K. P.; Herasymchuk, M.; Alieksieieva, D.; Lesyk, D.; Bas, Y. P.; Keda, T. Y.; Yatsymyrskiy, A. V.; Holota, Y.; Borysko, P.; Yarmolchuk, V. S.; Grygorenko, O. O. 3,3-Difluorooxetane – a versatile functional group for bioisosteric replacements in drug discovery. *Chem. Eur. J.* **2024**, *30*(72), e202403277. DOI: 10.1002/chem.202403277.

3.4. **Melnykov**, K. P.; Liashuk, O. S.; Holovach, S.; Shatnia, V.; Horbenko, A.; Lesyk, D.; Melnyk, V.; Skrypnik, D.; Beshtynarska, A.; Borysko, P.; Viniichuk, O.; Grygorenko, O. O. Physicochemical and biological evaluation of *gem*-difluorinated saturated oxygen heterocycles as bioisosteres for drug discovery *Chem. Eur. J.* **2024**, e202404390. DOI: 10.1002/chem.202404390.

3.5. Semeno, V. V., and K. P. **Melnykov**. Multigram Synthesis of *β*-Fluorinated Saturated Heterocyclic Methanamines. *Ukrainica Bioorganica Acta* **2023,** 18 (2), 16-21. DOI: 10.15407/bioorganica2023.02.016.

3.6. Pidvyshennyi, O.; **Melnykov**, K. P.; Liashuk, O.; Lesyk, D.; Holota, Y.; Borysko, P.; Grygorenko, O. O. Acidity of saturated (hetero)cyclic α-fluoro carboxylic acids and lipophilicity of their amide derivatives. *J. Fluorine Chem.* **2024**, *278*, 110316. DOI: 10.1016/j.jfluchem.2024.110316.

3.7. **Melnykov**, K. P.; Liashuk, O. S.; Smyrnov, O.; Lesyk, D.; Holota, Y.; Borysko, P.; Yakubovskyi, V.; Grygorenko, O. O. Lipophilicity effects of monofluorination at the tertiary aliphatic carbon as a function of α-substituent. *J. Fluorine Chem*. **2025**, *281*, 110384. DOI: 10.1016/j.jfluchem.2024.110384.

Тези конференцій

1. Олександр Григоренко, Костянтин **Мельников**, Сергій Головач, Олександр Демчук, Олександр Грищук, Антон Черних, Богдан Ващенко, Дмитро Волочнюк. Фізико-хімічні властивості насичених флуоровмісних карбо- та гетероциклів для потреб медичної хімії. *XIX наукова конференція «Львівські хімічні читання - 2023»,* 29-31 травня **2023** р., м. Львів, с.12

2. Бондарук А.А., **Мельников** К.П., Ляшук О.С., Григоренко О.О., Бас Ю.П., Кеда Т.Є. Нові пара-нітрофенольні естери пара-заміщених бензойних кислот як перспективні субстрати pNP-тесту. *XXV Міжнародна конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії»,* 15-17 травня **2024** р. Київ, с.39.

3. Федінчик А.В., Герасимчук М.В., **Мельников** К.П., Ляшук, О. С., Григоренко О.О. 3,3-Дифлуорооксетан-2-іл – перспективний флуоровмісний замісник для потреб медичної хімії. *XXV Міжнародна конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії»*, 15-17 травня **2024** р. Київ, с.124.

4. Шатня В.Ю., Горбенко А.Е., Головач С.М, **Мельников** К.П., Ляшук О.С., Григоренко О.О. Дослідження фізико-хімічних властивостей гем-дифлуорованих *О*-гетероциклів. *XXV Міжнародна конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії»,* 15-17 травня **2024** р. Київ, с.156

Розділ 4 НАСИЧЕНІ БІЦИКЛІЧНІ СПОЛУКИ ТА ЇХ ФЛУОРОВАНІ АНАЛОГИ – СИНТЕЗ ТА ДОСЛІДЖЕННЯ ВЛАСТИВОСТЕЙ

У контексті сучасних поглядів на складові фрагменти для перспективних у медичній хімії будівельних блоків (а саме превалювання жорстких структур над конформаційно рухливими, збільшення вкладу sp^3-гібридизованих атомів Карбону у скелет молекули та використання флуорованих замісників для тонкого налаштування фізико-хімічних параметрів бажаної сполуки) похідні *гем*-дифлуороспіро[2.2]пентану можна вважати дуже перспективними для подальшого використання у розробці лікарських засобів.

Синтез вихідної сполуки (2-метиленциклопропіл)метанолу **4.1** базувався на відомій реакції типу Віттіга оксафосфолану **4.2** з параформом у сульфолані за температури 100 °C (Схема 4.1). Після незначної оптимізації бажаний спирт був отриманий в кількості 42 г без додаткової очистки із виходом 63% на 2 стадії.[**4**.**1**]

Наступний крок включав оптимізацію *гем*-дифлуороциклопропанування подвійного зв’язку метиленциклопропану для отримання (4,4-дифлуор-спіро[2.2]пентан-1-іл)метанолу **4.4** як основного проміжного продукту. Для цього було використано комбінацію реагентів $TMSCF_3$ – NaI у киплячому ТГФ. У випадку малоактивних алкенів (саме таким виявився досліджуваний метиленциклопропан **4.1**) очікуваними були порівняно низькі виходи цільового продукту через низьку конверсію. Однак, після додаткової оптимізації методики та очистки продукту перегонкою під зниженим тиском було отримано цільову сполуку **4.4** із виходом 69% у кількості до 33 г за один підхід.

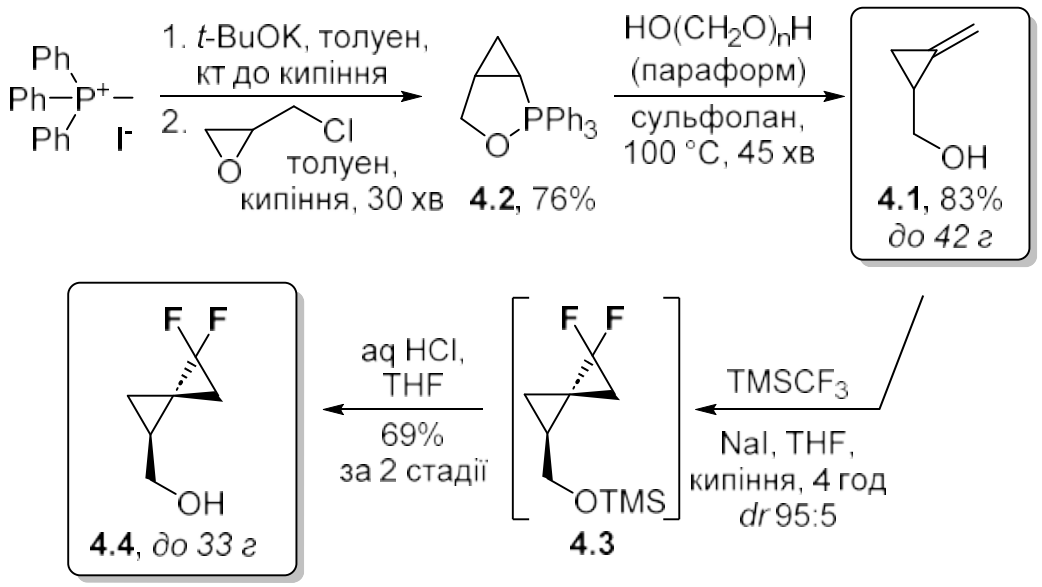


Схема 4.1. Синтез базової проміжної сполуки - спирту **67.**

Спирт **4.4** було використано для отримання всіх інших похідних 4,4-дифлуор-спіро[2.2]пентан-1-ілу. Так, у реакцією Апеля з Br_2 і PPh_3 було синтезовано бромід **4.5** з виходом 73% (Схема 4.3). Окислення сполуки **4.4** за допомогою $NaIO_4$ – $RuCl_3$ дало карбонову кислоту **4.6** у вигляді окремого діастереомеру з виходом 91%. Потім сполуку **4.6** було введено у реакцію Курціуса з використанням дифенілфосфорілазиду (DPPA), що дозволило отримати *N*-Boc-захищений амін **4.7** з виходом 62%. Після зняття захисту у кислих умовах було отримано гідрохлорид **2.8**·HCl, структуру якого було підтверджено за допомогою дифракції рентгенівських променів, які також дозволили встановити відносну конфігурацію (±)-(1*S*,3*R*) у всіх отриманих сполуках.

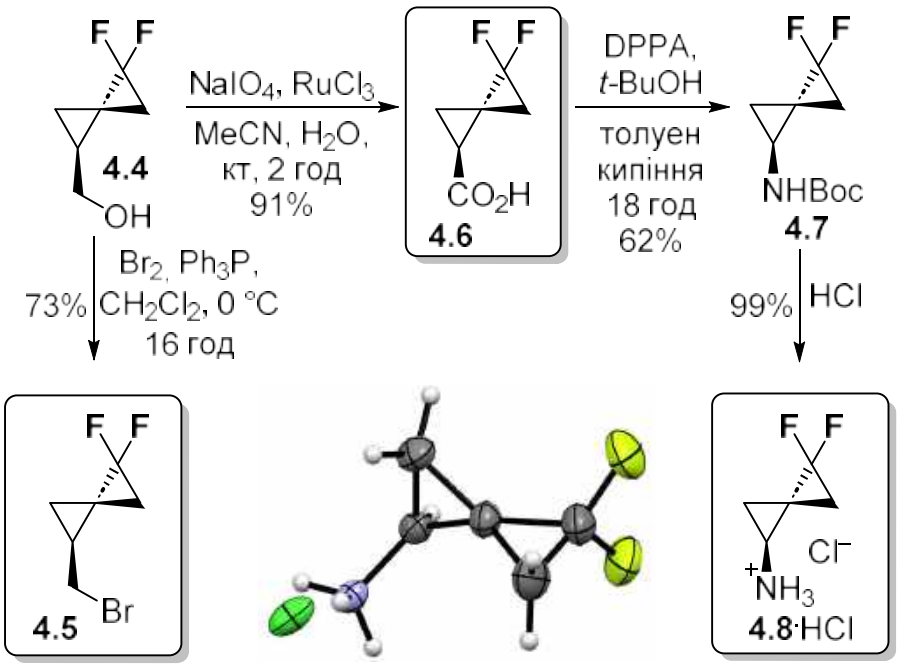


Схема 4.2. Прості хімічні перетворення базової сполуки **4.4** на шляху до цільових будівельних блоків **4.5**, **4.6**, **4.8.**

Мезилат **4.9** (отриманий зі спирту **4.4** шляхом сульфонілування MsCl у присутності Et_3N) використовували для отримання гомологічного первинного аміну **4.11** (Схема 4.3). Щоб досягти цього, синтезований мезилат **4.9** було залучено до нуклеофільного заміщення Boc_2NH у присутності K_2CO_3 в MeCN при 80 °C, що дало ди-*N*-Boc-заміщений амін **4.10** з виходом 72%. Після зняття захисних груп цільовий (4,4-дифлуорспіро[2.2]пентан-1-іл)метанаміній хлорид (**4.11**·HCl) було отримано із кількісним виходом. Альтернативно, мезилат **4.9** було введено в реакцію нуклеофільного заміщення з KSAc у DMF при 75 °C для отримання тіоацетату **4.12** з виходом 65%. Подальше окисне хлорування сполуки **4.12** за допомогою Cl_2 дозволило отримати сульфонілхлорид **4.13** із виходом 86%. Також було проведено гідроліз тіоацетату за допомогою K_2CO_3 в метанолі, що дало тіол **4.14** з виходом 76%.

Примітно, що в усіх вищезазначених перетвореннях 4,4-дифлуорспіро[2.2]пентан-1-ільний фрагмент залишився незмінним, що є беззаперечним доказом його хімічної стабільності.

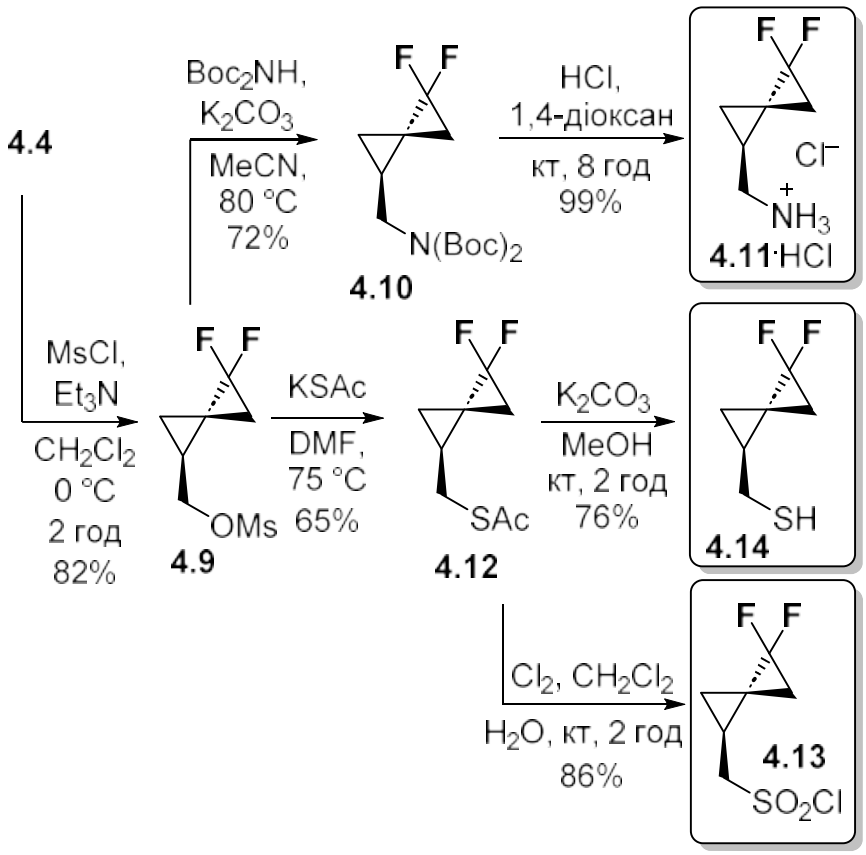


Схема 4.3. Прості хімічні перетворення базової сполуки **67** на шляху до цільових будівельних блоків **73-76**.

Для опису потенціалу синтезованих будівельних блоків було проведено вимірювання фізико-хімічних (а саме ліпофільності Log*P* та кислотності здатних до іонізації груп pK_a) та структурних характеристик їх модельних похідних і проведено порівняння цих значень із спорідненими циклічними структурами.

Зображення отриманих результатів у координатах Log*P* – pK_a показує, що 4,4-дифлуорспіро[2.2]пентил як замісник розташовується у верхньому лівому куті графіка (тобто менш основні та менш гідрофільні сполуки, Рисунок 4.1). Найближчі точки даних відповідають похідним 2,2-дифлуороциклобутану та 2,2-дифлуороциклопентану, однак, на відміну від останніх, 4,4-дифлуорспіро[2.2]пентан не схильний до елімінування HF і тому може розглядатися як більш стабільна їх альтернатива.

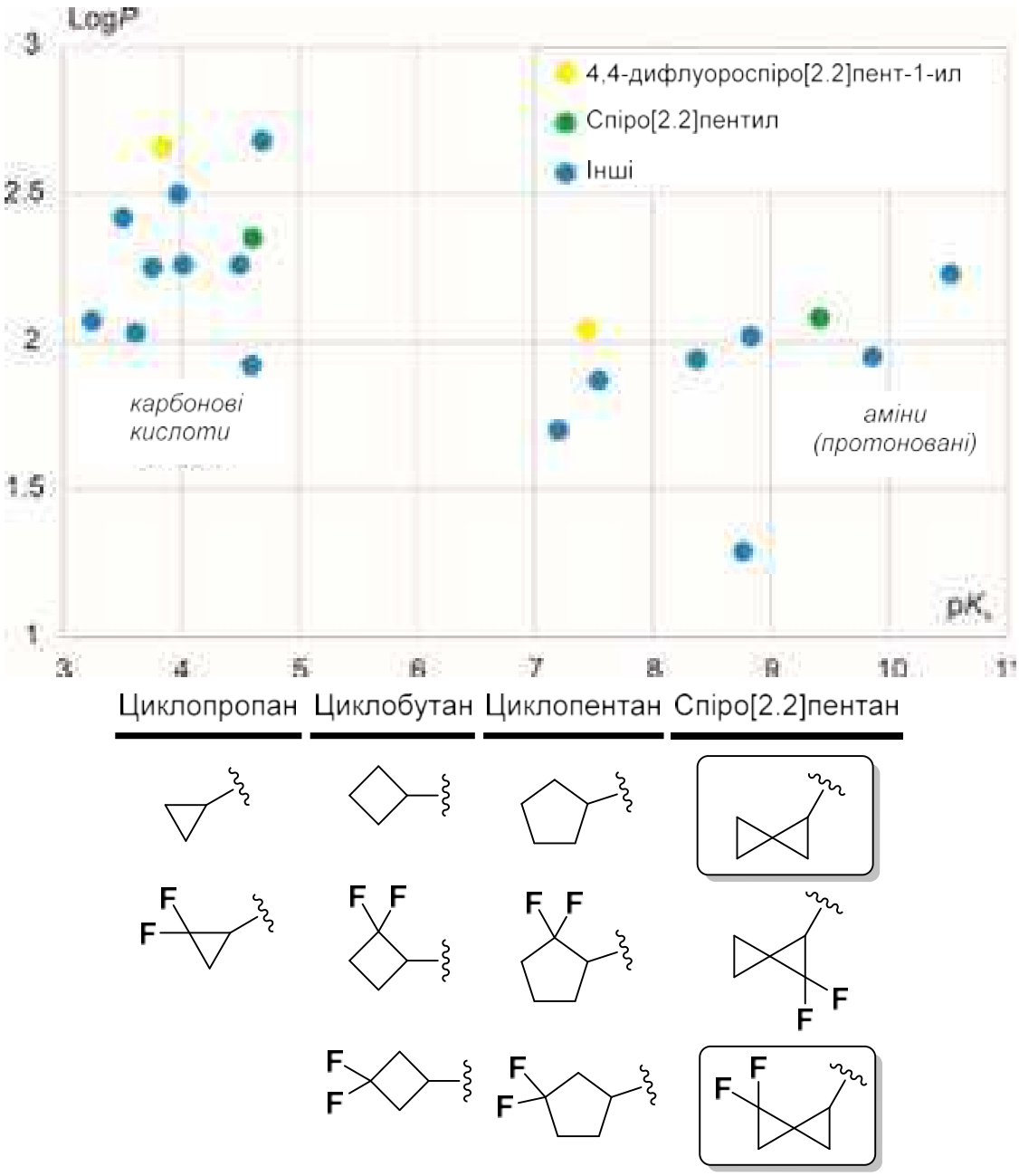


Рисунок 4.1. Порівняння фізико-хімічних характеристик досліджуваного фрагменту та споріднених до нього.

Для обговорення геометрії досліджуваних сполук та їх моноциклічних аналогів було використано метод вихідних векторів (exit vector plot, EVP). У цьому методі порівнюються відстані між двома точками приєднання фунціональних груп до досліджуваної структури («точки виходу») та плоскі і двогранні кути відповідних векторів (направлених із «точок виходу» до наступного атому замісника або за бісектрисою кута F–C–F для групи CF_2) Отримані результати демонструють високу тривимірність (і, очевидно, дещо більший розмір) спіро[2.2]пентанового каркасу порівняно з раніше

опублікованими даними для похідних циклобутану **4.15**·HCl і **4.16**·HCl (Таблиця 18).

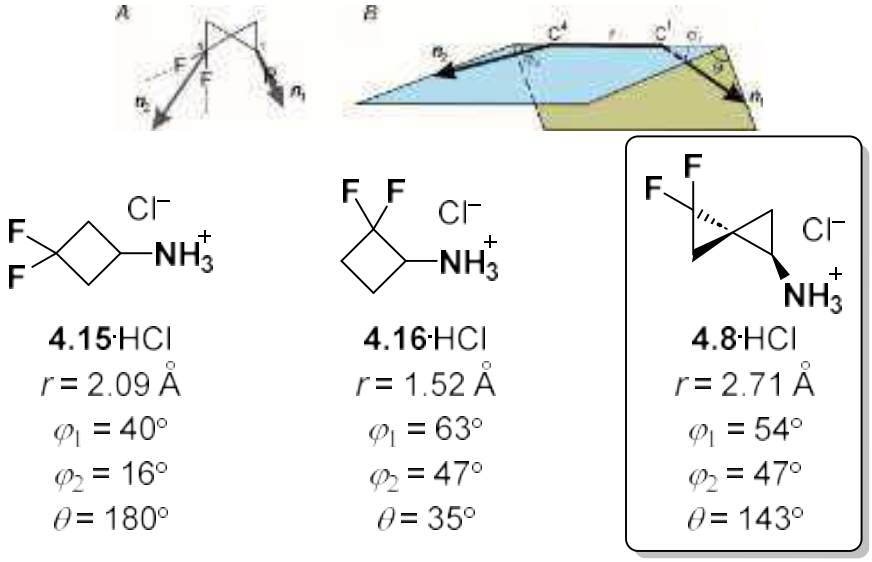


Рисунок 4.2. Концепція методу вихідних векторів (зверху) та відповідні значення параметрів для синтезованої сполуки та сполук порівняння (знизу).

У наступній частині дисертаційної роботи було запропоновано універсальний спосіб синтезу широкого ряду біциклічних будівельних блоків. Послідовність електрофільної функціоналізації подвійного зв'язку та внутрішньомолекулярного алкілування єноляту (англ. *electrophilic double bond desymmetrization (functionalization) – intramolecular enolate alkylation*, EDIEA) виявилась ефективним підходом для побудови незаміщених біцикло[m.n.k]алканів, що починаються (де k = 0 або 1) з відповідних ненасичених циклічних похідних карбонових кислот (тобто естерів або нітрилів) (Схема 4.4).[**4.2**]

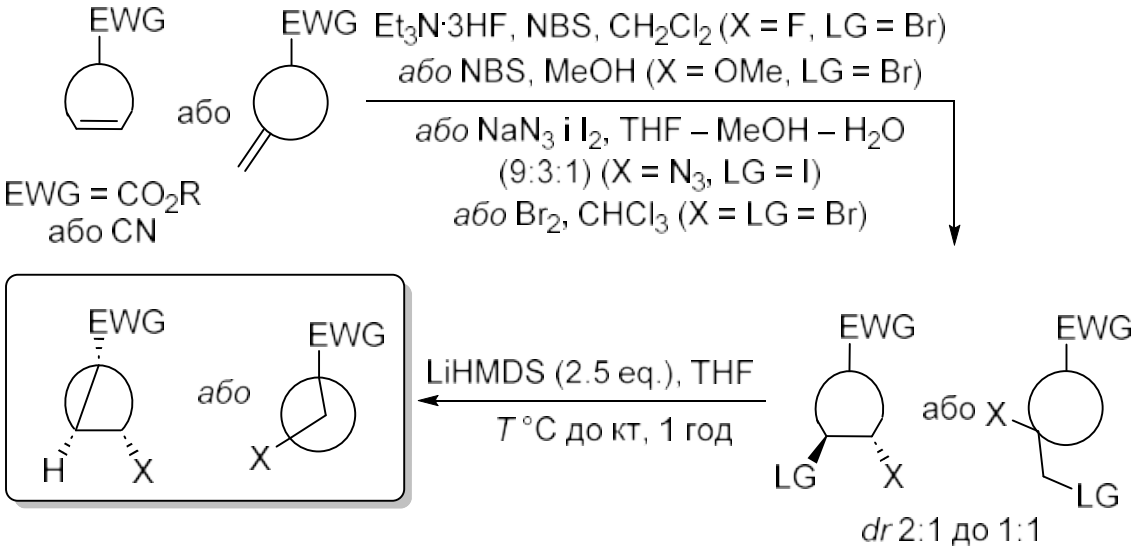


Схема 4.4. Послідовність електрофільної функціоналізації подвійного зв'язку – внутрішньомолекулярного алкілювання єноляту, що була використана для синтезу цільових будівельних блоків.

Виявилось, що область застосування субстратів з екзоциклічними подвійними зв'язками (які призводять до утворення місткових біциклічних кільцевих систем) обмежена розміром утвореного каркасу. Так, біцикло[2.2.1]гептан (утворений з 4-метиленциклогексанкарбоксилату) є найменшою циклічною системою, яку можна побудувати за допомогою цього підходу, хоча і з помірним виходом. Симетричні п'яти- та семичленні похідні циклоалкенкарбонових кислот добре працюють у послідовності EDIEA, даючи відповідні конденсовані біцикло[m.n.0]алкани.

Для несиметричних субстратів з ендоциклічним подвійним зв'язком (наприклад, похідних циклогексену) регіоселективність першої стадії стає проблемою. На щастя, стадія циклізації в цьому випадку є високоселективною. Тому, використовуючи симетричну модифікацію для стадії електрофільного приєднання (наприклад, бромування) з наступним регіоселективним внутрішньомолекулярним алкілуванням єноляту і нуклеофільним заміщенням, було отримано *транс*-ізомерні похідні відповідної конденсованої біциклічної системи (наприклад, біцикло[3.1.0]гексану). З іншого боку, несиметрична електрофільна функціоналізація також може бути використана, оскільки лише один з продуктів регіоізомерного приєднання піддається циклізації на другій

стадії; таким чином можна синтезувати *цис*-стереоізомери описаних вище сполук.

Розроблений метод було адаптовано для багатограмового синтезу моно- та біфункціональних похідних біцикло[4.1.1]- та -[3.2.1]октану, біцикло[2.2.1]- та -[3.2.0]гептану, біцикло[3.1.0]гексану, а також біцикло[2. 1.0]пентану (хаузану), включаючи похідні флуорованих амінів і карбонових кислот, амінокислот, монозаміщених діамінів та багато інших будівельних блоків для медичної хімії.

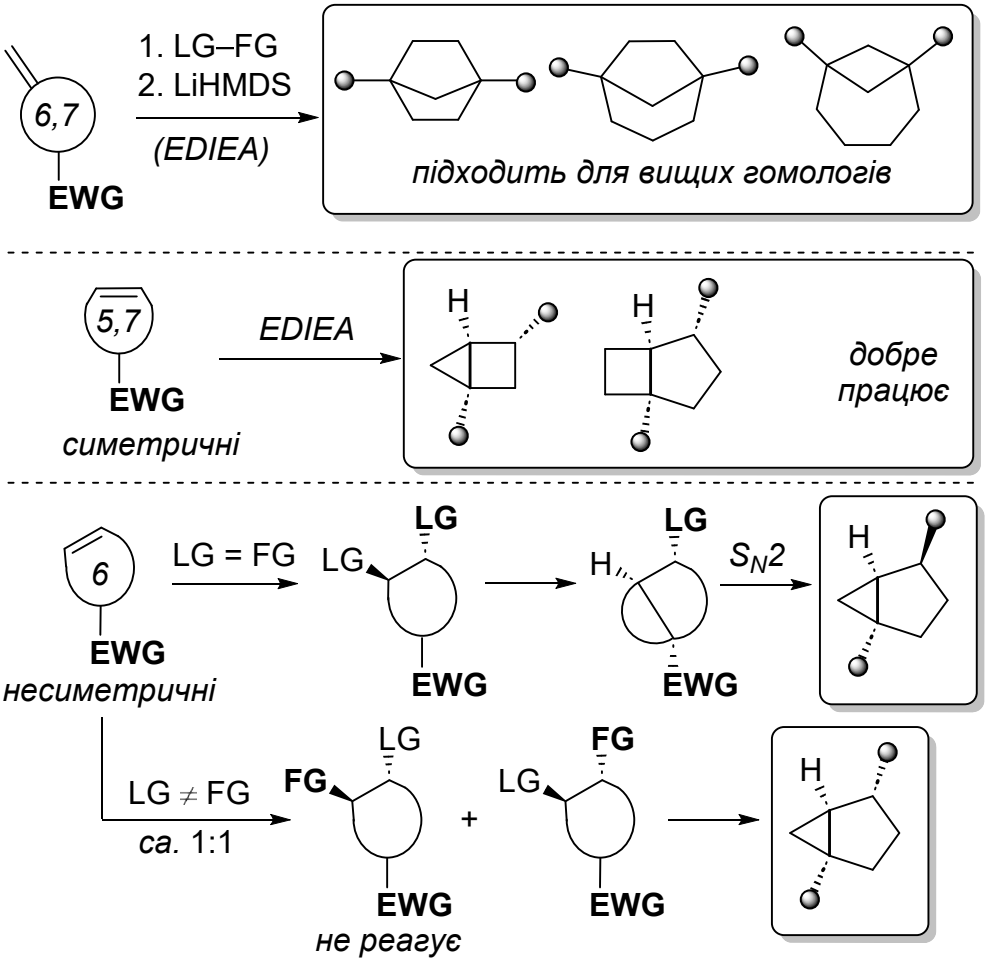


Схема 4.5. Узагальнення отриманих знань про синтез біциклічних сполук методом електрофільної функціоналізації подвійного зв'язку – внутрішньомолекулярного алкілювання єноляту.

Отримані значення pK_a для всіх насичених карбонових кислот варіювались в межах 4,0-4,6 одиниць і знаходилися між відповідними значеннями для m- і p-метоксибензойних кислот (3,8 і 4,7 відповідно). Довжина та кількість одинаринх C-C зв'язків між метокси- та карбоксильними

фрагментами є основним фактором, що визначає кислотність сполуки. Ці результати підтверджують, що індуктивний електронний ефект є найважливішим фактором, який визначає кислотність сполуки в досліджуваному ряду. Проте стереоелектронні ефекти також мають значний вплив на значення pK_a: так, сполуки з *цис*-орієнтацією метокси- та карбоксигруп виявилися на 0,1-0,2 одиниці pK_a дещо менш кислотними, ніж *транс*-ізомери. Однією з причин цього може бути дестабілізація негативно зарядженої форми для *цис*-ізомерів через несприятливу орієнтацію дипольних моментів.

Для біциклічних сполук збільшення кількості атомів вуглецю зазвичай призводило до зростання значень Log*P*, але цей ефект не був загальним. Зокрема, для метоксизаміщених похідних ліпофільність зростає в наступному ряду:

[3.1.0] (*6*)< [2.2.1] (*7*) < [2.2.2] (*8*) ≈ [3.2.1] (*8*) < [4.1.1] (*8*) < [3.2.0] (*7*)

(числа відповідають довжинам містків (квадратні дужки) і загальній кількості атомів карбону (круглі дужки) в біциклічній системі).

Слід зазначити, що відповідні флуорзаміщені похідні були дещо більш ліпофільними, ніж метоксизаміщені, але загальний тренд Log*P* залишився майже таким самим:

[3.2.0] (7) < [2.2.1] (7) < [3.2.1] (8) < [4.1.1] (8).

Знову ж таки, анілід біцикло[3.2.0]гептану виявився виключенням, цього разу з меншим значенням Log*P*. Імовірно, дещо вища гнучкість біцикло[3.2.0]гептанового каркаса може бути причиною спостережуваних відмінностей. Оскільки дипольний момент C-F зв'язку безпосередньо пов'язаний з циклічною системою, полярно флуоровані похідні повинні бути більш чутливими до зміни геометрії молекули.

Слід також прокоментувати ліпофільність анілідів, отриманих з *м*- та п-флуорбензойних кислот. Обидві сполуки виявилися менш ліпофільними, ніж

відповідні метоксипохідні, причому цей ефект був більш значним для *n*-ізомеру (Log*P* = 2.68 і 2.26, відповідно).

Узагальнені дані (у вигляді діаграми типу Крейга, Рисунок 4.3) показують, що біциклічні каркаси, досліджені в цій роботі, дозволяють тонко регулювати кислотність похідних циклоалканів в діапазоні близько 0,6 одиниць pK_a. Крім того, ліпофільність сполуки також може бути змінена в межах близько 0,9 одиниць Log*P* (і, ймовірно, буде зменшена, особливо у випадку заміщення бензолу).

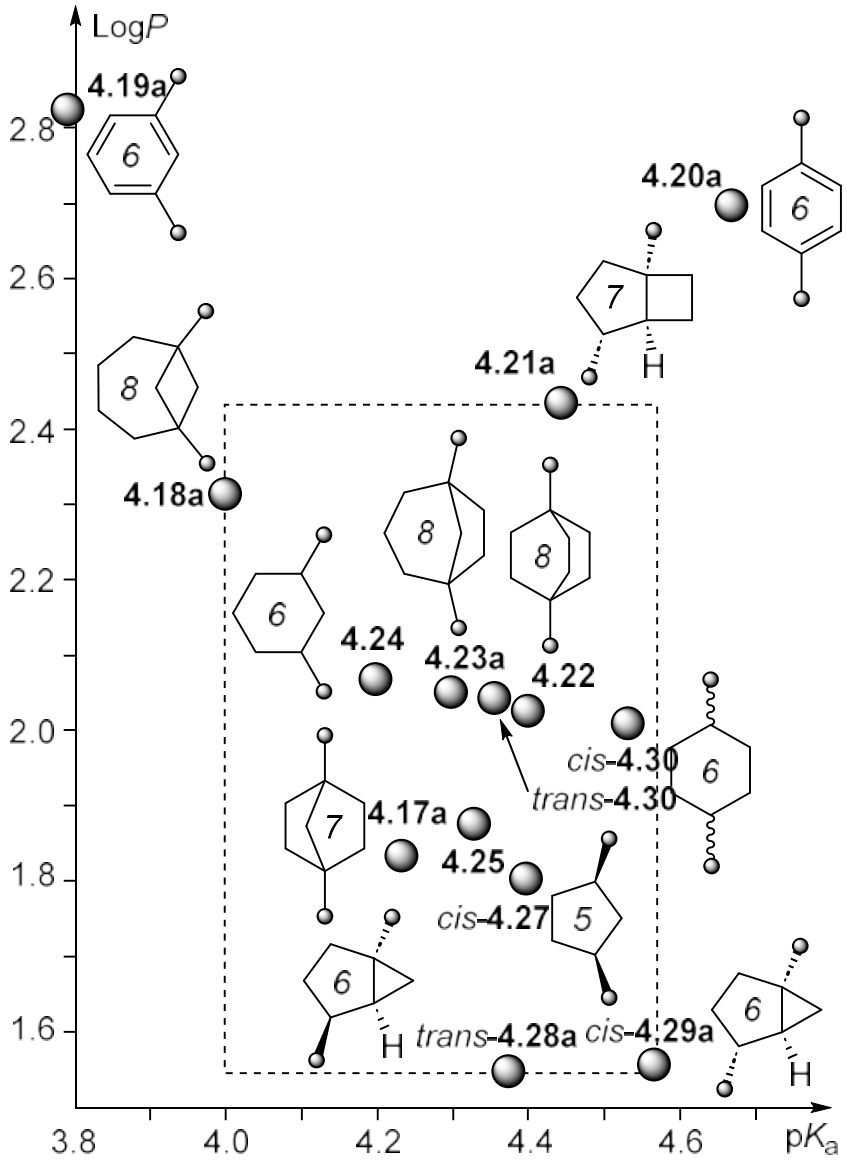


Рисунок 4.3. Діаграма типу Крейга для сполук, досліджених в цій роботі. Цифрами всередині структури вказано кількість атомів Карбону основного скафолду.

Згідно з аналізом методом вихідних векторів (EVP), заміщені похідні біцикло[2.2.1]гептану, біцикло[4.1.1]- і -[3.2.1]октану є близькими структурними аналогами *м*- і (меншою мірою) *п*-заміщеного бензолу, а також *цис*-1,3-заміщеного циклогексану. Конденсовані *цис*- та *транс*-ізомерні біцикло[3.m.0]алкани (m = 1 або 2) можуть бути використані як тривимірні аналоги *цис*- та *транс*-1,3-заміщених циклоалканів (C_5/C_6), відповідно.

Крім спіроциклічних сполук, біциклічні системи також викликають жвавий інтерес як яскраві представники концепції використання жорстких структур [**4.3**]. Як розвиток цієї ідеї у рамках цієї роботи було розроблено новий ефективний метод синтезу нітрогеновмісних біциклоалканів **4.31**, що містить α-CF_3 фрагмент біля вузлового атома Карбону.[**4.4**] Починаючи із комерційно доступних кетоестерів **4.32a–d**, шляхом приєднання реагенту Руперта-Пракаша до іміно групи у якості ключової стадії та подальшою циклізацією в лактам у присутності $AlMe_3$ сполуки **4.36a–d** були отримані у грамових кількостях із загальними виходами 10-42%.

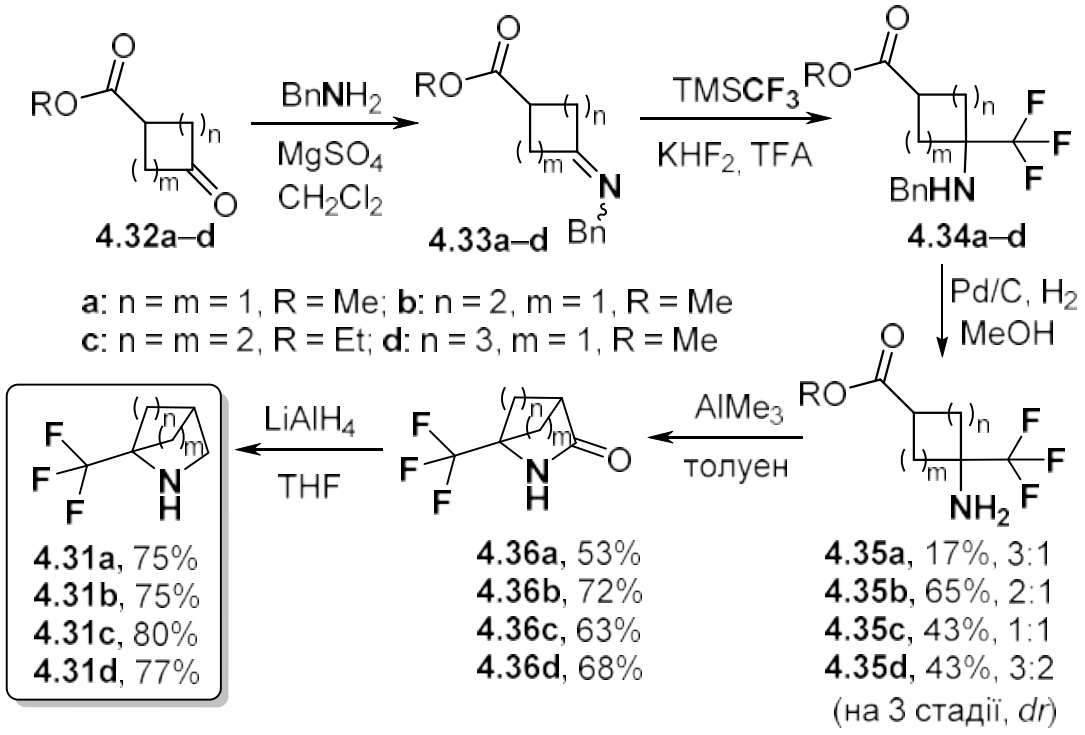


Схема 4.6. Шлях синтезу біциклічних аза-циклоалканів **4.31a–d**.

Як і очікувалось, введення трифлуорометильного фрагмента суттєво знижує значення pK_a для всіх сполук, причому дане зменшення знаходиться у

межах 4,2-5,2 одиниць із найбільшим значенням (5,23) для незаміщенного піролідину **4.31j** (Рисунок 4.4) . Варто відзначити, що поява місткових атомів Карбону у нефлуорованих сполуках зазвичай призводить до зменшення pK_a, то для флуорованих загалом спостерігається зворотна тенденція (крім жорсткого **4.31b**, для якого спостерігається відносно невелике зменшення відповідного значення).

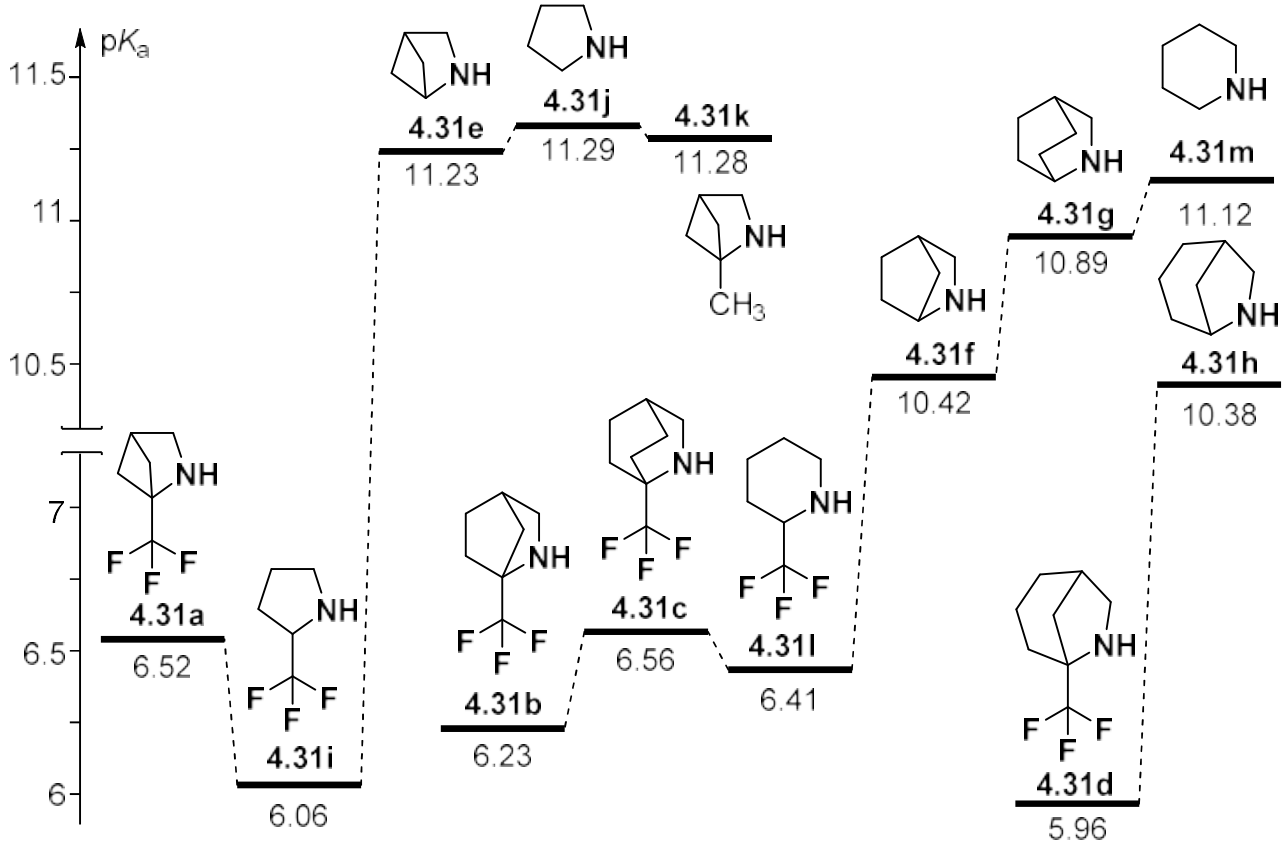


Рисунок 4.4. Порівняння відомих та виміряних значень основності сполук, що досліджуються в даній роботі.

Протилежна ситуація спостерігається для ліпофільності – трифлуорометильний замісник підвищує ліпофільність кожної із молекул (Рисунок 4.5). Цікавою є ситуація із впливом місткових атомів – у той час як додаткові метиленові ланки другого циклу у нефлуорованих об'єктах збільшують ліпофільність (що відповідає звичайній хімічній логіці), у випадку CF_3-вмісних молекул поява елементів жорсткості значно знижують ліпофільність, причому чим більш жорстка нова структура (менша кількість нових ланок), тим більший цей ефект.

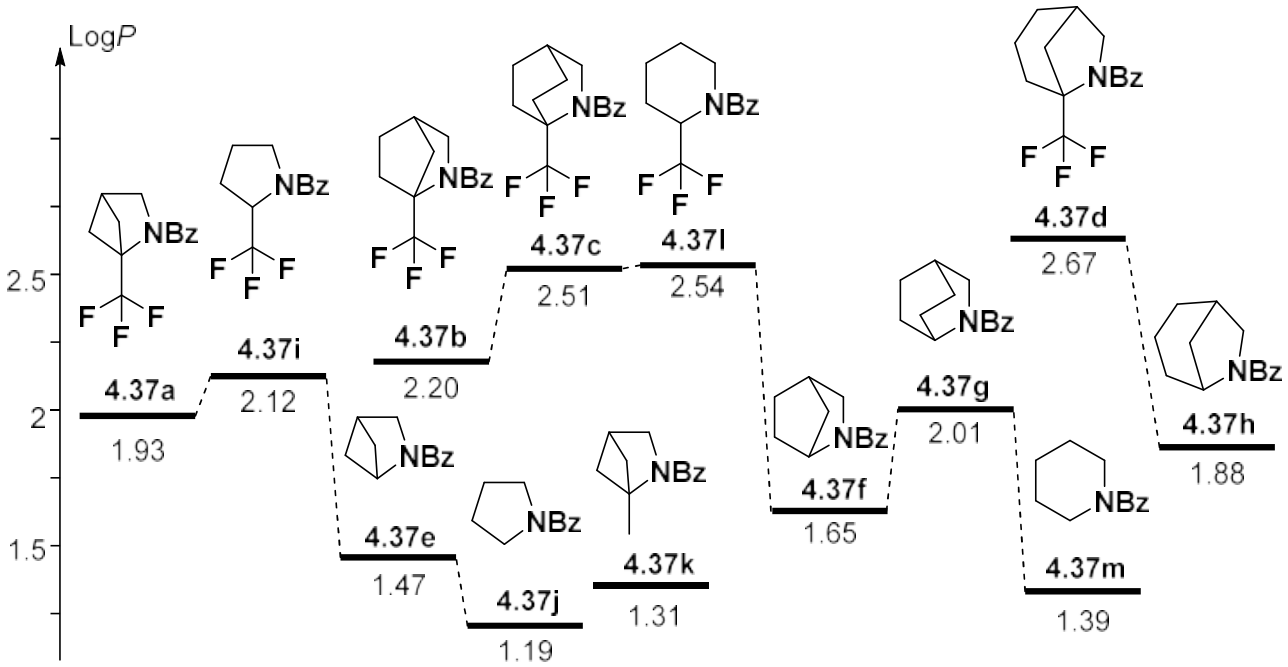


Рисунок 4.5. Порівняння відомих та виміряних значень ліпофільності сполук, що досліджуються в даній роботі.

Даний розділ було присвячено розробці методів синтезу функціоналізованих похідних біциклічних вуглеводнів та їх *аза*-аналогів. Переважно одержані методами внутрішньомолекулярної циклізації (для біциклічних сполук) або циклопропанування подвійного зв'язку (для спіроциклічних сполук), запропоновані нові будівельних блоки є суттєвим доповненням до існучого хімічного простору за багатьма параметрами – геометричними, фізико-хімічними тощо. Важливим аспектом цієї частини роботи є експериментальне визначення впливу підвищеної «тривимірності» (за рахунок місткових атомів чи зміни геометрії в спіросполуках) на фізико-хімічні параметри, що без сумніву стане в нагоді при розробці лікарських засобів.

Основні публікації за розділом:

4.1. K. P. **Melnykov**, O. V. Voloshyna, B. V. Vashchenko, O. P. Demchuk, O. V. Hryshchuk, O. O. Grygorenko. 4,4-Difluorospiro[2.2]-pentan-1-yl – a fluorinated substituent to expand the synthetic and medicinal chemists' toolbox. *Eur. J. Org. Chem.* **2022**, e202200863.

4.2. Semeno, V. V.; Vasylchenko, V. O.; Fesun, I. M.; Ruzhylo, L. Yu.; Kipriianov, M. O.; **Melnykov**, K. P.; Skreminskyi, A.; Iminov, R.; Mykhailiuk,

P.; Vashchenko, B. V.; Grygorenko, O. O. Bicyclo[m.n.k]alkane building blocks as promising benzene and cycloalkane isosteres: multigram synthesis, physicochemical and structural characterization. *Chem. Eur. J.* **2024**, 30 (12), e202303859. DOI: 10.1002/chem.202303859.

4.3. Ryabukhin, S.V.; **Melnykov**, K. P. Synthesis of α-spirocyclic pyrrolidines. *Chem. Heterocycl. Compd*. **2020,** *56,* 1411–1413.

4.4. Smyrnov, O.; **Melnykov**, K. P.; Semeno, V.; Liashuk, O. S.; Grygorenko, O. O. α-CF_3-Substituted saturated bicyclic amines: advanced building blocks for medicinal chemistry. *Eur. J. Org. Chem.* **2024**, *27* (1), e202300935. DOI: 10.1002/ejoc.202300935.

Тези конференцій

1. Волошина О.В., **Мельников** К.П., Шабликіна О.В., Григоренко О.О. Функціоналізовані похідні 4,4-дифлуороспіро[2.2]пентану. *XXIII Міжнародна конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії»*, 18-20 травня **2022** р. Київ, с.87.

Розділ 5 МЕТОДИ ВВЕДЕННЯ ФЛУОРОВАНИХ ФРАГМЕНТІВ

У той час як значна кількість робіт описує синтетичні підходи до сполук, що мають *гем*-дифлуороциклопропільну групу, приєднану до атома Карбону, а також їхні хімічні перетворення, відповідні *N*-заміщені аналоги вивчені значно менше. Більшість із них посилалися на вихідний *гем*-дифлуороциклопропіламін (**87**) або його похідні (Рисунок 5.1); слід зазначити, що подібні аліфатичні аміни (наприклад, **88**) мають обмежену стабільність при зберіганні.

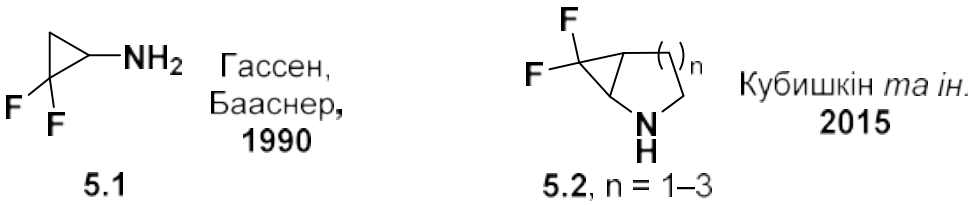


Рисунок 5.1. Приклади відомих *N*-заміщених дифлуороциклопропанів

Тому було вирішено розробити альтернативний підхід до *N*-дифлуороциклопропілзаміщених азолів, що виключав би необхідність синтезу малостійких проміжних сполук. Запропонований метод базується на дифлуороциклопропануванні відповідних *N*-вінілазолів **89a–g** за допомогою системи CF_3SiMe_3 – NaI.[**5**.**1**] Дана методика використання *in situ* генерованого дифлуорокарбену була розроблена групою Ола в 2011 році і з тих пір використовувався багатьма іншими дослідниками для циклопропанування. Плануючи дану роботу, очікувалось отримати продукти циклопропанування для ряду різноманітних азолів (Рисунок 5.2). Хоча цей метод виявився придатним лише для похідних піразолу, висока толерантність до функціональних груп дозволяє проводити цю реакцію для заміщених піразолів, що відкриває шлях для подальшої модифікації і використання їх як будівельних блоків для потреб медичної та агрохімії.

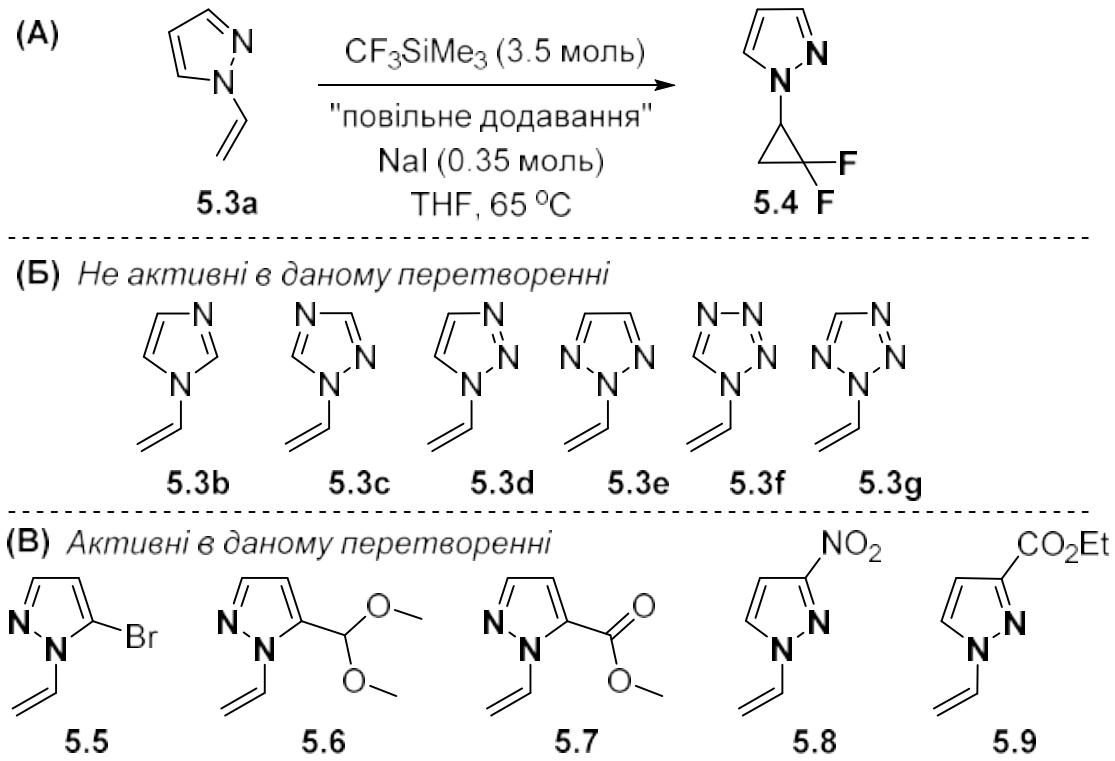


Рисунок 5.2. (А) Досліджуване перетворення; (Б) Сполуки, що не можуть бути перетвореними у бажаний продукт за даних умов; (В) Перелік заміщених піразолів, що можуть бути модифікованими за оптимізованих умов.

Крім того, подальші перетворення сполуки **5.4** показали високу стійкість *N-гем*-дифлуороциклопропілового фрагменту до умов низки типових органічних перетворень, включаючи нітрування, бромування, обробку кислотами та лугами, м'яке окиснення та відновлення, а також Pd-каталізоване крос-сполучення. У той же час даний фрагмент виявився нестійким до металорганічних сполук, таких як *n*-BuLi або аміди літію, сильних кислот Льюїса, таких як $AlCl_3$ та каталітичного відновлення (Схема 5.1). Будівельні блоки **5.11–14a–c, 5.15** описані в цій роботі, було отримано в масштабі до 50 г, що демонструє потенційну придатність застосовуваного протоколу для промислового масштабування.

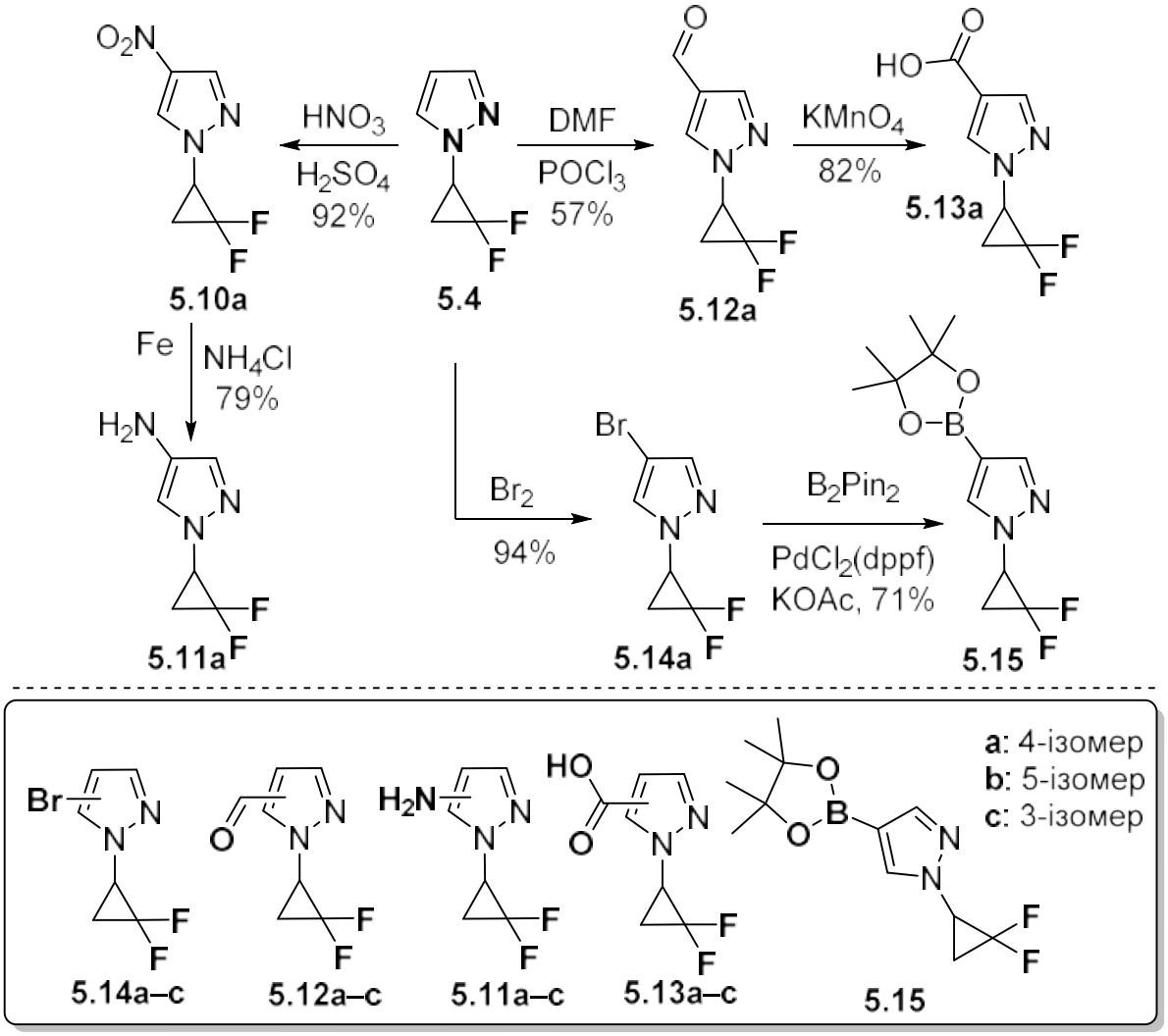


Схема 5.1. (Верх) Схеми простих хімічних перетворень основного продукту дифлуороциклопропанування **90**; (Низ) Будівельні блоки, синтезовані у цій роботі.

Крім синтезу та вивчення дифлуороциклопропанів як безпосередніх структурних фрагментів будівельних блоків, було вирішено дослідити поведінку таких об’єктів як інтермедіатів при синтезі більш складних систем, а саме флуорованих гетероциклів.[**5.2**] Найпростіший підхід до синтезу флуорованих гетероциклів – пряме флуорування – часто є складним завданням через високу лабільність вихідних сполук в присутності флуоруючих реагентів і сильні окисні властивості електрофільних флуоруючих реагентів. З іншого боку, використання прекурсорів, які вже містять атоми Флуору в бажаних положеннях, можна розглядати як альтернативний багатообіцяючий шлях до широкого спектру флуорованих сполук. Також варто зазначити, що структурні елементи, отримані комбінацією шестичленних і шести- або п’ятичленних

циклів, з'єднаних одинарним зв'язком, входять до десятка найбільш привілейованих циклічних систем в медичній хімії. Саме це мотивувало до розробки уніфікованого методу синтезу сполук, наведених на Рисунок 5.3.

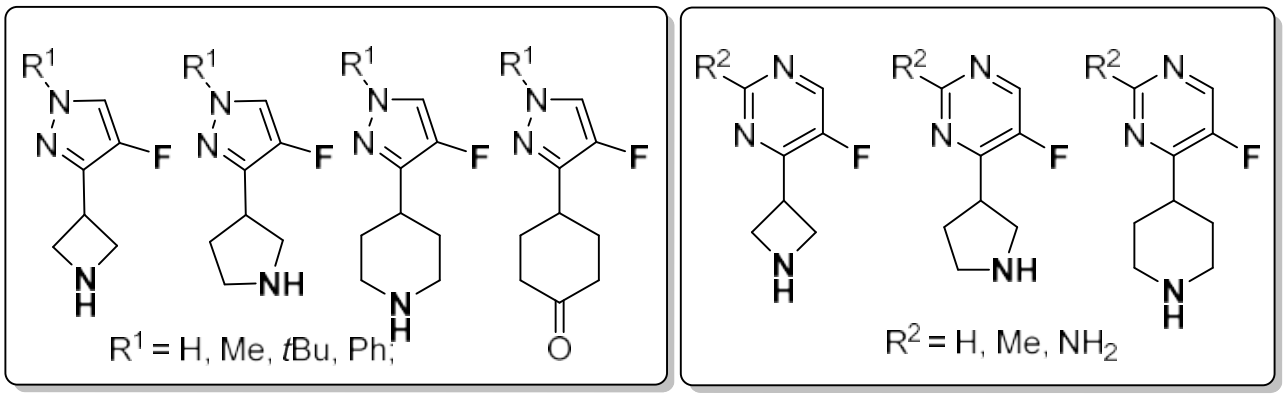


Рисунок 5.3. Цільові сполуки даного дослідження.

Дослідження розпочиналося з синтезу проміжних будівельних блоків за допомогою модифікації процедури, раніше розробленої групою Ділмана. Згідно з розробленою методикою комерційно доступні кетони **5.16a–e** було перетворено на силілєноляти **5.17a–e**, які не було виділено в чистому вигляді, а натомість оброблено джерелом дифлуорокарбену з отриманням циклопропанів **5.18a–e** (Схема 5.2). З урахуванням попереднього досвіду було вирішено використовувати реактив Рупперта – Пракаша у присутності NaI. Через обмежену стабільність циклопропани **5.18a–e** також не виділяли в чистому вигляді і одразу вводили в реакцію розкриття циклопропанового циклу з *N*-бромосукцинімідом, що дозволило отримати цільові флуоровані *β*-бромокетони **5.19a–e** з загальним виходом 42–65 % на 3 стадії та масштабі до 70 г цільового продукту за одне проходження синтетичної послідовності.

Беручи до уваги наявність кількох реакційних центрів, було вирішено дослідити реакцію отриманих сполук із бінуклеофілами. Встановлено, що реакція сполук **5.19a–e** з $N_2H_4 \cdot H_2O$ протікає гладко при кип'ятінні в метанолі, генеруючи відповідні продукти **5.20a–e,a–d** з виходом 58–92%. Однак, використовуючи *N*-заміщені гідразини (R^1 = Me, *t*Bu або Ph) вихід цільових піразолів виявився незначним, тому було вирішено використати більш жорсткі

умови - K_2CO_3, DMF, 130 °C або 85 °C у випадку похідних азетидину **5.20d**. Для обох способів відповідні продукти отримували з виходом 43–82% після очистки.

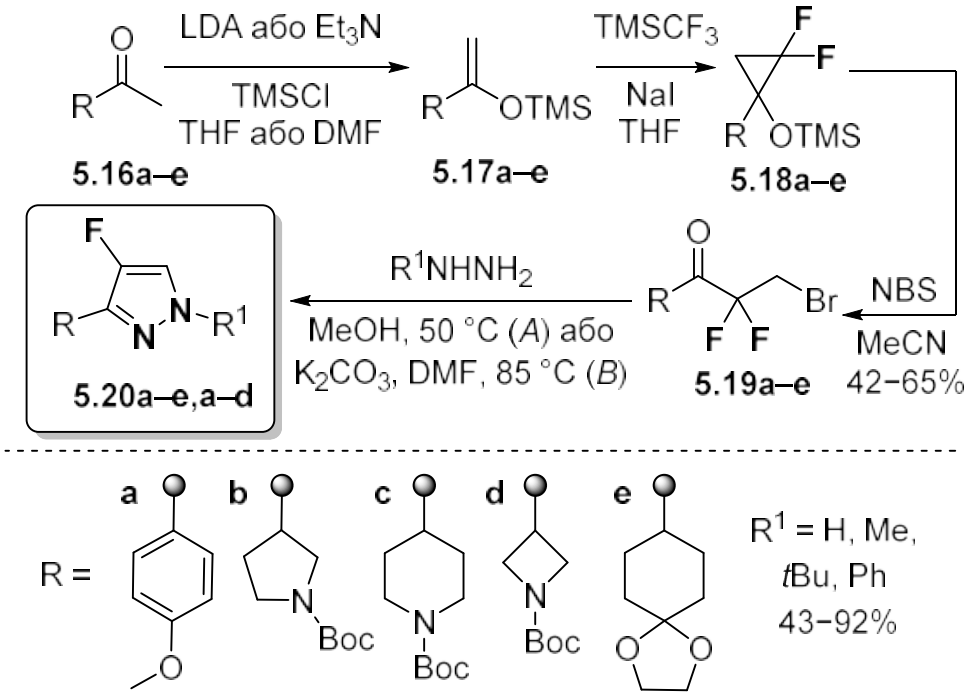


Схема 5.2. Синтетичний шлях до заміщених 4-флуорпіразолів.

Регіоселективність утворення піразолу була підтверджена експериментами NOESY, для продуктів **5.20cb**, **5.20db** та **5.20dd**. (Рисунок 5.4).

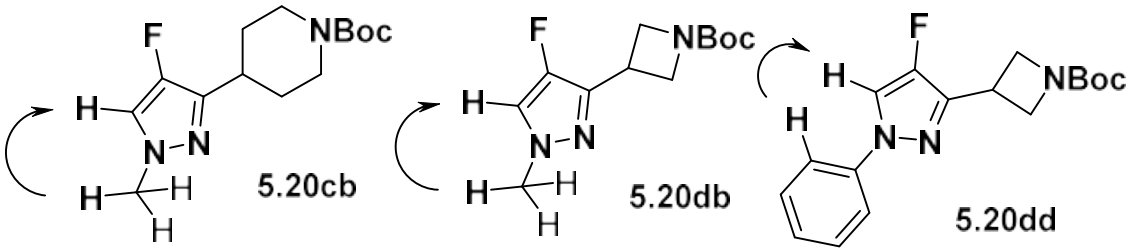


Рисунок 5.4. Основі кореляції NOESY, використані для доведення структури.

У продовження ідеї використання флуорованих прекурсорів для синтезу флуоровмісних гетероциклів, зокрема піримідинів типу **5.23a–e** було застосовано відомий підхід, що полягає у реакції єнамінонів із похідними амідину або гуанідину. Відповідні флуоровмісні прекурсори можуть бути отримані із α-флуорокетонів шляхом реакції з диметилформамід диметилацеталем. В свою чергу, дані флуоровані кетони легко отримуються із

незаміщених кетонів **5.16a–e** шляхом синтезу силілєнолятів із подальшим флуоруванням за допомогою комерційно доступного реагенту SelectFluor®. Варто зазначити нижчі виходи на всіх стадіях для азетидинвмісних сполук порівняно з іншими, що може бути пояснено низькою стабільністю малих циклів (особливо при підвищених температурах).

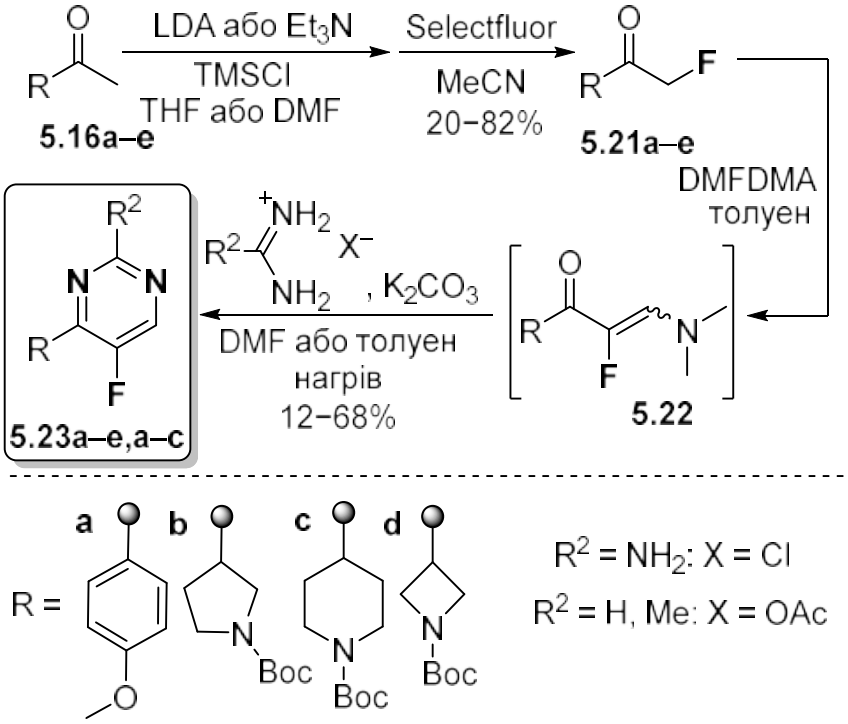
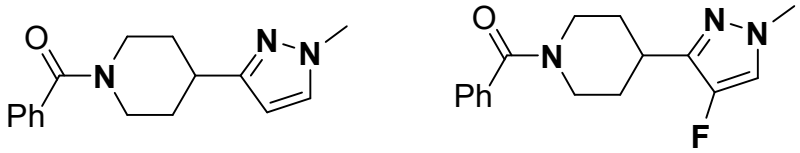


Схема 5.3. Синтетичний шлях до 5-флуоропіримідинів.

Крім того, для сполук **5.23ca–cc** було перевірено можливість для масштабування. Для сполук **5.23cb** та **5.23cc** результати для мультиграмового синтезу були співмірні із виходами початкових експериментів, тоді як для продукту **5.23ca** вихід у масштабі у 10 г був значно меншим очікуваного. Тим не менш, заміна DMF на менш полярний розчинник (толуен) дозволила провести дане перетворення із прийнятним (42%) виходом.

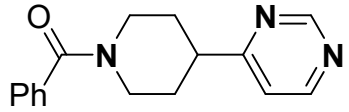
Оскільки було передбачено застосування синтезованих флуорованих гетероциклів як будівельних блоків для створення лікарських засобів, було досліджено їх фізико-хімічні властивості, а саме ліпофільність Log*P* і розчинність у воді S_w. Щоб оцінити вплив атома Флуору на Log*P* і S_w отриманих гетероциклів, з флуоровмісного піразолу, піримідину та їх нефлуорованих аналогів було отримано бензоїльовані похідні **5.24–5.27** (Рисунок 5.5). Як

випливає з отриманих результатів, атом Флуору дещо підвищував ліпофільність відповідних похідних (на 0,56 і 0,32 од. Log*P* для піразолового та піримідинового рядів відповідно). Вплив флуорування на розчинність у воді був менш однозначним: спостерігалося незначне підвищення для похідних піразолу та майже 2,5-кратне зниження – для піримідинів.

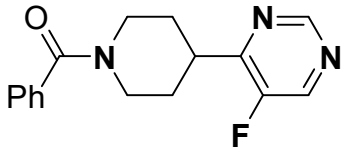


5.24, Log*P* = 1.44±0.01
S_w = 1.03±0.03 г/л

5.25, Log*P* = 2.00±0.01
S_w = 1.19±0.03 г/л



5.26, Log*P* = 1.20±0.01
S_w = 2.92±0.26 г/л



5.27, Log*P* = 1.52±0.01
S_w = 1.18±0.26 г/л

Рисунок 5.5. Розчинність та ліпофільність обраних сполук із даного дослідження та їх нефлуорованих аналогів.

Сульфоксіміни нещодавно привернули значну увагу дослідників як біоізостерні аналоги сульфонового, амідного, сульфонамідного й інших споріднених структурних фрагментів. Мета цієї частини дисертаційної роботи – розробка масштабованих протоколів синтезу 1-бромо-4-(*S*-(флуороалкіл)сульфонімідоїл)бензенів і встановлення впливу атомів Флуору та сульфоксімінового фрагменту на ліпофільність (порівняно з нефлуорованими аналогами та відповідними сульфонами).[**5.3**] На основі відомого підходу до синтезу сульфоксімінів, що передбачає введення імінового фрагменту шляхом окиснення відповідного жирноароматичного сульфіду за участі фенілйодозодіацетату у присутності карбамату амонію, розроблено масштабовані протоколи синтезу 1-бромо-4-(*S*-(флуороалкіл)сульфонімідоїл)-бензенів (флуороалкіл – CH_2F, CHF_2, CF_3).

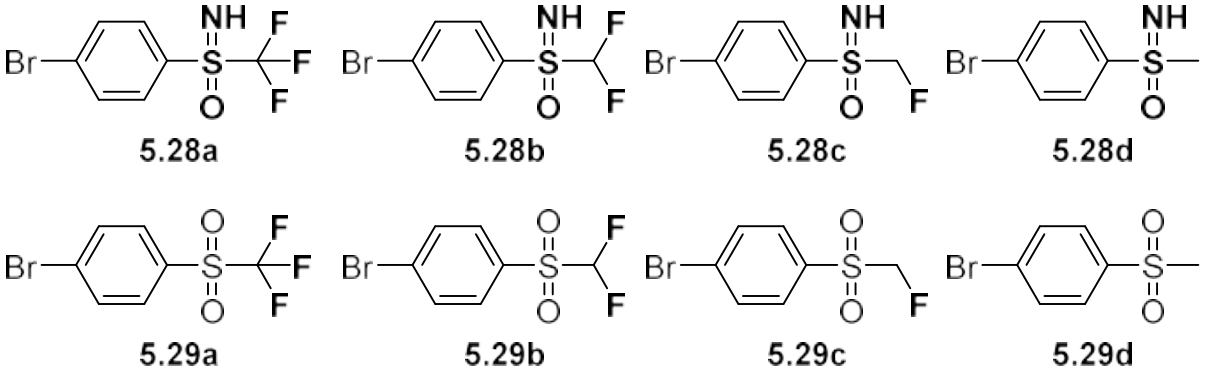


Рисунок 5.6. Ароматичні сульфоксиіміни – цільові сполуки дослідження.

Синтез цільових сполук **5.28a–c** розпочинався алкілуванням 4-бромотіофенолу CF_3I, CHF_2Cl або CH_2FI у при- сутності гідриду натрію у ДМФА за кімнатної температури. Одержані флуоровані жирноароматичні сульфіди **5.29'a–c** (вихід 81–90 %) було введено в реакцію з діацетоксийодобензеном (PIDA) і карбаматом амонію у трифлуороетанолі за способом Маньє та Ребула (Схема 5.4). Під час масштабування вищезгаданої методики було виявлено багато проблем, зокрема неповна конверсія на стадії окиснення. У ході досліджень було з'ясовано, що додаткове дво- або трикратне введення обох реагентів (PIDA – по 0.5 екв, карбамат амонію – по 1 екв) кожні 8 год сприяло підвищенню конверсії на 20–30 %. Водночас кількість утворених у реакції нецільових сольових продуктів також збільшувалася, проте це не впливало на чистоту продукту, оскільки вони кількісно відділялися під час обробки реакційної суміші. Після проведення стадії гідролізу цільові продукти було одержано в кількостях 17,9– 60,4 г із виходом 51–62 %.

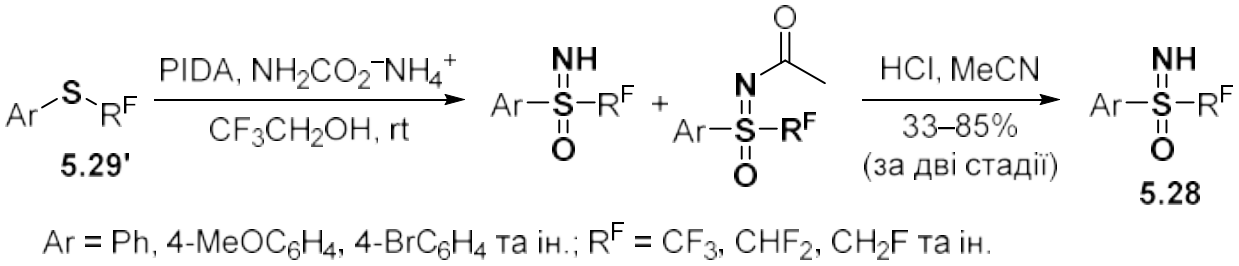


Схема 5.4. Синтез флуороалкільованих сульфоксиімінів.

Визначення ліпофільності одержаних сульфоксімінів **5.28a–c**, нефлуорованого аналогу **5.28d**, а також сульфонів **5.29a–d** показало, що в серії

сульфоксімінів флуорування приводило до підвищення значення Log*P* на 0.32±0.03, 0.58±0.03 і 1.00±0.03 одиниці для першого, другого та третього атома Флуору, відповідно (середнє значення 0.63±0.34) (Рисунок 5.7). У випадку сульфонів підвищення ліпофільності складало 0.53±0.02, 0.54±0.03 і 0.80±0.10 одиниці Log*P*, відповідно (середнє значення 0.62±0.15). Порівняння значень Log*P* для серії сульфоксімінів **5.28a–d** та сульфонів **5.29a–d** показує, що відповідні сульфоксіміни є більш гідрофільними – на 0.59±0.02 (**5.28d**/**5.29d**), 0.80±0.03 (**5.28c**/**5.29c**), 0.76±0.03 (**5.28b**/**5.29b**) та 0.56±0.10 (**5.28a**/**5.29a**) одиниці Log*P* (середнє значення 0.68±0.12).

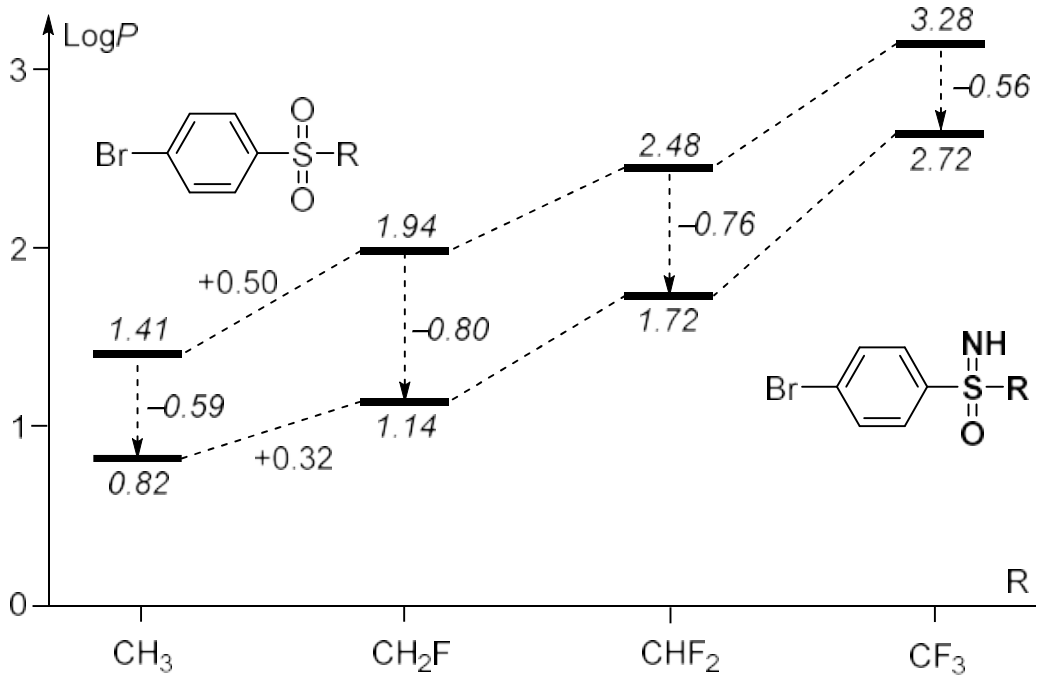


Рисунок 5.7. Ліпофільність (Log*P*) досліджуваних об’єктів.

Одноатомна модифікація скелету органічної молекули є потужною стратегією, яка значно розширює можливості хіміків по синтезу складних об’єктів. Наприклад, видалення атомів Нітрогену у вторинних амінах надає неочевидні можливості для модифікації на пізніх стадіях синтезу.

Нещодавно було описано декілька протоколів для селективного видалення Нітрогену, один із яких базується на використанні аномерного амідного реагенту **5.30** (Схема 5.5).

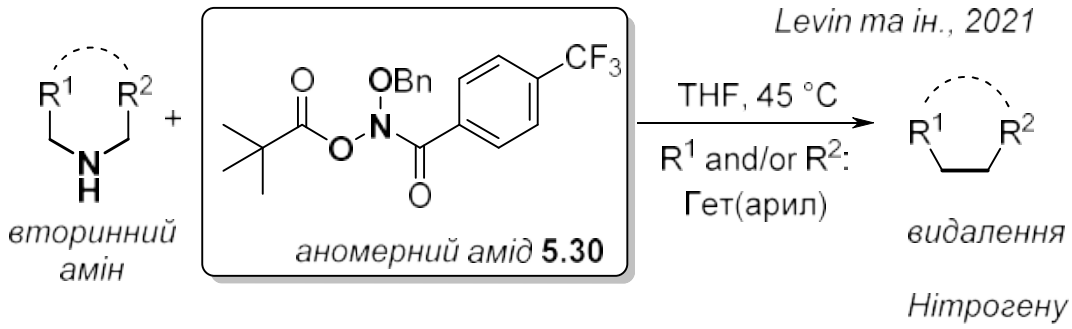


Схема 5.5. Загальне представлення реакції видалення Нітрогену.

Маючи досвід синтезу великої кількості бібліотек сполук, було припущено, що дане перетворення має значний потенціал для паралельного синтезу, враховуючи високу синтетичну доступність вторинних амінів. У цій роботі розглянуто реалізацію вищезазначеної ідеї шляхом розробки протоколу двоетапного паралельного синтезу, включаючи відновне амінування (гетеро)ароматичних альдегідів **5.31** первинними (гет)арилметил («бензиловими») амінами **5.32** з наступним видаленням азоту за допомогою **5.30**, без виділення проміжних вторинних амінів у чистому вигляді (Схема 5.6).[**5.4**] Також було оцінено застосовність методу для створення бібліотек лікарськоподібних сполук, а також властивості хімічного простору, що стають доступні завдяки цьому підходу.

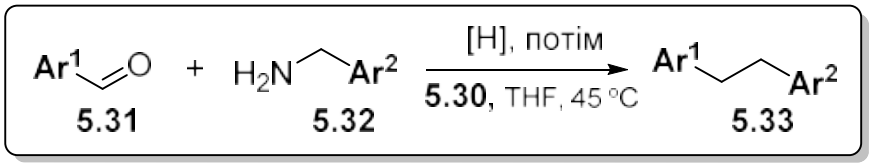


Схема 5.6. Досліджувана реакція.

На першому етапі було проведено розробка методики для паралельного синтезу. Попередні експерименти показали, що серед кількох методик паралельних процедур відновного амінування, підхід із використанням $NaBH_3CN$ як відновлюючого реагенту, метанолу як розчинника та подовженого часу утворення іміну (12 год) виявився найкращим для отримання неочищених проміжних вторинних амінів **5.34** найвищої чистоти (Рисунок 5.8). Неочищені проміжні продукти **5.34**, отримані згідно з наведеним вище оптимізованим протоколом, дали прийнятні результати на другому етапі, тобто реакції зі

сполукою **5.30** згідно з опублікованою процедурою. Таким чином, отримано відповідні продукти **5.33**{1,2}, **5.33**{2,1} та **5.33**{11,1} з виходом 45%, 36% та 7% відповідно (для простоти нумерація сполук **5.33** та **5.34**{*i*,*j*} відповідає сполукам, утворених з альдегіду **5.31**{*i*} та аміну **5.32**{*j*}).

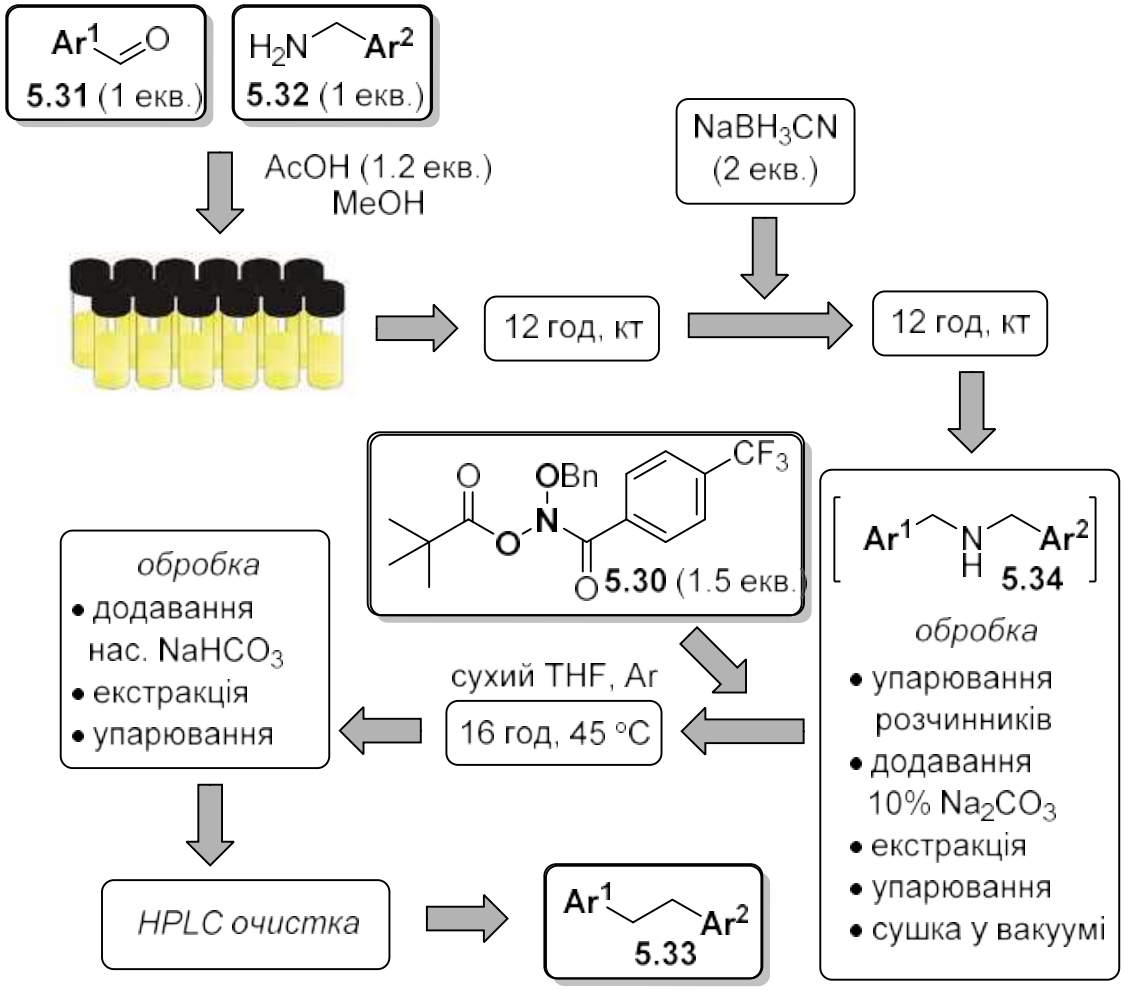


Рисунок 5.8. Схематичне зображення робочого процесу.

Використовуючи отримані результати як орієнтир, було відібрано набір реагентів **5.31** та **5.32**, що мають структурні особливості, які, на думку автора, можуть зацікавити медичних хіміків (Рисунок 5.9).

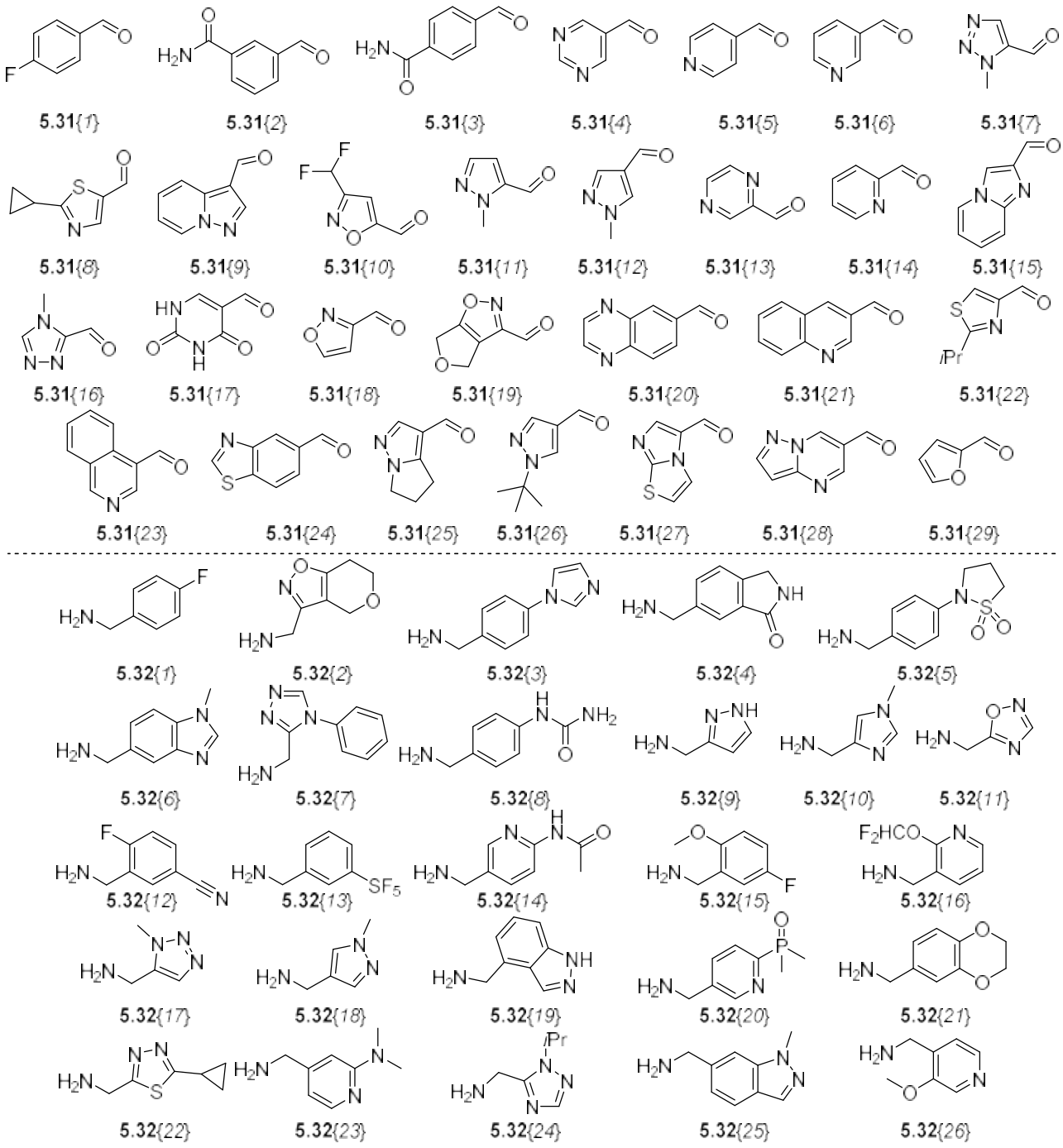


Рисунок 5.9. Набір сполук **5.31** та **5.32**, що були використані для генерації бібліотеки.

Використовуючи ці набори реагентів, для валідації методики було проведено паралельний синтез двох бібліотек – 17 (гетеро)ароматичних альдегідів **5.31**{*2–18*} із *p*-флуорбензиламіном (**5.32**{*1*}), та *p*-флуорбензальдегіду (**5.31**{*1*}) з 10 первинних амінів **5.32**{*2–11*} у якості вихідних сполук за схемою, вказаною на Рисунок 5.8. Встановлено, що будівельні блоки **5.31**{2–9} і **5.32**{2–5} забезпечують цільові продукти з виходом 10–45 %; субстрати **5.31**{10–13} і **5.32**{6–8} також дали цільові

сполуки, хоча й з низьким виходом (4–10%), тоді як відповідні реакції з **5.31**{14–18} і **5.32**{9–11} були не ефективними. Варто зазначити, що майже у всіх проблемних випадках стадія відновного амінування працювала з помірною або низькою ефективністю (згідно з даними РХ-МС), таким чином проміжний продукт **5.34** вводився в друге перетворення із низькою чистотою.

Маючи ці дані, було обрано із решти списку реагентів 33 пари сполук, і проведено синтез за аналогічною схемою. Відповідно до робочого процесу (Рисунок 5.8), 25 із 33 представників бібліотеки було успішно синтезовано (76% успіху синтезу, тобто відсоток запланованих представників бібліотеки, які було отримано та виділено в чистому вигляді); 18 із них (54% усієї бібліотеки) – з виходом 10–51% (Рисунок 5.10). Знову ж таки, у більшості невдалих прикладів (7 з 8) саме перший крок (тобто відновне амінування) дав проміжну сполуку **5.34** із помірною або навіть низькою чистотою згідно зі спектрами РХ-МС та/або ^{1}H ЯМР, що, ймовірно, було причиною збою загальної послідовності реакції.

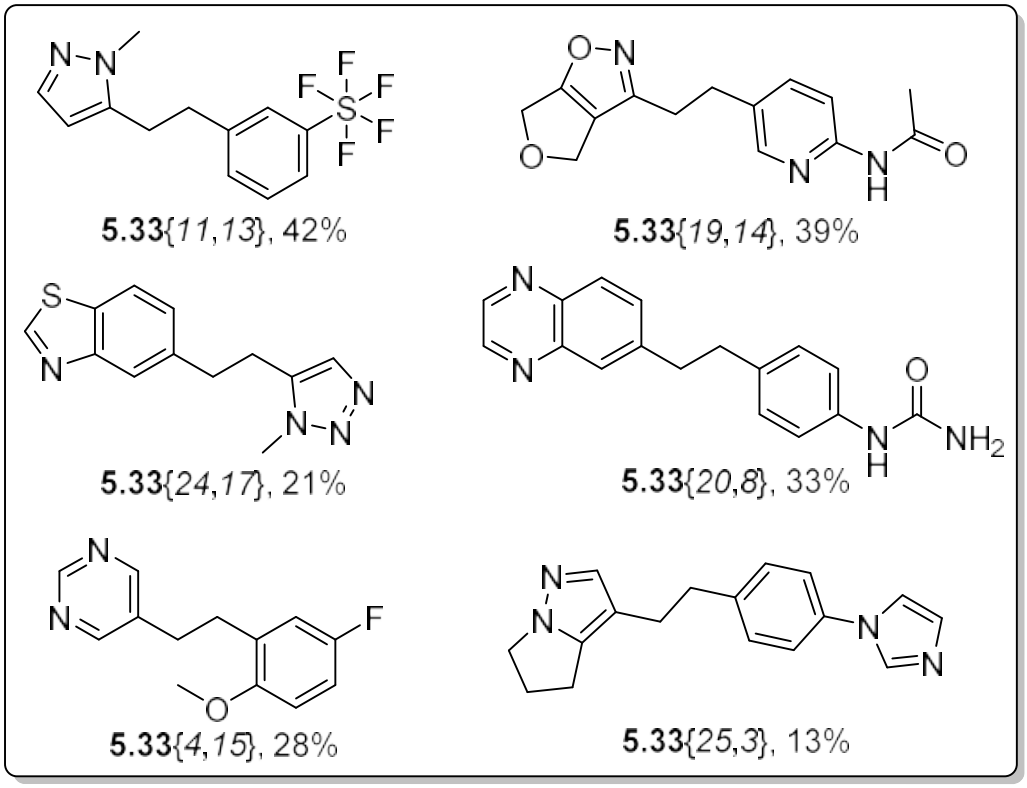


Рисунок 5.10. Деякі приклади синтезованих сполук.

Такий підхід до синтезу бібліотеки дозволив нам перерахувати властивості субстрату, які призводять до низької ефективності у паралельному синтезі (наприклад, похідні азину та 1,3-азолу, що містять групу CHO або CH_2NH_2 в α положенні гетероциклу), що в більшості випадків було наслідком недостатньої чистоти проміжного продукту, що утворюється після відновного амінування. Тим не менш, заснована на цих критеріях відбору, віртуальна бібліотека створює хімічний простір із 593713 представників. Порівняння цього простору з базами даних ChEMBL, PubChem і ZINC15, а також зі складом компанії «Єнамін» показало, що сполуки, отримані в цій роботі, в основному недоступні у наявних на даний момент колекціях сполук (Рисунок 5.11). Відповідно, лише 13 представників згенерованого хімічного простору було знайдено в базі даних ChEMBL, і з них деякі вже продемонстрували біологічну активність.

Проаналізувавши методику поєднання двох фрагментів шляхом відновного амінування – видалення Нітрогену у варіанті паралельного синтезу, було вирішено окремо дослідити можливість введення флуорованих циклоалканів за розробленим протоколом. Використовуючи умови, описані в попередній частині роботи було проведено 18 паралельних експериментів з використанням різних комбінацій вихідних сполук (Рисунок 5.12, *A* та *B*). В 12 з них були отримані цільові представники міні-бібліотеки **5.37**{1–6,1–8} (67 % успішності синтезу; приклади отриманих продуктів зображено на Рисунок 5.12, *C*).[**5.5**]

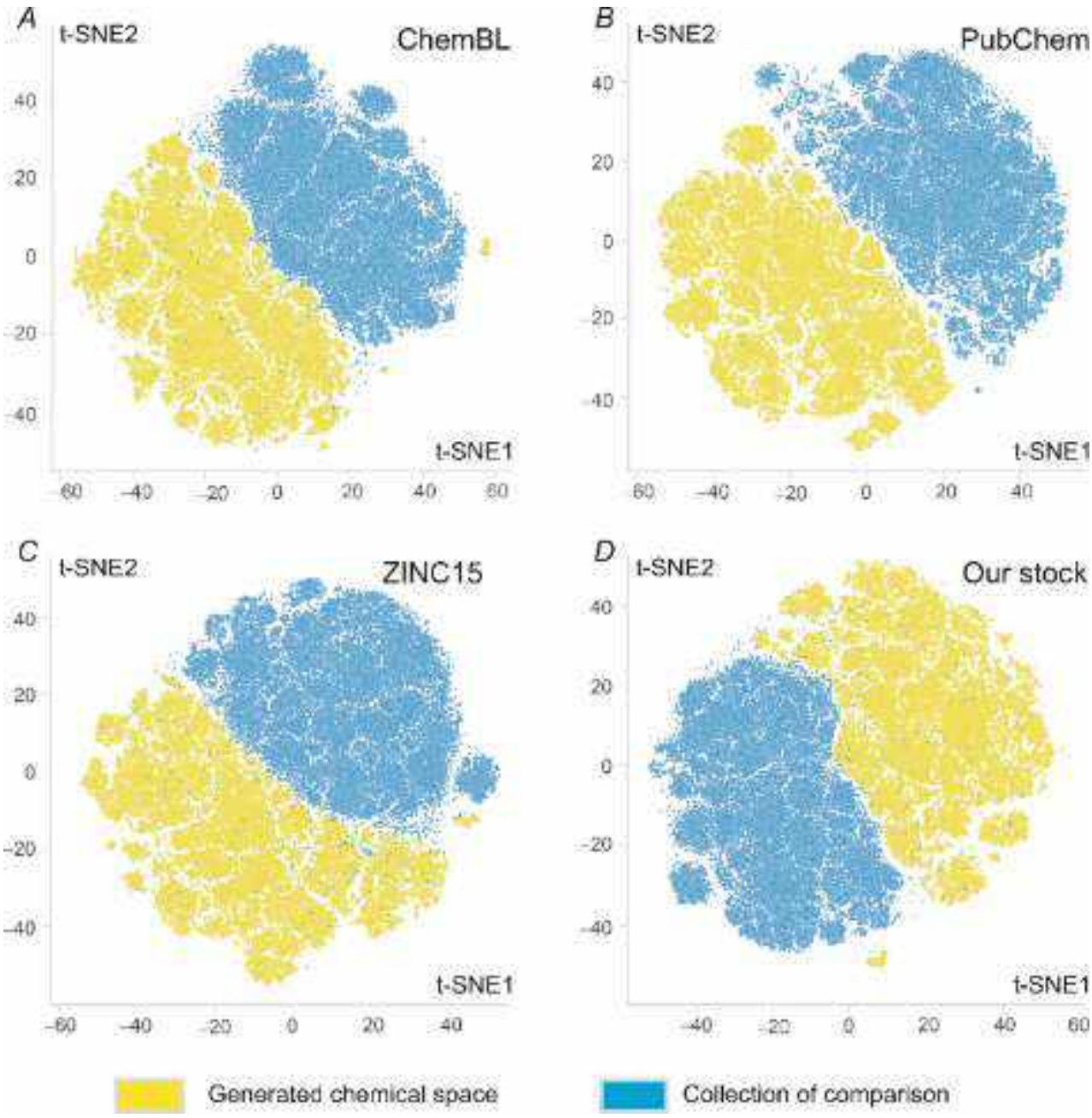


Рисунок 5.11. t-SNE порівняльний аналіз 50 тисяч різноманітних молекул, вибраних із згенерованого хімічного простору та (*A*) сполук ChemBL; (*B*) сполук PubChem; (*C*) сполук ZINC15; (*D*) колекції Enamine.

Загалом аміни з первинними алкільними замісниками (наприклад, **5.36**{8}) дають дещо вищі виходи продуктів (17–33%) порівняно з α-розгалуженими (наприклад, **5.36**{1}) (10–18%), що відповідає високій чутливості стадії «видалення азоту» до стеричних факторів. Що стосується альдегідного компонента, то сполуки, які продемонстрували дещо гірші результати у попередньому дослідженні[**5.4**] (наприклад, піримідин **5.35**{3} або піразол **5.35**{5}), взагалі не дозволили виділити цільові продукти). Варто

зазначити, що за даними спектрів LC-MS неочищеної реакційної суміші можна було зафіксувати утворення бажаних продуктів, однак їх виділення та очистка виявились неефективними.

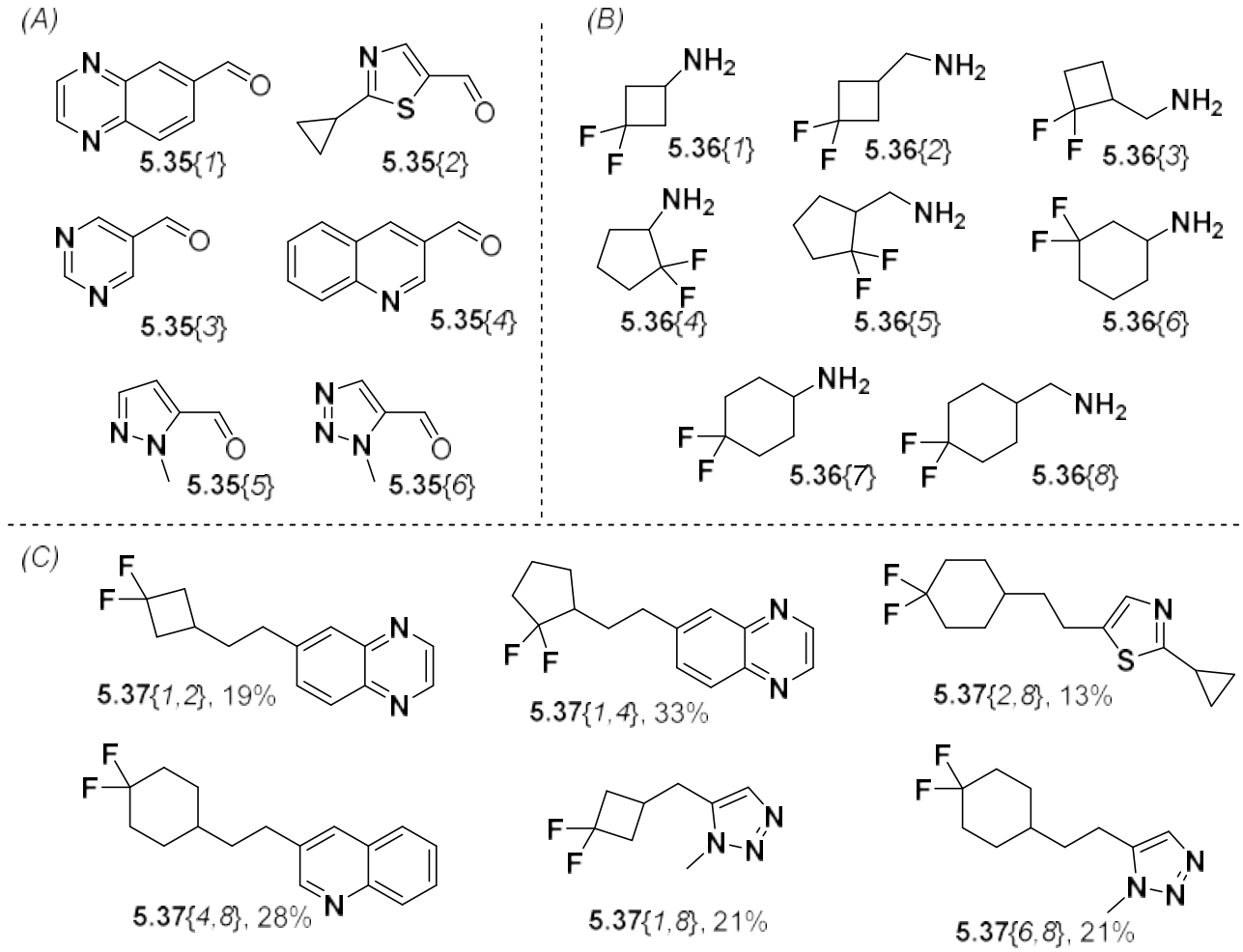


Рисунок 5.12. (*A* та *B*) Вхідні сполуки, використані для генерації бібліотеки; (*C*) Вибрані приклади синтезованих сполук.

Реакція видалення Нітрогену за Левіним є представником класу радикальних процесів; ще однією реакцією такого ж типу є реакція Мініші. В наступній частині роботи було проведено порівняльний аналіз реакції органотрифлуороборатів **5.39** та відповідних їм карбонових кислот **5.40** з гетероциклами **5.38** у синтезі комбінованих алкіл-гетарильних систем (Схема 5.7).[**5.6**]

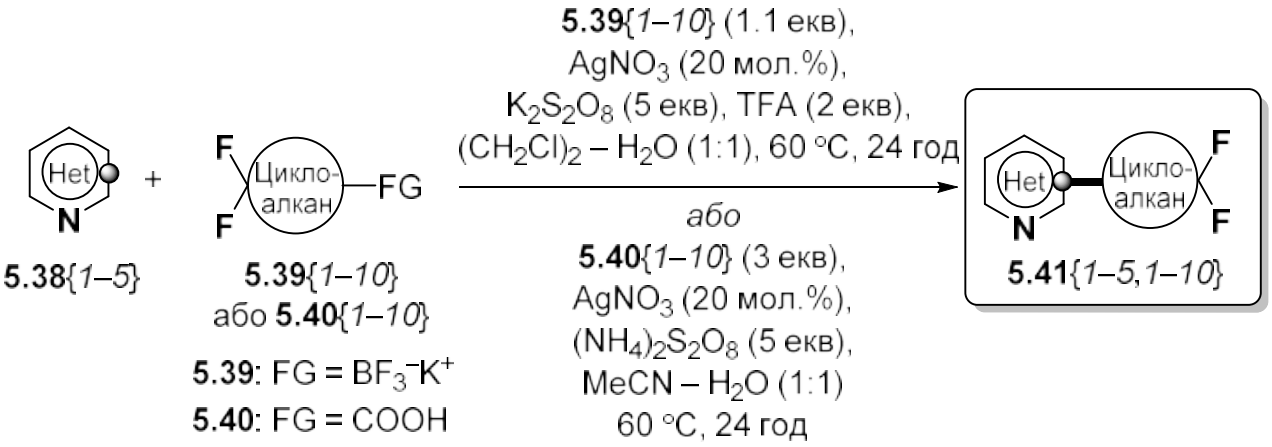


Схема 5.7. Досліджувана реакція Мініші.

Було виявлено, що карбонові кислоти демонструють дещо вищу ефективність (60%) як джерела радикалів у досліджуваній реакції в оптимізованих умовах порівняно з трифлуорборатами (48%) (Рисунок 5.13). Крім того, для кислот діапазон розподілу виходів був вужчим, що можна розглядати як показник кращої відтворюваності методу в умовах паралельного синтезу. З іншого боку, оптимізований протокол передбачав використання трикратного надлишку карбонових кислот, що в деяких випадках призводило до утворення продуктів подвійного алкілування - до 36%, що було виявлено методом аналітичної РХ-МС.

Окрім встановлення пріоритетних вихідних будівельних блоків для реакції з різними типами ароматичних сполук, метою цієї частини роботи було визначення потенціалу такого підходу для введення флуороалкільованих замісників в гетероароматичні фрагменти, особливо в концепції паралельного синтезу. Було виявлено, що на результат реакції значний вплив має положення атомів Флуору. Так, 4,4-дифлуоровані будівельні блоки мають майже таку ж ефективність, як і відповідні їм нефлуоровані аналоги, тоді як 3,3- і особливо 2,2-дифлуоровані сполуки (відносно активної функціональної групи) демонструють знижену активність. В останньому випадку хоча незначні кількості цільових продуктів було виявлено за допомогою РХ-МС, жоден з них не вдалося виділити в чистому вигляді. Крім того, циклогептановмісні

трифлуороборати показали відносно низькі результати порівняно з іншими субстратами.

З іншого боку, результат реакції сильно залежав від природи гетероциклічного партнера: найвищі середні виходи спостерігалися для 4-метилхіноліну (69%), а найнижчі – для бензотіазолу (37%) (Рисунок 5.13). Останній факт можна пояснити обмеженою стійкістю бензотіазолу до дії радикальних окисників (у тому числі системи $Ag^{+}/S_2O_8^{2-}$).

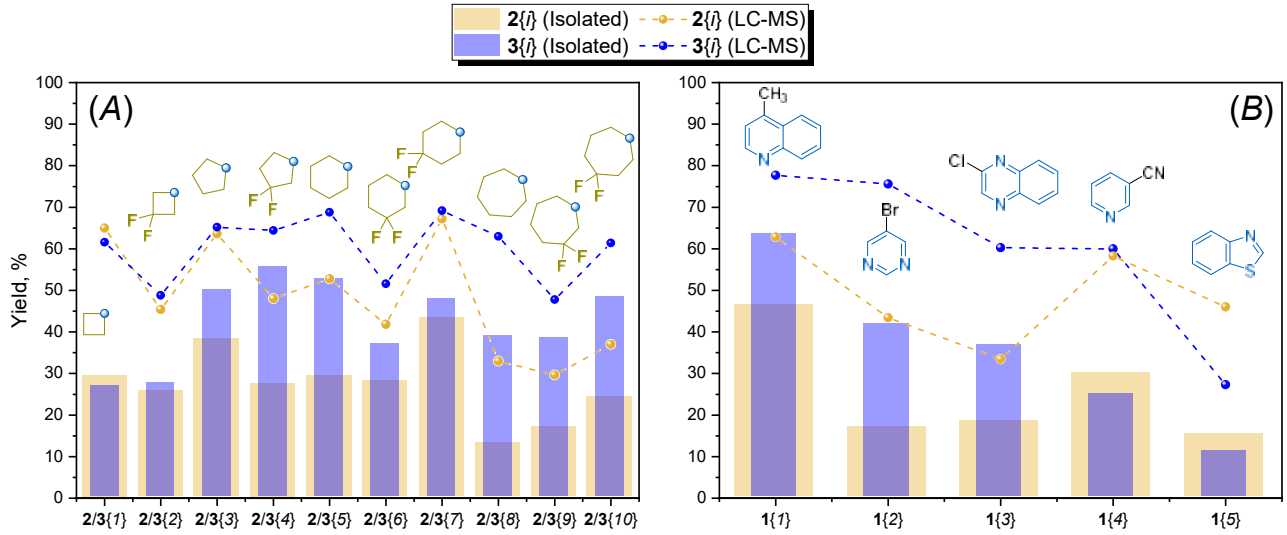


Рисунок 5.13. Узагальнений статистичний аналіз по будівельним блокам в реакції Мініші: (Зліва) Аліфатичні фрагменти (Зправа) Ароматичні фрагменти.

Цікаво, що трифлуороборати показували кращі результати у сполученні з цим гетероциклом краще в порівнянні з карбоновими кислотами (середній вихід продукту майже на 20% вищий). Потенціали окиснення, отримані з циклічних вольтамперограм досліджуваних трифлуорборатів, значно вищі для флуорованих сполук, тому вони можуть бути лише частково відповідальними за спостережувані ефекти. Слід також брати до уваги інші фактори, такі як нуклеофільність радикалу або ліпофільність циклоалкільного фрагменту (наприклад, для похідних циклогептану).

Для ароматичних субстратів з однозначно визначеним електрофільним центром (а саме, **5.38**{1}, **5.38**{3} та **5.38**{5}) утворився лише один продукт

моноалкілування **5.41** (Рисунок 5.14). Для похідних піримідину **5.41**{2,j} спостерігалося регіоспецифічне утворення продуктів алкілування С-4, що повністю узгоджується з раніше отриманими даними. Для похідних піридину **5.41{**4,j} утворювалися всі можливі ізомери (тобто С-2, С-4 і С-6). У більшості випадків переважало заміщення С-4 (близько 50%), і відповідні продукти **5.41a**{4,j} були виділені в чистому вигляді після обернено-фазової ВЕРХ. У той же час, розділення ізомерів С-2 і С-6 виявилося більш складним, так що можна було отримати їх суміші з різним співвідношенням, що містять до 40% ізомеру С-2 (за даними ^{1}H ЯМР-спектроскопії).

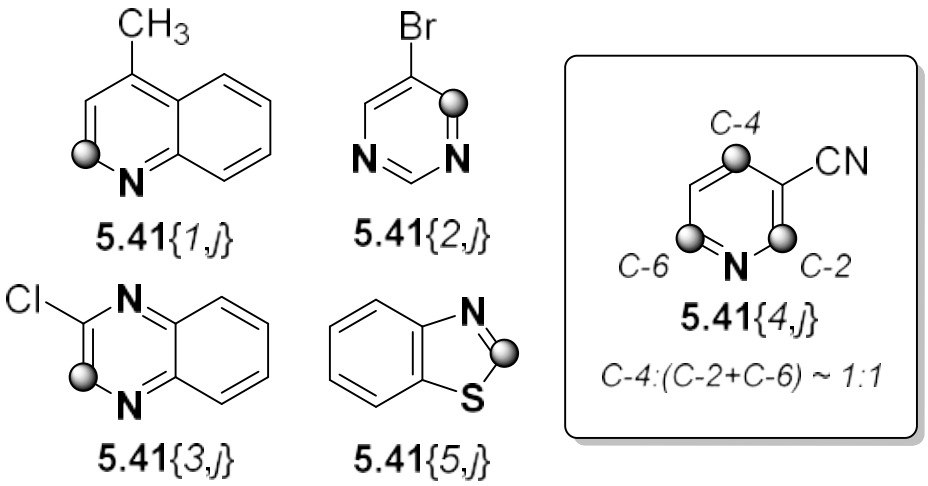


Рисунок 5.14. Регіоселективність приєднання.

У даному розділі увагу було приділено практичним аспектам застосування флуорованих будівельних блоків. На початку розділу розкривається питання високої активності донорно-акцепторних *гем*-дифлуорованих циклопропанів, за допомогою перетворень яких було синтезовано ряд раніше недоступних флуорованих похідних піразолу та піримідину з додатковими карбо- та гетероциклічними замісниками. Потенціал та перепони до використання флуорованих будівельних блоків (кислот, амінів та похідних боронатів) було визначено при дослідженні радикальних реакції видалення Нітрогену за Левіним та реакції Мініші. Окрім демонстрації можливостей паралельного синтезу бібліотек такими методами, було виокремлено ряд механістичних особливостей, що стосуються впливу атома Флуору на реакційну здатність вказаних будівельних блоків. Крім того, було

запропоновано ряд нових сполук на основі флуороалкільованих сульфоксиімінів – потенціальних замінників сульфоновмісних сполук при розробці лікарських засобів.

Основні роботи за розділом

5.1. Nosik, P. S.; Poturai, A. S.; Pashko, M. O.; Melnykov, K. P.; Ryabukhin, S. V.; Volochnyuk, D. M.; Grygorenko, O. O. *N*-Difluorocyclopropyl-substituted pyrazoles: synthesis and reactivity. *Eur. J. Org. Chem.* **2019**, *27*, 4311–4319.

5.2. Fedinchyk, A.; Herasymchuk, M.; Smirnov, O. V.; **Melnykov**, K. P.; Yarmoliuk, D. V.; Kyrylchuk, A. A.; Grygorenko, O. O. Fluorine-containing sp^3-enriched building blocks for the multigram synthesis of fluorinated pyrazoles and pyrimidines with (hetero)aliphatic substituents. *Eur. J. Org. Chem.* **2022**, e202200274. DOI: 10.1002/ejoc.202200274.

5.3. **Мельников**, К., Підвишенний, О., Смирнов, О., Григоренко, О. Флуоровані сульфоксіміни жирноароматичного ряду: масштабований синтез і вплив структурних елементів на ліпофільність. *ВІСНИК Київського національного університету імені Тараса Шевченка* **2024**, *1* (59), 1–5. DOI: 10.17721/1728-2209.2024.1(59)

5.4. Holovach, S.; **Melnykov**, K. P.; Poroshyn, I.; Iminov, R. T.; Dudenko, D.; Kondratov, I. S.; Levin, M.; Grygorenko, O. O. C–C coupling through Nitrogen deletion: application to library synthesis. *Chem. Eur. J.* **2023**, *29*, e202203470. DOI: 10.1002/chem.202203470.

5.5. Holovach, S. M.; **Melnykov**, K. P.; Poluektova, M. S.; Rozhenko, O. B.; Grygorenko, O. O. Incorporation of *gem*-difluorocycloalkyl substituents into heterocycles via the Levin's "nitrogen deletion" strategy. *J. Org. Pharm. Chem.* **2023**, 21(3), 11–16. DOI: 10.24959/ophcj.23.278321.

5.6. Holovach, S.; Poroshyn, I.; **Melnykov**, K. P.; Liashuk, O. L.; Pariiska, O. O.; Kolotilov, S. V.; Rozhenko, A. B.; Volochnyuk, D. M.; Grygorenko, O. O. Parallel Minisci reaction of *gem*-difluorocycloalkyl building blocks. *ACS Org. Inorg. Au* **2024**, *4*(4), 424–431. DOI: 10.1021/acsorginorgau.4c00028.

Тези конференцій

1. Головач С., **Мельников** К., Порошин І., Григоренко О., Волочнюк Д., Роженко О. Впровадження методу утворення С-С зв'язку шляхом «видалення азоту» у комбінаторну хімію. *XIX наукова конференція «Львівські хімічні читання - 2023»*, 29-31 травня **2023** р., м. Львів, с.41.

2. Полуектова М., Головач С., **Мельников** К. П., Григоренко О. О. Введення *гем*-дифлуороциклоалкільних замісників у гетероцикли через стратегію «видалення нітрогену» Левіна. *XXIV Міжнародна конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії»,* 17-19 травня **2023** р., м. Київ, с.107.

3. Федінчик А.В, Герасимчук М.В., **Мельников** К.П., Григоренко О.О. Синтез флуорованих піразолів та піримідинів зфрагментами насичених гетероциклічних амінів. *XXIII Міжнародна конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії»*, 18-20 травня **2022** р., м Київ, с.64.

4. Підвишенний О.Р., Смирнов О.К., **Мельников** К.П., Григоренко О.О. Сульфоксіміни ароматичного ряду з флуоровмісними замісниками. *XXIII Міжнародна конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії»*, 18-20 травня **2022** р., м. Київ, с.81.

ВИСНОВКИ

У дисертаційному дослідженні запропоновано низку синтетичних підходів до флуорованих насичених карбо- та гетероциклічних будівельних блоків з розміром циклу від 3-х до 7-ми атомів та їх біциклічних аналогів. Встановлено оптимальні варіанти введення атомів Флуору у перелічені вище фрагменти та більш складні органічні молекули на їх основі. Шляхом системних експериментальних досліджень встановлено основні закономірності природи флуоровмісного угрупування на фізико-хімічні характеристики синтезованих та відомих раніше речовин, зокрема таких, як кислотність/основність (pK_a) та ліпофільність (Log$P$). Показано, що кислотність/основність (pK_a) може бути з достатньою точністю описана лінійними емпіричними залежностями, тоді як закономірності варіацій ліпофільності та розчинності у воді мають більш складний характер і не можуть бути описані простими правилами.

1. Показано, що класичні реагенти для введення флуоровмісних замісників (зокрема, реагенти деоксофлуорування чи реагент Руперта-Пракаша) можуть бути використані для синтезу *N*-заміщених дифлуороциклопропанів, 1,2-дизаміщених CF_3-, CHF_2 та CH_2F-вмісних циклобутанів, похідних 4,4-дифлуороспіро[2.2]пентану, всіх ізомерних *гем*-дифлуорованих похідних циклогептану та нітрогеновмісних біциклоалканів, що містять α-CF_3 фрагмент біля вузлового атома Карбону. Стратегією послідовних реакцій функціоналізації подвійного зв’язку з внутрішньомолекулярним алкілуванням єноляту було отримано доступ до похідних біцикло[4.1.1]- та -[3.2.1]октану, біцикло[2.2.1]- та -[3.2.0]гептану, біцикло[3.1.0]гексану, а також біцикло[2.1.0]пентану (хаузану). Також продемонстровано, що з використанням нестабільних дифлуороциклоропанів як джерела флуорованого фрагменту можна легко отримати флуоровмісні ароматичні гетероцикли, що містять насичені циклічні фрагменти, та *гем*-дифлуоровані оксетани.

2. Встановлено, що у випадку нітрогеновмісних гетероциклів кислотно-основні властивості переважно залежать від положення флуоровмісного замісника, і найбільший ефект очікувано проявляється для α-флуороалкіл-заміщених гетероциклів та є пропорційним кількості атомів Флуору у замісннику. Виявлено, що за появи додаткових місткових атомів Карбону у біциклічних амінів вплив флуороалкільного замісника на pK_a частково компенсується, тоді як введення атомів Флуору безпосередньо в цикл також призводить до зниження основності атома Нітрогену, що є особливо вираженим для *гем*-дифлуорованих похідних. Виявлено, що введення флуороалкільних замісників підвищує (за деякими винятками) ліпофільність модельних похідних гетероциклічних амінів, тоді як ведення окремих атомів Флуору має немонотонний ефект – монофлуоропохідні є менш ліпофільними за нефлуоровані сполуки, тоді як *гем*-дифлуоровані – зазвичай більш ліпофільними.
3. Для похідних насичених оксигеновмісних гетероциклів продемонстровано адитивність впливу окремих структурних елементів (ендоциклічного атома Оксигену та екзоциклічних атомів Флуору) на кислотність/основність функціональних груп. У той же час передбачення ліпофільності з використанням простих адитивних моделей давало значні відхилення, і у цьому випадку закономірності мали складний немонотонний характер.
4. За допомогою представлення одержаних результатів у координатах pK_a – Log$P$ показано, що досліджувані у роботі насичені флуоровмісні циклічні системи при введенні у потенційні нові лікарські засоби можуть бути як взаємозамінними (тобто мати близькі фізико-хімічні характеристики за значних структурних відмінностей), так і взаємодоповнюваними (тобто значно відрізнятися за фізико-хімічними характеристиками за схожих структурних особливостей), що може бути використано для раціональної оптимізації у медичній хімії.
5. Висловлено гіпотезу про опосередкований вплив флуорування на ліпофільність насичених карбо- та гетероциклічних похідних та

одержано низку експериментальних і розрахункових доказів на її користь. Зокрема, введення атома флуору в аліфатичні похідні викликає значне підвищення поляризації сусідніх зв'язків C–H, що може бути причиною часто спостережуваного зниження значення Log*P*. Навпаки, у випадку наявності у молекулі інших електроноакцепторних замісників заміна зв'язків C–H, що легко поляризуються сусідніми акцепторами електронної густини, на несприйнятливі до такої поляризації зв'язки C–F може приводити до підвищення ліпофільності.

6. Показано, що синтезовані у межах даної роботи будівельні блоки є ефективними для введення флуорованих насичених циклічних замісників в умовах паралельного синтезу, зокрема, з використанням двостадійної послідовності відновного амінування – «видалення Нітрогену» за Левіним або ж реакції Мініші.

ДОДАТОК 1. СПИСОК ПУБЛІКАЦІЙ ЗДОБУВАЧА

Статті в іноземних виданнях:

1. Grygorenko O. O.; **Melnykov K. P.**; Holovach S.; Demchuk O. Fluorinated cycloalkyl building blocks for drug discovery. *ChemMedChem* **2022**, *17*, e202200365. DOI: 10.1002/cmdc.202200365. [**Q1**]. *(Особистий внесок здобувача: аналіз літературних даних, участь у написанні статті).*

2. **Melnykov K. P.**; Nazar, K.; Smyrnov O.; Skreminskyi A.; Pavlenko S.; Klymenko-Ulianov O.; Shishkina S.; Volochnyuk D. M.; Grygorenko O. O. Mono- and difluorinated saturated heterocyclic amines for drug discovery: systematic study of their physicochemical properties. *Chem. Eur. J.* **2023**, *29* (47), e202301383. DOI: 10.1002/chem.202301383. [**Q1**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, участь у написанні статті).*

3. **Melnykov** K. P.; Tavlui O.; Skreminskiy A.; Kuchkovska Y. O.; Grygorenko O. O. Impact of fluoroalkyl substituents on physicochemical properties of saturated heterocyclic amines. *Chem. Eur. J.* **2022**, e202201601. DOI: 10.1002/chem.202201601. [**Q1**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, участь у написанні статті).*

4. Liashuk O. S.; Fedinchyk A.; **Melnykov K. P.**; Herasymchuk M.; Alieksieieva D.; Lesyk D.; Bas Y. P.; Keda T. Y.; Yatsymyrskiy A. V.; Holota Y.; Borysko P.; Yarmolchuk V. S.; Grygorenko O. O. 3,3-Difluorooxetane – a versatile functional group for bioisosteric replacements in drug discovery. *Chem. Eur. J.* **2024**, *30*(72), e202403277. DOI: 10.1002/chem.202403277. [**Q1**]. *(Особистий внесок здобувача: планування дослідження, участь у написанні статті).*

5. Semeno V. V.; Vasylchenko V. O.; Fesun I. M.; Ruzhylo L. Yu.; Kipriianov M. O.; **Melnykov K. P.**; Skreminskyi A.; Iminov R.; Mykhailiuk P.; Vashchenko

B. V.; Grygorenko O. O. Bicyclo[m.n.k]alkane building blocks as promising benzene and cycloalkane isosteres: multigram synthesis, physicochemical and structural characterization. *Chem. Eur. J.* **2024**, 30 (12), e202303859. DOI: 10.1002/chem.202303859. [**Q1**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних).*

6. **Melnykov K. P.**; Liashuk O. S.; Holovach S.; Shatnia V.; Horbenko A.; Lesyk D.; Melnyk V.; Skrypnik D.; Beshtynarska A.; Borysko P.; Viniichuk O.; Grygorenko O. O. Physicochemical and biological evaluation of *gem*-difluorinated saturated oxygen heterocycles as bioisosteres for drug discovery *Chem. Eur. J.* **2024**, e202404390. DOI: 10.1002/chem.202404390. [**Q1**]. *(Особистий внесок здобувача: планування дослідження, участь у написанні статті).*

7. Nosik P. S.; Poturai A. S.; Pashko M. O.; Melnykov K. P.; Ryabukhin S. V.; Volochnyuk D. M.; Grygorenko O. O. *N*-Difluorocyclopropyl-substituted pyrazoles: synthesis and reactivity. *Eur. J. Org. Chem.* **2019**, *27*, 4311–4319. [**Q1**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних).*

8. Holovach S.; **Melnykov K. P.**; Poroshyn I.; Iminov R. T.; Dudenko D.; Kondratov I. S.; Levin M.; Grygorenko O. O. C–C coupling through Nitrogen deletion: application to library synthesis. *Chem. Eur. J.* **2023**, *29*, e202203470. DOI: 10.1002/chem.202203470. [**Q1**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, участь у написанні статті).*

9. Holovach S.; Poroshyn I.; **Melnykov K. P.**; Liashuk O. L.; Pariiska O. O.; Kolotilov S. V.; Rozhenko A. B.; Volochnyuk D. M.; Grygorenko O. O. Parallel Minisci reaction of *gem*-difluorocycloalkyl building blocks. *ACS Org. Inorg. Au* **2024**, *4*(4), 424–431. DOI: 10.1021/acsorginorgau.4c00028. [**Q1**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, участь*

у написанні статті).

10. Grygorenko O. O.; **Melnykov K. P.** Fluorinated building blocks in drug design: new pathways and targets. *Future Med. Chem.* **2024,** *16(14)*, 1375–1378. [**Q2**]. *(Особистий внесок здобувача: аналіз літературних даних, участь у написанні статті)*.

11. Herasymchuk M.; **Melnykov K. P.**; Yarmoliuk D. V.; Serhiichuk D.; Rotar V.; Pukhovoi T.; Kuchkovska Yu. O.; Holovach S.; Volochnyuk D. M.; Ryabukhin S. V.; Grygorenko O. O. Last of the *gem*-difluorocycloalkanes 2: synthesis of fluorinated cycloheptane building blocks. *Eur. J. Org. Chem.* **2021**, 6568–6576. DOI: 10.1002/ejoc.202001530. [**Q2**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, участь у написанні статті).*

12. Demchuk O. P.; Hryshchuk O. V.; Vashchenko B. V.; Trofymchuk S. A.; **Melnykov K. P.**; Skreminskiy A.; Volochnyuk D. M.; Grygorenko O. O. Fluoroalkyl-containing 1,2-disubstituted cyclobutanes: advanced building blocks for medicinal chemistry. *Eur. J. Org. Chem.* **2021**, 87–95. DOI: 10.1002/ejoc.202001345. [**Q2**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, участь у написанні статті).*

13. **K. P. Melnykov**, O. V. Voloshyna, B. V. Vashchenko, O. P. Demchuk, O. V. Hryshchuk, O. O. Grygorenko. 4,4-Difluorospiro[2.2]-pentan-1-yl – a fluorinated substituent to expand the synthetic and medicinal chemists' toolbox. *Eur. J. Org. Chem.* **2022**, e202200863. [**Q2**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, участь у написанні статті).*

14. Smyrnov O.; **Melnykov K. P.**; Semeno V.; Liashuk O. S.; Grygorenko O. O. α-CF_3-Substituted saturated bicyclic amines: advanced building blocks for medicinal chemistry. *Eur. J. Org. Chem.* **2024**, *27* (1), e202300935. DOI: 10.1002/ejoc.202300935. [**Q2**]. *(Особистий внесок здобувача: планування*

дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, участь у написанні статті).

15. Fedinchyk A.; Herasymchuk M.; Smirnov O. V.; **Melnykov K. P.**; Yarmoliuk D. V.; Kyrylchuk A. A.; Grygorenko O. O. Fluorine-containing sp^3-enriched building blocks for the multigram synthesis of fluorinated pyrazoles and pyrimidines with (hetero)aliphatic substituents. *Eur. J. Org. Chem.* **2022**, e202200274. DOI: 10.1002/ejoc.202200274. [**Q2**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, участь у написанні статті).*

16. Pidvyshennyi O.; **Melnykov K. P.**; Liashuk O.; Lesyk D.; Holota Y.; Borysko P.; Grygorenko O. O. Acidity of saturated (hetero)cyclic *α*-fluoro carboxylic acids and lipophilicity of their amide derivatives. *J. Fluorine Chem.* **2024**, *278*, 110316. DOI: 10.1016/j.jfluchem.2024.110316. [**Q3**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, участь у написанні статті).*

17. **Melnykov** K. P.; Liashuk O. S.; Smyrnov O.; Lesyk D.; Holota Y.; Borysko P.; Yakubovskyi V.; Grygorenko O. O. Lipophilicity effects of monofluorination at the tertiary aliphatic carbon as a function of *α*-substituent. *J. Fluorine Chem*. **2025**, *281*, 110384. DOI: 10.1016/j.jfluchem.2024.110384. [**Q3**]. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, участь у написанні статті).*

18. Ryabukhin S.V.; **Melnykov K. P.** Synthesis of α-spirocyclic pyrrolidines. *Chem. Heterocycl. Compd*. **2020,** *56,* 1411–1413. [**Q4**]. *(Особистий внесок здобувача: аналіз літературних даних, участь у написанні статті).*

Статті у наукових фахових виданнях України:

19. Semeno, V. V., and **K. P. Melnykov**. Multigram Synthesis of *β*-Fluorinated Saturated Heterocyclic Methanamines. *Ukrainica Bioorganica Acta* **2023,** 18 (2), 16–21. DOI: 10.15407/bioorganica2023.02.016. *(Особистий внесок*

здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, написання статті).

20. **Мельников К.**, Підвишенний О., Смирнов О., Григоренко О. Флуоровані сульфоксіміни жирноароматичного ряду: масштабований синтез і вплив структурних елементів на ліпофільність. *ВІСНИК Київського національного університету імені Тараса Шевченка* **2024**, *1* (59), 1–5. DOI: 10.17721/1728-2209.2024.1(59). *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, участь у написанні статті).*

21. **Holovach** S. M.; **Melnykov**, **K. P.**; Poluektova M. S.; Rozhenko O. B.; Grygorenko O. O. Incorporation of *gem*-difluorocycloalkyl substituents into heterocycles via the Levin's "nitrogen deletion" strategy. *J. Org. Pharm. Chem.* **2023**, 21(3), 11–16. DOI: 10.24959/ophcj.23.278321. *(Особистий внесок здобувача: планування дослідження, аналіз експериментальних даних, узагальнення отриманих результатів, участь у написанні статті).*

ТЕЗИ НАУКОВИХ ДОПОВІДЕЙ

1. Герасимчук М.В., **Мельников** К.П., Рябухін С.В. Синтез білдінг-блоків на основі *гем*-дифлуорциклогептанів. *XX Міжнародна конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії»*, 15-17 травня **2019** р., м. Київ, с.103.

2. Олександр Григоренко, Костянтин **Мельников**, Сергій Головач, Олександр Демчук, Олександр Грищук, Антон Черних, Богдан Ващенко, Дмитро Волочнюк. Фізико-хімічні властивості насичених флуоровмісних карбо- та гетероциклів для потреб медичної хімії. *XIX наукова конференція «Львівські хімічні читання - 2023»*, 29-31 травня **2023** р., м. Львів, с.12

3. Бондарук А.А., **Мельников** К.П., Ляшук О.С., Григоренко О.О., Бас Ю.П., Кеда Т.Є. Нові пара-нітрофенольні естери пара-заміщених бензойних кислот як перспективні субстрати pNP-тесту. *XXV Міжнародна*

конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії», 15-17 травня **2024** р., м. Київ, с.39.

4. Федінчик А.В., Герасимчук М.В., **Мельников** К.П., Ляшук, О. С., Григоренко О.О. 3,3-Дифлуорооксетан-2-іл – перспективний флуоровмісний замісник для потреб медичної хімії. *XXV Міжнародна конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії»*, 15-17 травня **2024** р., м. Київ, с.124.

5. Шатня В.Ю., Горбенко А.Е., Головач С.М, **Мельников** К.П., Ляшук О.С., Григоренко О.О. Дослідження фізико-хімічних властивостей *гем*-дифлуорованих о-гетероциклів. *XXV Міжнародна конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії»*, 15-17 травня **2024** р., м. Київ, с.156

6. Волошина О.В., **Мельников** К.П., Шабликіна О.В., Григоренко О.О. Функціоналізовані похідні 4,4-дифлуороспіро[2.2]пентану. *XXIII Міжнародна конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії»*, 18-20 травня **2022** р., м. Київ, с.87.

7. Головач С., **Мельников** К., Порошин І., Григоренко О., Волочнюк Д., Роженко О. Впровадження методу утворення С-С зв’язку шляхом «видалення азоту» у комбінаторні хімію. *XIX наукова конференція «Львівські хімічні читання - 2023»,* 29-31 травня **2023** р., м. Львів, с.41.

8. Полуектова М., Головач С., **Мельников** К. П., Григоренко О. О. Введення *гем*-дифлуороциклоалкільних замісників у гетероцикли через стратегію «видалення нітрогену» Левіна. *XXIV Міжнародна конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії»*, 17-19 травня **2023** р., м. Київ, с.107.

9. Федінчик А.В, Герасимчук М.В., **Мельников** К.П., Григоренко О.О. Синтез флуорованих піразолів та піримідинів з фрагментами насичених гетероциклічних амінів. *XXIII Міжнародна конференція студентів,*

аспірантів та молодих вчених «Сучасні проблеми хімії», 18-20 травня **2022** р., м. Київ, с.64.

10. Підвишенний О.Р., Смирнов О.К., **Мельников** К.П., Григоренко О.О. Сульфоксіміни ароматичного ряду з флуоровмісними замісниками. *XXIII Міжнародна конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії»*, 18-20 травня 2022 р., м. Київ, с.81.

ДОДАТОК 2. ОСНОВНІ ПУБЛІКАЦІЇ ЗА ТЕМОЮ ДИСЕРТАЦІЇ. КОПІЇ СТАТЕЙ

Fluorinated Cycloalkyl Building Blocks for Drug Discovery

Oleksandr O. Grygorenko,*[a,b] Kostiantyn P. Melnykov,[a,b] Serhii Holovach,[a,c] and Oleksandr Demchuk[a,c]

Dedicated to the memory of Oleksandr Korsun, a chemistry researcher who was killed in the shelling of Kharkiv on April 7, 2022



[a] Enamine Ltd.
Chervonoltatska Street 78, Kyiv 02094, Ukraine
URL: www.enamine.net
[b] Taras Shevchenko National University of Kyiv
Volodymyrska Street 60, Kyiv 01601, Ukraine
E-mail: gregor@univ.kiev.ua
[c] Institute of Organic Chemistry, National Academy of Sciences of Ukraine
Murmanska Street 5, Kyiv 02660, Ukraine

Abstract: The review covers various aspects of fluorinated cycloalkyl (C_3–C_7) building blocks for drug discovery, including their synthesis, key physicochemical properties, and biological and medicinal applications of their derivatives. The discussed synthetic methods include classical nucleophilic fluorinations of various substrates, the addition of fluorine and another heteroatom to double bonds, cycloadditions and other transformations of fluorine-containing substrates, as well as some newer reactions like fluorination of non-activated and remotely activated C–H bonds, decarboxylative and deborylative fluorinations, etc. The known data on the effect of introducing the fluorinated cycloalkyl groups on the compound's key in vitro parameters (such as acidity/basicity, lipophilicity, conformational behavior, and short contact capabilities) are surveyed. Finally, applications of fluorinated cycloalkyl building block derivatives in the design of biologically active compounds (including marketed drugs Maraviroc, Ivosidenib, and Sitafloxacin) are covered, with a focus on the fluorination impact.

1. Introduction

It is widely recognized that organofluorine compounds have a special place in drug discovery.[1–7] Sooner or later, almost any modern medicinal chemistry project comes to structural modifications involving fluorine atoms or fluorinated substituents.[5,8–11] Typically, such modifications are aimed at fine-tuning the compound's physicochemical properties such as acidity/basicity, lipophilicity, or solubility, as well as improving its metabolism.[5,8,12–14] On the other hand, fluorine atoms provide numerous possibilities to improve the compound's affinity to biological targets through weak non-covalent interactions, resulting in increased potency.[15–19] Also, conformational effects can be involved.[20]

Until recently, the fluorine-containing drugs were dominated by monofluoro and trifluoromethyl derivatives of (hetero)aromatic systems.[21] The situation seems to be changing: more and more attention is being paid to other fluorinated moieties – a part of a more general trend in medicinal chemistry focusing on unusual, often historically overlooked, motifs.[22] In an excellent recent book edited by Cahard and Ma, such "emerging fluorinated motifs" have been surveyed thoroughly.[3] Most of them were small fluorinated groups, often including additional heteroatoms (e.g., CHF_2, CH_2F, OCF_3, SCF_3, or SF_5).

In this paper, we would like to focus on other structural motifs that were to some extent overlooked by the previous authors – fluorinated cycloalkyl substituents. Indeed, although we have contributed a chapter into the book mentioned above on *gem*-difluorocyclopropanes[23] (there are also other reviews on fluorinated cyclopropanes[24–30]) and briefly discussed other *gem*-difluorinated cycloalkanes in a recent review on building blocks for medicinal chemistry,[22] fluorine-substituted cycloalkanes were not surveyed in the literature in general to date. Meanwhile, four non-steroid drugs bearing such moieties have already been introduced into the market:[31] an anti-HIV agent Maraviroc, anti-cancer agents Ivosidenib and Belzutifan, and positron emission tomography (PET) tracer Fluciclovine (Figure 1), which clearly demonstrates significance of the fluorinated cycloalkanes in medicinal chemistry.

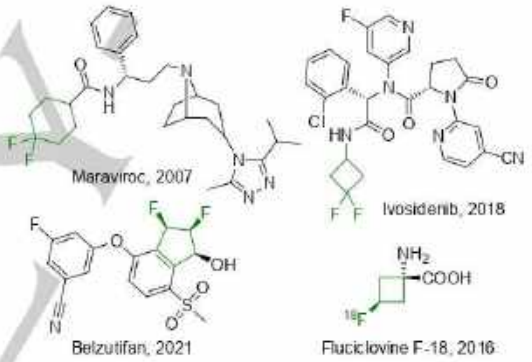


Figure 1. FDA-approved drugs containing fluorinated cycloalkane motifs

This review discusses advanced building blocks that can be used to incorporate fluorinated cycloalkyl substituents (C_3 to C_7) into molecules of interest to drug discovery. The title compounds are categorized according to the number of fluorine atoms (mono-, di-, and polyfluorinated), fluorination position(s), and the cycloalkane ring size. The discussion is limited to the compounds bearing the parent fluorinated cycloalkyl moieties without any additional substituents in the ring apart from the fluorine atoms and the functional group (attached either directly or through a linker). Synthetic approaches to such building blocks, successful examples of their application in medicinal chemistry, and properties relevant to drug discovery are covered. Special attention is paid to positive effects achieved upon the fluorination in the hit-to-lead or lead-to-candidate optimization process (if the corresponding information is available in the original work). At the end, fluorinated cycloalkyl substituents and the corresponding building blocks types not known or underrepresented in the literature are outlined.

2. Synthesis of monofluorinated cycloalkyl building blocks

All 16 theoretically possible monofluorinated C_3–C_7 building block types have been reported in the literature to date (the stereochemistry is not taken into account at this point). Among them, monofluorinated cyclopropyl, 3-fluorocyclobutyl, and 2-fluorocyclohexyl derivatives were presented particularly well, whereas 2-fluorocyclobutyl, 3-fluorocyclohexyl, and monofluorinated cycloheptyl counterparts – more or less scarcely (Figure 2).

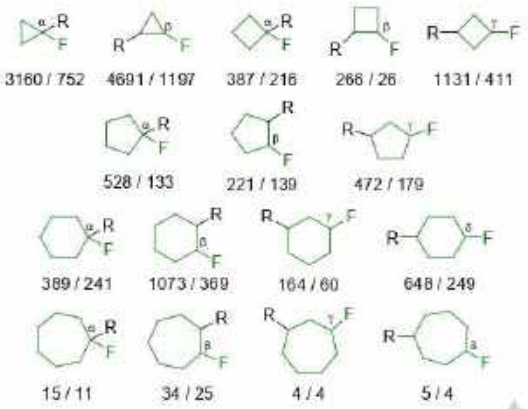


Figure 2. Number of compounds bearing monofluorinated C_3–C_7 cycloalkyl substituents / document referring to them in *Reaxys*® Database (accessed on 11-03-2022)

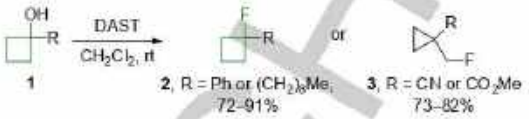
2.1. Synthesis of α-fluorinated cycloalkyl building blocks

The known synthetic approaches to α-fluorinated cycloalkyl building blocks can be categorized into one of the following categories:

- nucleophilic substitution with fluoride;
- spirocyclic oxirane ring opening with fluoride;
- addition of fluorine and another heteroatom to double bond;
- electrophilic α-fluorination;
- fluorination at the non-activated C–H bonds;
- other fluorinative methods;
- cyclizations and cycloadditions of fluorinated intermediates;
- transformations of compounds already containing the α-fluorinated cycloalkyl moiety.

Nucleophilic substitution with fluoride. This approach is challenging in the case of α-fluorinated cycloalkyl building blocks since it requires the nucleophilic attack at the tertiary carbon center, where elimination and rearrangements are common. For example, deoxyfluorination of tertiary cyclobutanols **1** with diethylaminosulfur trifluoride (DAST) succeeded only with alkyl- or aryl-substituted substrates; with more interesting substrates bearing electron-withdrawing groups (R = CN or CO_2Me), cyclopropane derivatives **3** were obtained instead of the target products (Scheme 1).[32] Nevertheless, this method might still be considered for the synthesis of building blocks with a functional group attached to the ring through an aliphatic chain.

In 2016, Nishikata and co-workers addressed the nucleophilic fluorination issue in tertiary α-bromocarbonyl compounds using a copper catalyst – CsF system.[33] The method worked well for a series of α-bromoanilides including alicyclic ones (Scheme 2). Later in 2021, Mizuta and co-authors described alternative conditions for this transformation using AgF as the fluoride source.[34] Unfortunately, none of the authors demonstrated the possibility of hydrolyzing amides **5** to obtain the corresponding carboxylic acids.



Scheme 1. Deoxyfluorination of tertiary cyclobutanols



Prof. Dr. Oleksandr O. Grygorenko received MS (2004), PhD (2007), and Dr.Sc. (2019) in organic chemistry from Taras Shevchenko National University of Kyiv. At present, he shares his time between his *alma mater* as full professor and senior researcher, and Enamine Ltd. (Kyiv, Ukraine) as consulting scientist. His scientific interests focus between organic synthesis and medicinal chemistry, including lead-oriented synthesis, organoboron, -fluorine, and -sulfur chemistry, non-proteinogenic amino acids, etc. Oleksandr is a co-author of more than 180 papers and 5 monograph chapters.



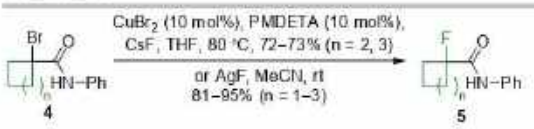
Dr. Kostiantyn P. Melnykov received MS (2013) and PhD (2020) in organic chemistry from Taras Shevchenko National University of Kyiv. At the moment, he is scientific researcher at his *alma mater* and group leader at Enamine Ltd. His scientific interests include organofluorine, organometallic, heterocyclic, and medicinal chemistry. Kostiantyn is a co-author of 15 papers.



Serhii Holovach received MS in organic chemistry from Taras Shevchenko National University of Kyiv in 2001. Today, he is PhD student at Institute of Organic Chemistry, NAS of Ukraine, and group leaded at Enamine Ltd. He is interested in organic synthesis, organoboron, -fluorine, and -sulfur chemistry, and medicinal chemistry. Serhii is also a co-author of 10 papers and 2 patents.

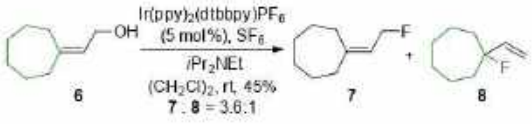


Oleksandr Demchuk received MS in chemistry from Taras Shevchenko National University of Kyiv in 2019. At present, he is PhD student at Institute of Organic Chemistry, NAS of Ukraine, and chemist at Enamine Ltd. His scientific interests include organofluorine, organoboron and organometallic chemistry. Oleksandr is a co-author of 3 papers.



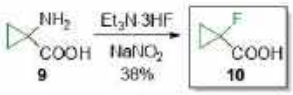
Scheme 2. Fluorination of alicyclic tertiary α-bromoamides (PMDETA – *N,N,N',N'',N''*-pentamethyldiethylenetriamine)

An interesting deoxyfluorination reaction (albeit of limited applicability to the target molecules of this review) was reported by McTeague and Jamison in 2016.[35] Under photoredox activation, normally inert sulfur hexafluoride reacted with allylic alcohol **6** to give a mixture of unsaturated fluorides **7** and **8** (Scheme 3).



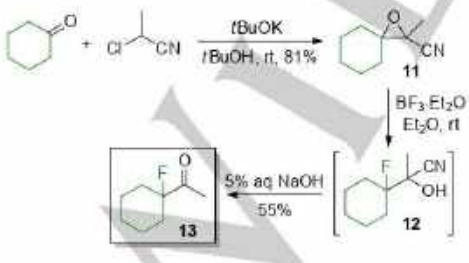
Scheme 3. Deoxyfluorination of alcohol **6** with SF_6 (ppy – 2-(pyridin-2-yl)phenyl, dtbppy – 4,4-di-*tert*-butyl-2,2-dipyridyl)

Also, synthesis of α-fluorocyclopropane carboxylic acid (**10**) by fluorinative diazotization of corresponding amino acid **9** was disclosed in a recent Chinese patent (Scheme 4).[36]



Scheme 4. Fluorinative diazotization of amino acid **9**

Spirocyclic oxirane ring opening with fluoride. In 1960, Stork and co-authors described the reaction of the so-called "glycidonitrile" **11** (in turn obtained by the Darzens reaction of cyclohexanone and α-chloropropionitrile) with BF_3·Et_2O (Scheme 5).[37] After basic work-up of intermediate cyanohydrin **12**, α-fluoroketone **13** was obtained in 55% yield (with a minor HF elimination by-product).

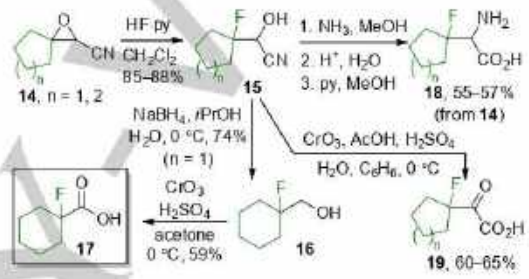


Scheme 5. Synthesis of α-fluoroketone **13**

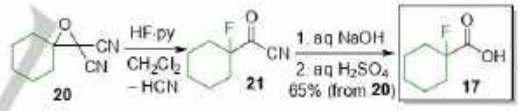
Later in the 1980s, cyanohydrins **15** or the corresponding α-hydroxy esters were obtained in a similar fashion from spirocyclic glycidonitriles (**14**) and glycidic esters, respectively, and used to synthesize several α-fluorocycloalkyl building blocks, e.g. carboxylic acid **17**,[38] amino acids **18**,[39–41] α-ketoacids **19**,[42] or derivatives thereof[41,43] (Scheme 6).

Alternatively, carboxylic acid **17** or its derivatives were obtained via ring opening of spirocyclic dinitriles **20** (Scheme 7).[44] Analogously, α-ketoester **24** was prepared from cyanoester **22** (Scheme 8).[45]

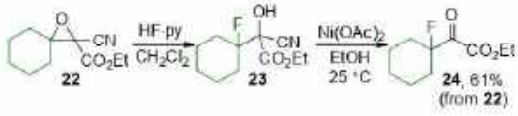
Addition of fluorine and another heteroatom to double bond. Electrophilic addition to an exocyclic double bond accompanied by reaction with nucleophilic fluorine source is a general approach to α-fluorinated cycloalkyl building blocks. Typically, Cl, Br or I are used as the electrophile; the reported conditions include the use of I_2 – AgF in MeCN,[46] *t*BuOCl, *t*BuOBr, or MeOCl – Et_3N·3HF in CH_2Cl_2,[47] and NBS – Et_3N·3HF in CH_2Cl_2.[48,49] The latter method worked well for C_4 to C_7 cycloalkanes **25** (Scheme 9). With methylenecyclopropane, the reaction was not regioselective, and the target product of type **25** was the minor one.[48]



Scheme 6. Synthesis of α-fluorocycloalkyl building blocks via ring opening of spirocyclic glycidonitriles **14**



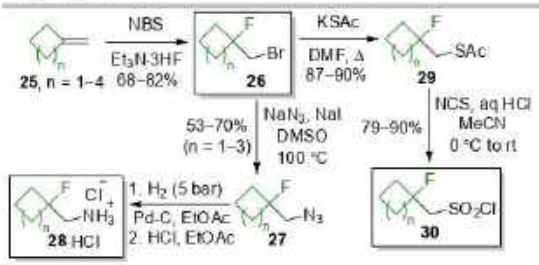
Scheme 7. Synthesis of carboxylic acid **17** from spirocyclic dinitrile **20**



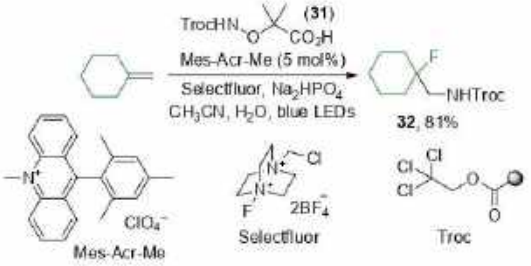
Scheme 8. Synthesis of α-ketoester **17** from spirocyclic cyanoester **20**

Apart from fluorinated bromides **26** and other halides, the approach was applied for the preparation of other building blocks, including azides **27**, amines **28**,[48] and sulfonyl chlorides **30**.[49]

In 2018, Jiang and Studer reported a somewhat related process, namely, metal-free radical amidofluorination, that was applied successfully to methylenecyclohexane (Scheme 10).[50] The reaction starts with oxidative cleavage of precursor **31** giving CO_2, acetone, and amidyl radical TrocHN•. The latter intermediate then adds to the double bond of the substrate, and the tertiary radical formed abstracts the fluorine atom from Selectfluor, eventually giving target product **32**.

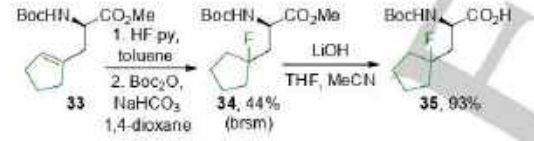


Scheme 9. Synthesis of α-fluorocycloalkyl building blocks via addition of bromine and fluorine to exocyclic double bond



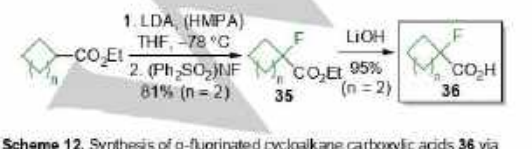
Scheme 10. Metal-free radical amidofluorination of methylenecyclohexane

Jackson and co-workers reported hydrofluorination of cyclopentene derivative **33** giving *N*-Boc-protected amino acid **35** after an additional hydrolysis step (Scheme 11).[51]



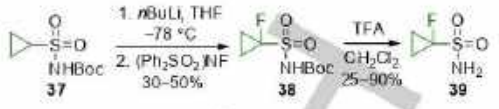
Scheme 11. Synthesis of *N*-Boc protected amino acid **35** (brsm – based on recovered starting material)

Electrophilic α-fluorination. The reaction of lithium or silyl enolates obtained from alicyclic carboxylates with electrophilic fluorinating agents provides straightforward access to α-fluorinated cycloalkane carboxylic acids **36** (Scheme 12). This method was used for the preparation of the corresponding C_4 to C_7 building blocks (albeit for the cyclobutane[52] and cyclopentane[53] derivatives, this was documented only in patents). *N*-fluorobis(benzenesulfon)imide (NFSI),[52,53] acetyl hypofluorite (generated in situ from F_2 and AcONa),[54] and $FClO_3$[55] were used as the fluorinating agents.



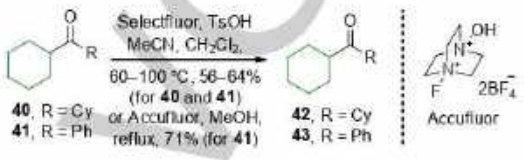
Scheme 12. Synthesis of α-fluorinated cycloalkane carboxylic acids **36** via electrophilic fluorination

Nearly the same method was also used for the synthesis of α-fluorinated sulfonamide **37** (Scheme 13).[56]



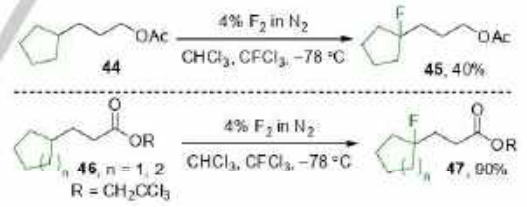
Scheme 13. Synthesis of α-fluorinated sulfonamide **39** via electrophilic fluorination

In the case of ketones **40** and **41**, direct flurination with Selectfluor or Accufluor[57] reagents was possible, without preliminary enolate formation (Scheme 14).



Scheme 14. Direct electrophilic fluorination of ketones **40** and **41**

Fluorination at the non-activated C–H bonds. Fluorination at the C–H bonds remote from the functional groups is an exciting approach to the fluorinated building blocks, and it has received much attention recently.[58] For the substrates discussed in this section, the situation is somewhat facilitated with the tertiary position of the reacting C–H bond. In this case, the required regioselectivity could be achieved even with F_2 as the fluorinating reagent (Scheme 15).[59,60] The authors proposed an electrophilic reaction mechanism involving the formation of a complex between F_2 and the solvent ($CHCl_3$).



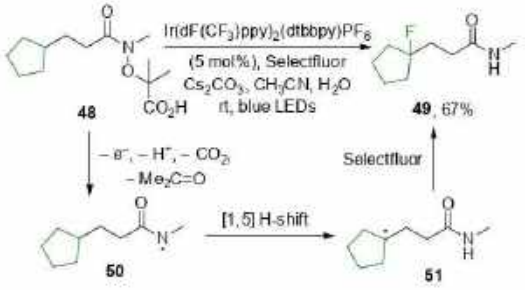
Scheme 15. Synthesis of functionalized α-monofluorinated cycloalkanes via the fluorination of non-activated C–H bonds with F_2

Recent achievements in this area rely on the use of milder fluorinating reagents. In particular, Leonori and co-workers reported remote fluorination of amide **48** involving formation of electrophilic nitrogen radical **50** (Scheme 16; compare with Scheme 10).[61]

Similar idea was used by Yu and co-workers; in this case, the corresponding oxygen-centered radical intermediate was formed after the cleavage of precursor **52** (Scheme 17).[62] Analogously, Liu and co-authors described iron-catalyzed fluorination of peroxide **54** also providing alcohol **53** (Scheme 18).[63]

In one more mechanistically related example, iodine-catalyzed remote fluorination of sulfonamide **56** occurred upon the action of I_2, iodine (III)-based oxidant, and $Et_3N·3HF$ (Scheme 19).[64] A significant difference is that a nucleophilic source of fluorine was

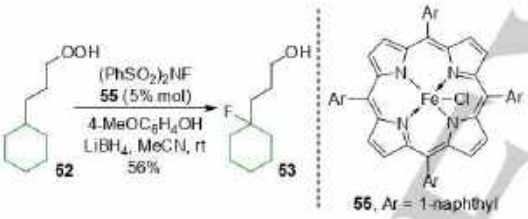
used for the latter reaction; also, much more accessible starting material was involved.



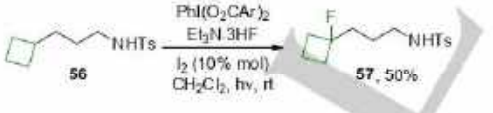
Scheme 16. Remote fluorination of amide **48**



Scheme 17. Remote fluorination of oxime **52** (4CzIPN – 2,3,5,6-tetra(carbazol-9-yl)benzene-1,4-dicarbonitrile)

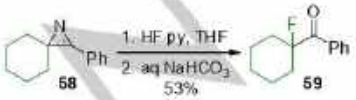


Scheme 18. Remote fluorination of peroxide **54**



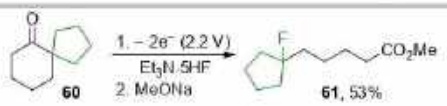
Scheme 19. Remote fluorination of sulfonamide **56**

Other fluorinative methods. In 1978, Alvernhe and co-authors reported ring opening of azirine **57** with HF-py leading to the formation of α-fluorinated ketone **58** (Scheme 20).[65]



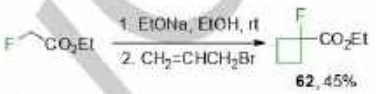
Scheme 20. Reaction of azirine **58** with liquid HF

Oxidative electrolytic cleavage of spirocyclic ketone **60** in $Et_3N{\cdot}5HF$ as an electrolyte followed by methanolysis with MeONa gave α-flurinated ester **61** (Scheme 21).[66]



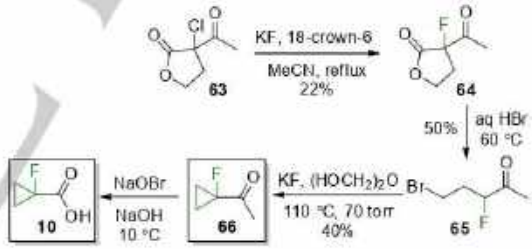
Scheme 21. Reaction of azirine **58** with liquid HF

Cyclizations and cycloadditions of fluorinated intermediates. In 1956, Bergmann and Szinal reported that base-promoted alkylation of α-fluoroacetate with allyl bromide resulted in the formation of α-fluorocyclobutane carboxylate **62** (Scheme 22).[67] In our opinion, the structure of this product should be likely checked by newer spectroscopic methods since the initial assignment was done based on IR spectrum, elemental analysis, and low susceptibility towards hydrogenation.

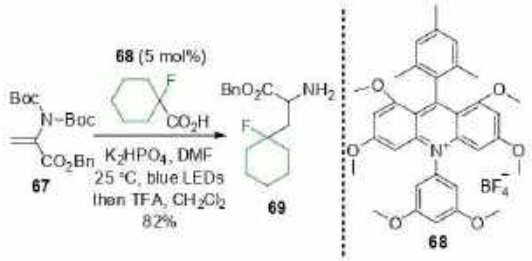


Scheme 22. Base-promoted reaction of α-fluoroacetate and allyl bromide

An important classical work by Fitjer published in 1977 described synthesis of α-fluorocyclopropyl methyl ketone (**66**) from 2-acetyl-2-chlorobutanolide (**63**) via halogen exchange, hydrolysis with aq HBr, and base-promoted cyclization (Scheme 23).[68] Later, compound **63** was used to synthesize carboxylic acid **10** via the haloform reaction.[69]



Scheme 23. Synthesis of α-fluorinated ketone **66** and carboxylic acid **10**



Scheme 24. Synthesis of amino acid derivative **69**

Transformations of compounds already containing the α-fluorinated cycloalkyl moiety. Of course, there are many more or less trivial (functional group) transformations that lead to the α-fluorinated cycloalkyl building blocks. They are not covered in this section, but some of them were already provided above. We

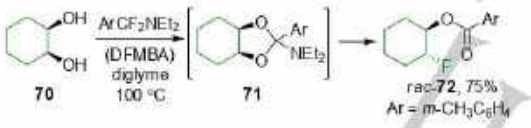
would like to mention here the work of Shah and co-authors published in 2020.[70] They described synthesis of amino acid derivative **69** via visible-light-mediated decarboxylative conjugate addition to dehydroalanine derivative **67** (Scheme 24).

2.2. Synthesis of β-fluorinated cycloalkyl building blocks

β-Fluorinated cycloalkyl building blocks appear to be most explored synthetically. The known approaches to their preparation resemble those for the α-fluorinated counterparts and can be categorized into one of the following categories:

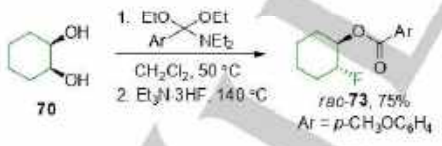
- nucleophilic substitution with fluoride;
- bicyclic oxirane ring opening with fluoride;
- bicyclic aziridine ring opening with fluoride;
- addition of fluorine and another heteroatom to cycloalkene;
- electrophilic C–H fluorination;
- fluorination at the non-activated C–H bonds;
- decarboxylative and deborylative fluorination;
- other fluorinative methods;
- cyclizations and cycloadditions of fluorinated intermediates;
- transformations of compounds already containing the α-fluorinated cycloalkyl or related moiety.

Nucleophilic substitution with fluoride. To date, this approach was limited with the cyclopentane and cyclohexane derivatives. In particular, Hara and co-workers reported selective deoxyfluorination of *cis*-cyclohexane-1,2-diol with *N,N*-diethyl-α,α-difluoro(*m*-methylbenzyl)amine (DFMBA) (Scheme 25).[71] The reaction proceeded with stereoinversion and likely included formation of cyclic amide acetal **71**.



Scheme 25. Monofluorination of *cis*-cyclohexane-1,2-diol (**70**) with DFMBA

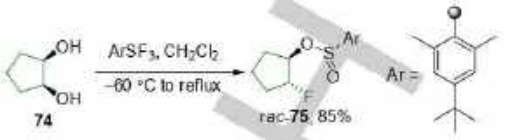
In a similar way, compound **73** was obtained by reaction of diol **70**, *N,N*-diethyl-*p*-methoxybenzamide diethyl acetal, and $Et_3N{\cdot}3HF$ (Scheme 26).[72]



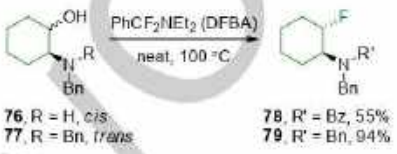
Scheme 26. Monofluorination of *cis*-cyclohexane-1,2-diol (**70**) with *N,N*-diethyl-*p*-methoxybenzamide diethyl acetal and $Et_3N{\cdot}3HF$

Umemoto and co-workers reported that 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride also can be used for monofluorination of 1,2-diols (Scheme 27).[73] Interestingly, sulfinate **75** was obtained with high diastereoselectivity (*dr* 95:5), which is however of little practical significance.

N,N-diethyl-α,α-difluorobenzylamine (DFBA), a close analog of DFMBA, was found to be efficient for the deoxyfluorination of amino alcohols **76** and **77** (Scheme 28).[74] Interestingly, the reaction was stereoinvertive with secondary amine **76** and stereoretentive – with tertiary one (**77**); moreover, *trans*-isomer of **76** gave a complex mixture of products. It was suggested that in the first case, five-membered intermediate of type **71** is in action, whereas in the latter one, aziridinium intermediate is formed instead (so double inversion occurred).

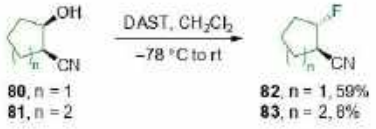


Scheme 27. Monofluorination of *cis*-cyclopentane-1,2-diol (**74**) described by Umemoto and co-authors



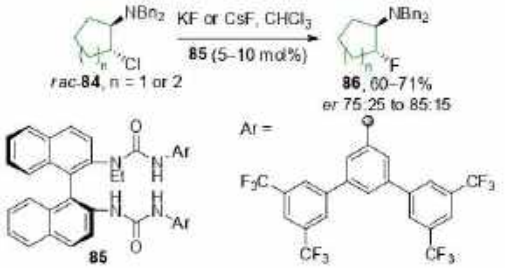
Scheme 28. Deoxyfluorination of amino alcohols **76** and **77** (relative configurations are shown)

It should be noted that more classical deoxyfluorination reagents like diethylaminosulfur trifluoride (DAST) do not work with the aforementioned 1,2-bifunctional substrates and give complex mixtures of products (see, however, the work of Chong and co-workers[75]). Nevertheless, the reaction of nitriles **80** and **81** with DAST allowed preparation of target fluorides, albeit the yield was very low for the second substrate, likely due to the elimination process (59% and 8%, respectively) (Scheme 29).[76]



Scheme 29. Deoxyfluorination of β-hydroxynitriles **80** and **81** (relative configurations are shown)

In 2019, Gouverneur and co-authors reported asymmetric synthesis of fluorinated dibenzylamines **86** involving the use of chiral hydrogen bonding phase-transfer catalyst **85** (Scheme 30).[77] Albeit the method had moderate enantioselectivity, it could be used at up to 200 g (0.5 mol% of **85**, CsF as the fluoride source, n = 2) since the *er* value of the product could be improved to 98:2 after a single recrystallization.[78]



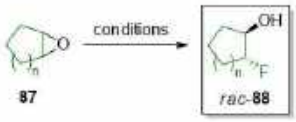
Scheme 30. Asymmetric synthesis of β-fluoroamines **86**

Obviously, the reaction mechanism involved the formation of symmetric bicyclic aziridinium intermediates (see also below).

Bicyclic oxirane ring opening with fluoride. This reaction is one of the oldest and most widely used approaches to β-fluorinated cycloalkyl building blocks. It provides the target compounds in a diastereospecific manner and opens further synthetic possibilities through stereoinvertive substitution at the hydroxyl group.

The first example of fused bicyclic oxirane ring opening with fluoride was described as early as in 1962.[79] Thus, 2-fluorocyclohexanol was obtained in 21% yield by the reaction of cyclohexene oxide and $NaHF_2$ at 150–180 °C (Table 1, Entry 1). Since then, many other conditions were developed; cyclopentane, -hexane, and -heptane derivatives were obtained (Table 1, Entries 2–11). In recent works and patents, $Et_3N{\cdot}3HF$, HF·py (Olah's reagent), or a combination thereof are typically used.

Table 1. Examples of cycloalkene oxide ring opening with fluoride sources

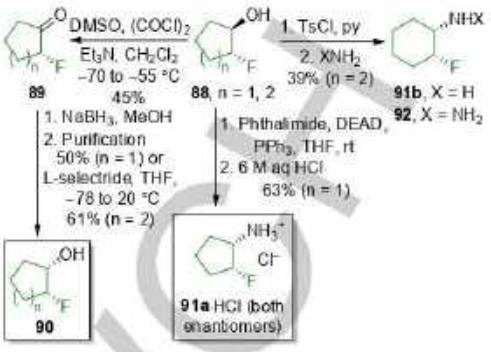


#	n	Conditions	Yield, %	Ref.
1	2	$NaHF_2$, 150–180 °C	21	[79]
2	2	HF, MeCN, 0 °C	33	[80]
3	1, 2	HF·py (42% w/w), $CHCl_3$, 20 °C	65–80	[81]
4	2	$Bu_4N^+H_2F_3^-$ (10 mol%), KHF_2, 120 °C	71	[82]
5	1	TBAF, HF·py, 0 °C to rt	50	[83]
6	2	KH_2F_3, $(CH_2Cl)_2$, 80 °C	8	[84]
7	2	$Bu_4N^+HF_2^-$ (10 mol%), KHF_2, heptane, 120 °C	71	[85]
8	2, 3	$Et_3N{\cdot}3HF$, 115–155 °C	69–71	[86]
9	2	$Et_3N{\cdot}3HF$, μW, 2 min	61	[87]
10	2	[emim]F·2.3HF,[a] MeOH (cat.), CH_2Cl_2, 25 °C	55	[88]
11	1	$Et_3N{\cdot}3HF$, HF·py, rt	50	[89]

[a] emim = 1-ethyl-3-methylimidazolium

trans-2-Fluorocycloalkanols **88** (n = 1, 2) were used to prepare other building blocks via the common functional group transformations, e.g. α-fluoroketones **89**,[89–91] *cis*-2-fluorocycloalkanols **90**,[89,91,92] *cis*-2-fluorocycloalkylamines **91**,[89,93] or *cis*-2-fluorocycloalkylhydrazines **92**[94] (Scheme 31).

For both *cis*- and *trans*-2-fluorocyclopentanols (**91a** and **88a**, respectively), efficient enzymatic resolution methods were developed, allowing for the preparation of both enantiomers with 96–99% *ee* on gram scale.[86,89,91]



Scheme 31. Building blocks prepared by common transformations of fluorinated alcohols **88** (relative configurations are shown unless noted otherwise)

Some efforts were also put into development of asymmetric ring opening in oxiranes **87** with fluoride.[95] In particular, Haufe and co-workers used chiral salen complex **93** (0.5–1 eq) with AgF – $Bu_4N^+H_2F_3^-$ as the fluorinating agent in acetonitrile (Figure 3).[96,97] They achieved 62–72% *ee* for corresponding products (*5,5*)-**88** (n = 1–3, yield 80–90%). Nearly a decade later, Kalow and Doyle reported that a cooperative dual-catalyst system including chiral salen complex **94** (10 mol%) and (–)-tetramisole (**95**, 8 mol%) with benzoyl fluoride – HFIP as the HF source in *t*BuOMe gives better enantioselectivities for the same substrates (*ee* 85–93%, yield 65–82%).[98] A variation of the latter method was also used for the synthesis of ^{18}F-labelled compounds.[99]

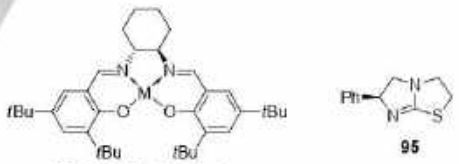
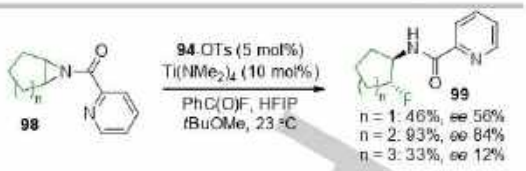


Figure 3. Catalysts for the asymmetric synthesis of chiral alcohols **89**

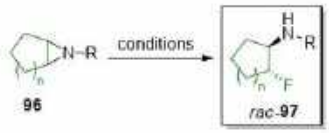
Bicyclic aziridine ring opening with fluoride. This approach provides a convenient access to *trans*-β-fluorocycloalkylamines. The first examples were described in early 1980s;[100,101] since then, many variations of the method were reported (Table 2). While the classical Olah reagent (HF·py, but not liquid HF itself) worked well with the parent substrates, most of the "milder" fluorinating systems required activated aziridine derivatives (e.g. R = Bz or Ts). We would like to draw attention of the reader to the conditions proposed by Doyle and co-workers (DBN (20 mol%, PhC(O)F, hexafluoroisopropanol (HFIP), *t*BuOMe, 50 °C) (Table 2, Entry 10).[102] While being very mild (the fluorinating reagent is generated in situ), they were efficient for both non-activated and activated substrates. Also, the method of Hou and co-workers ($BF_3{\cdot}Et_2O$, *i*PrOH (cat.), CH_2Cl_2, 25 °C)[103] could be later implemented in a flow version (Table 2, Entry 11).[104]

Kalow and Doyle attempted to extend their approach to enantioselective oxirane ring opening (see Figure 3 and the accompanying discussion) to aziridines.[105] Unfortunately, the optimized method gave satisfactory stereoselectivity only with picolinic acid derivative **98**, n = 2 (Scheme 32).



Scheme 32. Asymmetric bicyclic aziridine ring opening with fluoride

Table 2. Examples of fused aziridine ring opening with fluoride sources

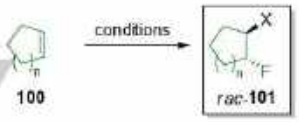


#	n	R	Conditions	Yield, %	Ref.
1	2	H	HF·py (70% w/w), MeCN, 70 °C	70	[100]
2	2	H	HF·py (70% w/w), –78 °C to rt, 46 h	70[a]	[101]
3	2	Bz	Et_3N – HF·py (70% w/w), CH_2Cl_2, rt	70	[101]
4	1, 2	Ts	$BF_3{\cdot}Et_2O$, *i*PrOH (cat.), CH_2Cl_2, 25 °C	49–82	[103]
5	1–3	Ts	TBAF, THF, 45 °C	87–99	[106]
6	1–3	Ts	KF·2H_2O, $Bu_4N^+HSO_4^-$, MeCN, 45 °C	85–96	[106]
7	2	Bn, Bz	same as above	75–91	[106]
8	1, 3	Ns	KF·2H_2O, [bmim]BF_4[b]	70–85	[107]
9	1, 2	Ts	$NF_3{\cdot}xH_2O$, TBAF, *i*PrOH, 90 °C	57–82	[108]
10	1, 2	Boc, Cbz, Bn	DBN (20 mol%), PhC(O)F, HFIP, *t*BuOMe, 50 °C	82–92	[102]
11	2	Ns	$BF_3{\cdot}Et_2O$, *i*PrOH, $CHCl_3$, rt (flow reactor)	63	[104]
12	2	Ts	$[Et_3N{=}SF_2]^+BF_4^-$ (XtalFluor-E), 1,4-dioxane, reflux	91	[109]
13	2	Ts	DMPU – HF, $(CH_2Cl)_2$, rt	96	[110]

[a] Isolated as *N*-benzoyl derivative [b] bmim = 1-butyl-2-methylimidazolium

Addition of fluorine and another heteroatom to cycloalkene. When this second heteroatom is Cl, Br, or I, the approach is yet another of the oldest and most widely used for the preparation of β-fluorinated cycloalkyl building blocks. The first examples were described in 1960 and included reactions of cyclohexene, *N*-bromoacetamide or *N*-iodosuccinimide, and HF at –80 °C (Table 3, Entries 1 and 2).[111] As with the epoxide ring opening, numerous fluoride and second halogen sources were explored in these transformations since then (Table 3). In our own experience, the method introduced initially by Haufe and co-workers[112] (*N*-halosuccinimide, $Et_3N{\cdot}3HF$) (Table 3, Entries 6 and 22) is very convenient for the multigram preparation of the target building blocks.[49] We have applied it to the synthesis of β-fluorinated C_4 to C_7 cycloalkyl derivatives on ca. 20 g scale.

Table 3. Addition of fluorine and another halogen to cycloalkenes

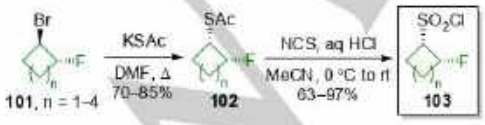


#	n	X	Conditions	Yield, %	Ref.
1	2	Br	MeC(O)NHBr, HF, –80 °C	42	[111,113]
2	2	I	NIS, HF, –80 °C	61	[111]
3	2, 3	I	I_2, F_2, $CFCl_3$, $CHCl_3$, –78 °C	45–64	[114,115]
4	2	Br	Br_2, F_2, $CFCl_3$, $CHCl_3$, –78 °C	61	[115]
5	2	Cl, Br, I	*N*-halosuccinimide, $Et_3N{\cdot}3HF$, CH_2Cl_2, 0 to 20 °C	75–88	[112]
6	1, 2	I	I(collidine)$_2$]$^+BF_4^-$, CH_2Cl_2, rt	53–58	[116]
7	2, 3	Cl, Br, I	*N*-halosuccinimide, $Bu_4N^+HF_2^-$, CH_2Cl_2, rt	53–91	[117,118]
8	2	Br, I	1,3-dibromohydantoin, NBS, or NIS, $Bu_4P^+H_2F_3^-$, CH_2Cl_2, 0 or 20–25 °C	75–86	[119]
9	2, 3	Br	1,3-dibromohydantoin or NBS, poly-4-vinylpyridinium poly(hydrogen fluoride), CH_2Cl_2, 0 to 20 °C	70–83	[120]

10	2	I	NIS, 1 M HF, KHF_2, TBAF $3H_2O$ (10 mol%), CH_2Cl_2, rt	75	[121]
11	2	Br, I	1,3-dibromohydantoin or NIS, KH_4F_5, CH_2Cl_2, rt	50–56	[122]
12	2	I	I_2, XeF_2, CH_2Cl_2, rt	90	[123]
13	2	Cl, Br	*t*BuOCl, MeOCl, or *t*BuOBr, Et_3N·3HF, CH_2Cl_2, rt	90–100	[47]
14	2	I	$-2e^-$ (1.0 V), Et_4NI or NaI, Et_3N·5HF, CH_2Cl_2, rt	90–100	[124]
15	2, 3	Br	NBS, Et_2O·5HF, CH_2Cl_2, –20 to –30 °C	71–80	[125]
16	2	Br, I	NBS or NIS, [emim]F·2.3HF,[a] CH_2Cl_2, rt	90–95	[88]
17	3	Br	BrF_3, $CFCl_3$, 0 °C	50	[126]
18	2	Br, I	trihaloisocyanuric acid, HF·py, CH_2Cl_2, rt	75–88	[127]
19	2	Br, I	1,3-dibromohydantoin or NIS, (*Z*)-$Et_2NCF{=}CHCF_3$, HMPA, CH_2Cl_2, –30 °C to rt	46–59	[128]
20	2	I	IF_5, py·HF, Sn, CH_2Cl_2, rt	54	[129]
21	2, 3	I	1-fluoro-3,3-dimethyl-3*H*-benzo[*d*][1,2]iodoxole, $PdCl_2(MeCN)_2$ (5 mol%), $CDCl_3$, 40 °C	40–50	[130]
22	0–3	Br	NBS, Et_3N·3HF, CH_2Cl_2, 5 °C to rt	59–94	[49]
23	2	I	I_2, py·9HF, $Na_2S_2O_8$, CH_2Cl_2, rt	49	[131]

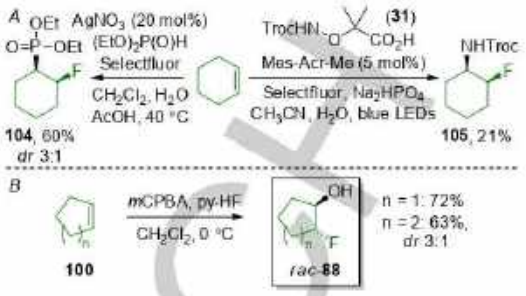
[a] emim = 1-ethyl-3-methylimidazolium

Bromides **101** were used for the synthesis of sulfonyl chlorides **103** (Scheme 33).[49] To the best of our knowledge, a possibility to obtain other building blocks (e.g. amines or azides) by a similar scheme was not demonstrated so far.



Scheme 33. Synthesis of sulfonyl chlorides **103** (relative configurations are shown)

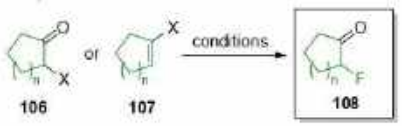
Several other addition reactions involving cyclohexene or cyclopentene and leading to β-fluorinated building blocks have been developed recently. Thus, two radical processes, namely, phosphonofluorination[132] and amidofluorination,[50] are worth outlining (Scheme 34, *A*). Also, direct *anti*-hydroxyfluorination of cyclic alkenes with *m*CPBA and py·HF should be mentioned as an alternative to epoxide ring opening (Scheme 34, *B*).[133]



Scheme 34. (*A*) Phosphonofluorination and amidofluorination of cyclohexene (relative configurations are shown; see also Scheme 10) (*B*) Hydroxyfluorination of cyclic alkenes

Electrophilic C–H fluorination. This reaction is a general approach to α-fluorinated cycloalkanones. The first examples were described in 1959, including reactions of 2-hydroxymethylenecyclohexanone sodium salt[134] or 1-ethoxycyclohex-1-ene[135] with $FClO_3$ that gave 2-fluorocyclohexanone (Table 4, Entries 1 and 2). Of many newer protocols developed since then, direct fluorination methods based on the use of Selectfluor or Accufluor are worth outlining (Table 4, Entries 17–21).

Table 4. Electrophilic fluorination of cycloalkanones and their derivatives

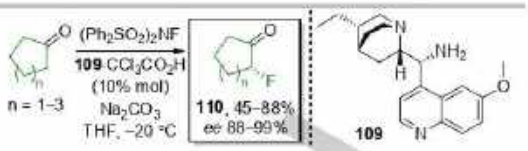


#	n	Substrate	X	Conditions	Yield, %	Ref.
1	2	**106**	=CHONa	$FClO_3$, EtOH	40	[134]
2	2	**107**	OEt	$FClO_3$, py, 0 °C	N/A	[135]
3	2	**106**		$FClO_3$, DMF, 10°C to rt, then AcONa, aq EtOH, reflux	12	[136]
4	2, 3	**107**	morpholino	NaF_2, py, CH_2Cl_2, 0 °C	35–53	[137]
5	2, 3	**107**	OAc	XeF_2, HF (cat.), CH_2Cl_2, rt	58–85	[138, 139]
6	2	**107**	$OSiMe_3$	CF_3OF, $CFCl_3$, –70 °C	74	[140]
7	1–3	**107**	OAc	$CsSO_4F$, CH_2Cl_2, rt or 35 °C	70–88	[141, 142]

8	2	**107**	morpholino	1-fluoro-2-pyridone, CH_2Cl_2, reflux	44	[143]
9	1, 2	**107**	$OSiMe_3$	XeF_2, py·xHF, CH_2Cl_2, 0 °C to rt	70–90	[144]
10	2	**107**	morpholino	NFQNF,[a] CH_2Cl_2, –196 to 20 °C	43–61	[145, 146]
11	1, 2	**107**	$OSiMe_3$	5% F_2 in N_2, $CFCl_3$, –78 °C	73–78	[147]
12	2	**107**	$OSiMe_3$	pyF$^+$OTf$^-$, CH_2Cl_2, rt	78	[148, 149]
13	2	**107**	$OSiMe_3$	pyF$^+$$B_2F_7^-$, MeCN, 0 °C	37	[150]
14	2	**107**	morpholino	CH_2Cl_2, 20 °C	81	[151]
15	2	**107**	$OSiMe_3$	o-$C_6H_4(SO_2)_2NF$, $CDCl_3$, rt	62–79	[152]
16	2	**107**	$OSiMe_3$	$(PhSO_2)_2NF$, $CDCl_3$, rt	43	[152]
17	1–3	**106**	H	Accufluor,[a] MeCN, 80 °C	80–92	[153]
18	2	**106**	H	Selectfluor,[a] CF_3COOH, L-proline, MeCN, 0 °C	73	[154]
19	2, 3	**106**	H	Selectfluor, MeCN, reflux	37–85	[155]
20	3	**106**	H	Selectfluor, [pmim(SO_3H)]OTf_2 (bmim)PF_6, 80° C[d]	69	[156]
21	2	**106**	H	Selectfluor, AcOH, MeCN, 82° C	82	[92]
22	3	**106**	H	Selectfluor, MeOH, 82° C	53	[157]

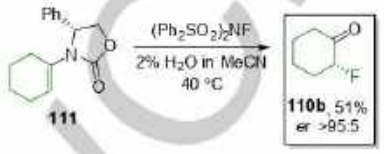
[a] NFQNF – *N*-fluoroquinuclidinium fluoride [b] See Scheme 14 [c] See Scheme 10 [d] pmim(SO_3H) – 1-methyl-3-(propyl-3-sulfonyl)imidazolium, bmim – 1-butyl-3-methylimidazolium

The reaction was also conducted in an enantiospecific manner. One example is listed in Table 4, Entry 18;[154] however, the *ee* values did not exceed 34% in that case. Nevertheless, MacMillan and co-workers reported the use of quinine-derived organocatalyst **109** allowed for the preparation of chiral α-fluoroketones **110** with 88–99% *ee* in 45–88% yield (Scheme 35).[158]



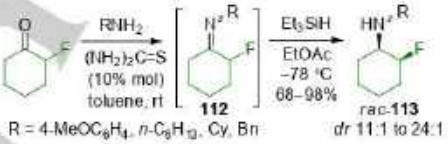
Scheme 35. Asymmetric organocatalytic α-fluorination of cycloalkanones

Also, diastereoselective fluorination of enamide **111** was reported (Scheme 36).[159]



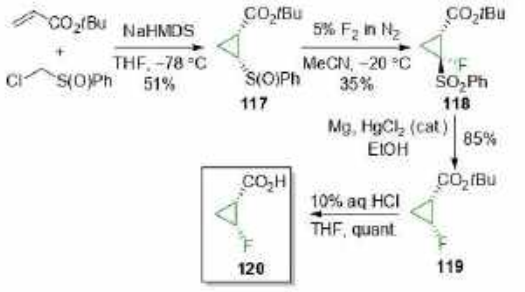
Scheme 36. Diastereoselective fluorination of enamide **111**

Further transformations of α-fluorinated ketones **108** for the synthesis of monofluorinated building blocks included reduction to alcohols of type **90** (see Scheme 31)[89,91,92] and reductive aminations. In particular, highly diastereoselective reduction of imines **112** with triethylsilane was described by Davis and co-authors (Scheme 37).[160]



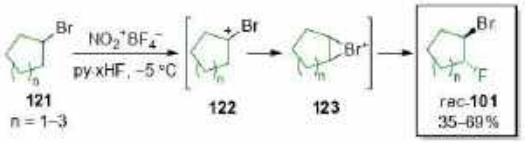
Scheme 37. Diastereoselective reduction of imines **112**

Finally, synthesis of *cis*-2-fluorocyclopropanecarboxylic acid (**120**) via the fluorination of sulfoxide **117** should be mentioned (Scheme 38).[161] Importantly, the fluorination step proceeded preferably via stereoinversion, which was addressed to the initial attack of the electrophile at the sulfur atom. The scheme was also applied to the *trans*-isomer of **117** (obtained if NaH was used as a base instead of NaHMDS at the first step). In this case, an additional stereoinversion step was required to transform the corresponding fluorination product into **118**.



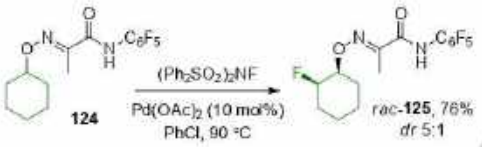
Scheme 38. Synthesis of *cis*-2-fluorocyclopropanecarboxylic acid **120** (relative configurations are shown)

Fluorination at the non-activated C–H bonds. As mentioned above, this approach has received much attention recently.[58] Nevertheless, an unusual β-fluorination of cycloalkyl bromides by their treatment with $NO_2^+BF_4^-$ in HF – pyridine solution was described by Olah and co-workers already in 1987 (Scheme 39). It was suggested that bromonium ions **123** were formed as intermediates in the reaction.



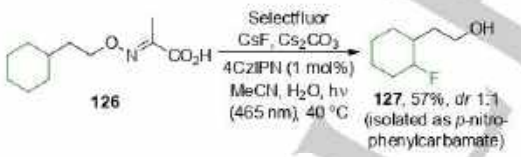
Scheme 39. Fluorination of cycloalkyl bromides with $NO_2^+BF_4^-$ in HF·py

In 2018, Xu and co-workers reported a Pd-catalyzed β-fluorination of alcohols with NFSI using a removable bidentant oxime-based activating auxiliary (Scheme 40).[162] The proposed reaction mechanism involved a Pd(II)/Pd(IV) catalytic cycle.

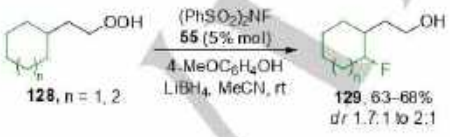


Scheme 40. β-Fluorination of alcohol derivative **124**

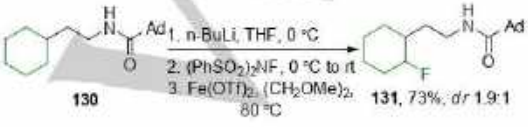
Other recent approaches included δ-fluorination of non-activated C–H bonds via the *O*-[62,63] or *N*-radical[163,164] generation and further [1,5] hydrogen shift as shown in Scheme 16 (Schemes 41–44; compare with Schemes 17 and 18).



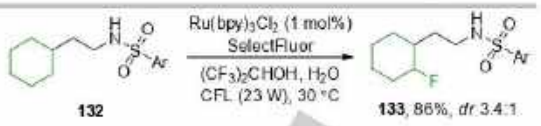
Scheme 41. Remote fluorination of oxime **126**



Scheme 42. Remote fluorination of peroxides **128**

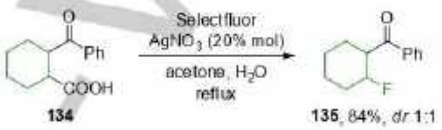


Scheme 43. Remote fluorination of amide **130** (Ad – 1-adamantyl)

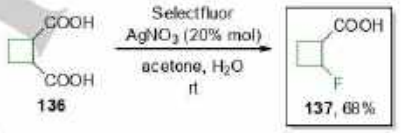


Scheme 44. Remote fluorination of sulfonamide **132** (Ar = 4-$MeOC_6H_4$; CFL – compact fluorescent lamp)

Decarboxylative and deborylative fluorination. Li and co-workers described silver-catalyzed decarboxylative fluorination of δ-keto acid **134** providing fluorinated ketone **135** in 84% (Scheme 45).[165] This method was also used for the preparation of β-fluorocyclobutane carboxylic acid (**137**) disclosed in a recent Chinese patent (Scheme 46).[166] Due to the radical nature of the process, the products were obtained as mixtures of diastereomers in both cases. Compound **137** was used to synthesize a series of related (β-fluorocyclobutyl)methyl-substituted building blocks including alcohol, azide, and amines, via standard functional group transformations.

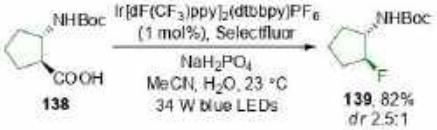


Scheme 45. Decarboxylative fluorination of δ-keto acid **134**



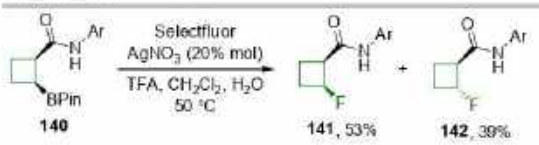
Scheme 46. Decarboxylative fluorination of dicarboxylic acid **136**

McMillan and co-workers described an Ir-photocatalyzed decarboxylative fluorination of *N*-Boc-protected amino acid **138**; again, the process had moderate diastereoselectivity (Scheme 47).[167] An organophotocatalytic version of this method was applied to carboxylic acid **134** to give product **135** in 53% yield.[168]

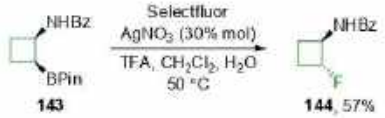


Scheme 47. Decarboxylative fluorination of *N*-Boc-protected amino acid **138** (relative configurations are shown)

Silver-catalyzed fluorination with Selectfluor was also very successfully applied to boropinacolates **140** and **143**. In the first case, both pure *cis*- and *trans*-isomeric products **141** and **142** could be isolated in an excellent overall yield of 92% (Scheme 48).[169,170] With **143**, only *trans* isomer **144** was obtained in 57% yield (Scheme 49).[171]

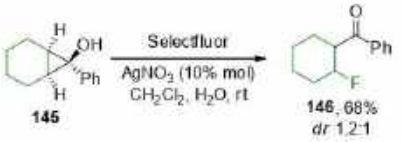


Scheme 48. Decarboxylative fluorination of boropinacolate **140**

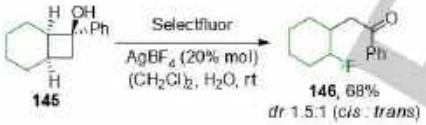


Scheme 49. Decarboxylative fluorination of boropinacolate **143** (relative configurations are shown)

Other fluorinative methods. In 2015, silver-catalyzed oxidative cleavage of bicyclic cyclopropanol **145** and cyclobutanol **147** as an approach to fluorinated ketones **146** (Scheme 50)[172] and **148** (Scheme 51)[173] was described. Stereoselectivity of the process and other experimental data were evident of the radical reaction mechanism.



Scheme 50. Fluorinative cleavage of cyclopropanol **145**

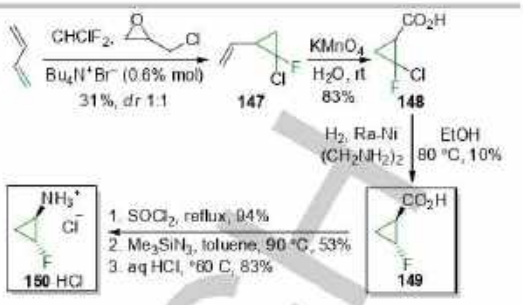


Scheme 51. Fluorinative cleavage of cyclobutanol **147**

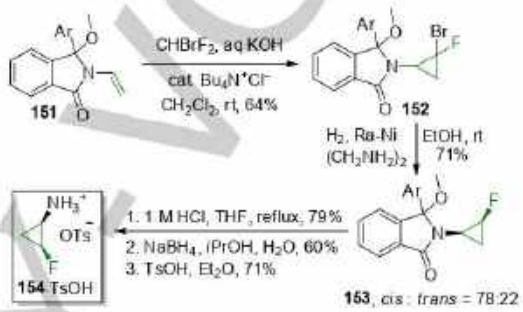
Cyclizations and cycloadditions of fluorinated intermediates. Most reactions described in this section include (formal) monofluorocyclopropanation of various functionalized alkenes. One of the early approaches was based on the reaction of butadiene with $CHClF_2$ (Scheme 52).[174] Product **147** was oxidized with $KMnO_4$ and then subjected to highly diastereoselective catalytic hydrogenolysis in the presence of Ni-Ra – ethylenediamine. In this way, carboxylic acid **149** was obtained (albeit in only 10% yield). Also, amine **150** was synthesized via a modified Curtius degradation of **149**.

Esters of **149** (ethyl to *n*-hexyl) obtained by this method were subjected successfully to a microbial resolution.[175] Up to 80% and 98% *ee* values were achieved for the hydrolysed (1*R*,2*R*)-**149** and remaining (1*S*,2*S*)-esters, respectively.

A variation of the above approach was also applied to a straightforward synthesis of *cis*-isomer **154**, a building block for the synthesis of antibacterial drug Sitafloxacin, commencing from isoindolone derivative **151** (Scheme 53).[176]

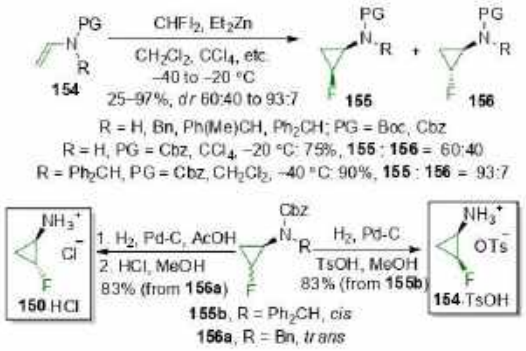


Scheme 52. Synthesis of carboxylic acid **149** and amine **150** (relative configurations are shown)



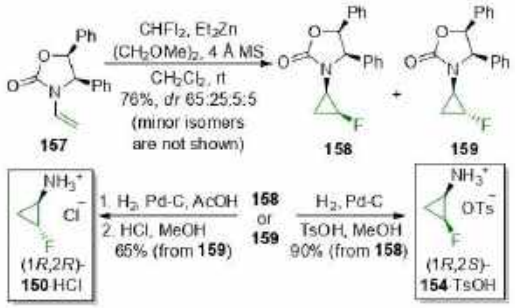
Scheme 53. Synthesis of amine **154** (relative configurations are shown)

Other approaches to the synthesis of compounds **150** and **154** were based on the Simmons-Smith monofluorocyclopropanation of enamides. A detailed study around enamides **155** showed that the best *cis*-diastereoselectivity is observed for Ph_2CH-substituted representatives (*dr* 93:7), whereas Bn-substituted counterparts allowed to prepare both *cis* and *trans* isomers **154** and **150** via diastereomer separation (*dr* as low as 60:40) (Scheme 54).[177,178] An attempted asymmetric synthesis with α-phenylethyl chiral auxiliary was not fruitful; nevertheless, enantiomer resolution was achieved for the *cis* isomer through menthol-derived carbamates.



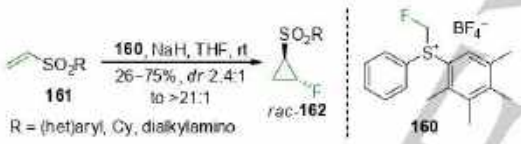
Scheme 54. Synthesis of amines **150** and **154** via the Simmons-Smith monofluorocyclopropanation (relative configurations are shown)

Asymmetric version of this approach relied on the use of an Evans-type oxazolidone auxiliary (Scheme 56).[179,180] The method provided a good stereochemistry control at the center adjacent to the protected amino group (only 10% of minor isomers), while the *cis* : *trans* diastereoselectivity was modest (*dr* 65:25).



Scheme 56. Asymmetric synthesis of amines (1*R*,2*R*)-**150** and (1*R*,2*S*)-**154** via the Simmons-Smith monofluorocyclopropanation (relative configurations are shown)

In 2019, Veliks and co-workers reported diarylsulfonium reagents of type **160** allowing the Corey-Chaikovsky-type monofluorocyclopropanation of electron-poor alkenes, such as vinyl sulfones **161** (Scheme 57)[181] or β-nitrostyrenes.[182]

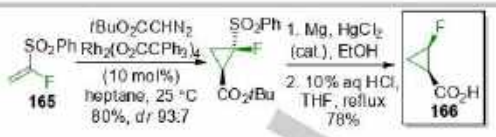


Scheme 57. The Corey-Chaikovsky-type monofluorocyclopropanation

A different [2+1] approach to monofluorinated cyclopropanes includes cyclopropanation of vinyl fluoride. For example, both *cis*- and *trans*-1-bromo-2-fluorocyclopropanes **163** and **164** were obtained by this method (Scheme 58).[183] A similar idea was used by Haufe and co-workers: they studied reactions of α-fluorostyrene and alkyl diazoacetates (that are somewhat beyond the scope of this review).[184] Meanwhile, Shibue and Fukuda successfully applied the method to α-fluorinated vinyl sulfone XX; after removal of the sulfone moiety and protective group, *cis*-2-fluorocyclopropanecarboxylic acid (**166**) was obtained with high stereoselectivity (Scheme 59).[185] Furthermore, both enantiomers of **166** (as well as amine **154** after the DPPA-mediated Curtius reaction) were also obtained using menthol-derived diazoacetate as a chiral auxiliary allowing diastereomer separation.

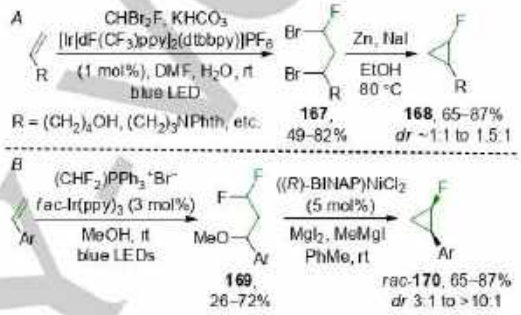


Scheme 58. Synthesis of 1-bromo-2-fluorocyclopropanes **163** and **164**



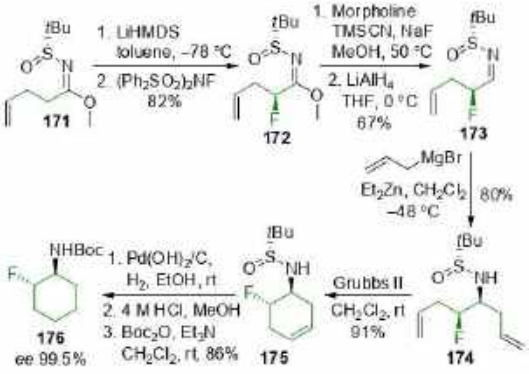
Scheme 59. Synthesis of cis-2-fluorocyclopropanecarboxylic acid (**166**) (relative configurations are shown)

In 2021, Qing and co-workers described zinc-mediated cyclization of 1,3-dibromo-1-fluoroalkane derivatives **167** following the classical Wurtz reaction pathway (Scheme 60, *A*).[186] In turn, substrates **167** were obtained by photoredox reaction of terminal alkenes with dibromofluoromethane. Formally, the above two-step reaction sequence can be considered as alkene monodifluorocyclopropanation.



Scheme 60. Two-step reaction sequences resulting in formal alkene monofluorocyclopropanaiton

Another photoredox-based method that can also be considered as a formal two-step monofluorocyclopropanation commenced with Ir-catalyzed reaction of alkenes with (difluoromethyl)triphenylphosphonium bromide in methanol (Scheme 60, *B*).[187] Then, resulting adducts **169** underwent Ni-catalyzed cross-electrophile cyclization to monofluorinated cyclopropanes **170**. Albeit the demonstrated scope was limited by styrenes or their hetero-analogs lacking usable functional groups, we believe that the method still has potential for the building block synthesis.

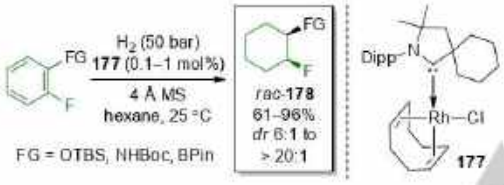


Scheme 61. Synthesis of (1*S*,2*S*)-2-fluorocyclohexylamine derivative **175**

Finally, ring-closing methatesis was used as a key step in the synthesis of enantiopure (1*S*,2*S*)-2-fluorocyclohexylamine (as *N*-Boc derivative **176**, Scheme 61).[188,189] The enantioselectivity was achieved at the earlier steps via diastereoselective α-fluorination of *N*-*tert*-butylsulfinyl imidate **171**.

Transformations of compounds already containing the β-fluorinated cycloalkyl or related moiety. As earlier, common organic chemistry transformations are not covered in this section; some of them were mentioned above. A work of Craig and co-workers describing non-selective chlorination of fluorocyclobutane can be mentioned here.[190] All five theoretically possible chlorofluorocyclobutanes were obtained and separated by preparative gas chromatography (isomer ratio: 1,1- : *trans*-1,3 : *trans*-1,2- : *cis*-1,3- : *cis*-1,2 = 1:1.06:1.44:0.87:0.25). Analogously, gas-phase chlorination of fluorocyclohexane was reported.[191] Nevertheless, we believe that this approach is of little practical utility.

In 2017, Glorius and co-workers described highly efficient *cis*-stereoselective hydrogenation of fluorinated arenes.[192] Among other interesting products, β-fluorinated building blocks **178** were obtained (Scheme 62).



Scheme 82. Hydrogenation of β-fluorinated arenes (Dipp – 2,6-diisopropylphenyl)

2.3. Synthesis of γ-and δ-fluorinated cycloalkyl building blocks

The following methods have been used to synthesize the remaining (γ-and δ-) monofluorinated building blocks:

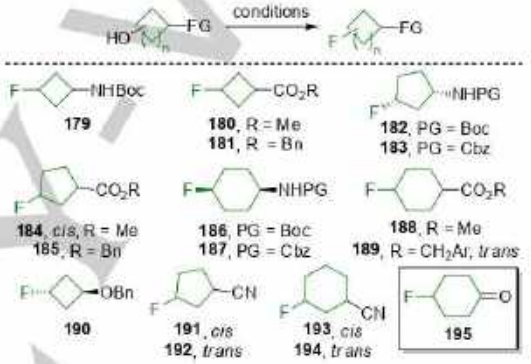
- nucleophilic substitution with fluoride;
- radical functional group fluorinations;
- fluorination at the non-activated C–H bonds;
- other fluorinative methods;
- cyclizations and cycloadditions of fluorinated intermediates;
- transformations of compounds already containing the α-fluorinated cycloalkyl or related moiety.

Nucleophilic substitution with fluoride. At first glance, this method looks very promising for the synthesis of the target building blocks. Indeed, quite a number of examples have been disclosed in recent patents, including the synthesis of the monofluorinated C_4–C_6 amines and carboxylic acids via deoxyfluorination of the corresponding alcohols followed by deprotection (not shown) (Table 5, Entries 1–10). Moreover, whenever reported, inversion of the configuration was observed. However, these and further examples (Table 5, Entries 11–17) show that there are some inconsistencies in the literature data. The product yields vary significantly for the cyclobutane series but are modest in most cases. The yields are even lower for the cyclohexane series, likely due to the competing elimination.[193,194] The method seems to work well for the cyclopentane series, although the number of properly documented literature precedents is insufficient.

An alternative approach includes preliminary transformation of the corresponding alcohol into a sulfonate ester (e.g., tosylate or nosylate), followed by reaction with KF in the presence of a phase-transfer catalyst (e.g., $N(CH_2CH_2OCH_2CH_2OCH_2CH_2)_3N$ (Kryptofix-2.2.2)). This method was used for the synthesis of diastereopure 3- and 4-^{18}F-labelled cyclohexanecarboxylic acid derivatives.[195,196]

Radical functional group fluorinations. An interesting deoxyfluorination method was developed by McMillan and co-workers in 2019.[197] It involved Ir-catalyzed photoredox reaction of Selectfluor and oxalate half-esters **197** (Scheme 83). The method worked well for many substrates where the classical deoxyfluorination performed poorly, including functionalized cyclohexanols **196**. Unfortunately, low to moderate diastereoselectivity was observed due to the radical nature of the process.

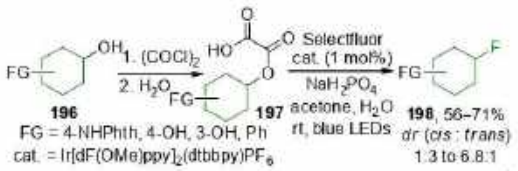
Table 5. Synthesis of monofluorinated C_4–C_6 building blocks by deoxyfluorination of the corresponding alcohols



#	Product	Alcohol configuration	Conditions	Yield, %	Ref.
1	**179**	N/A	DAST, CH_2Cl_2, –70 °C to rt	31	[198]
2	**180**	N/A	DAST, CH_2Cl_2, –70 °C to rt	96	[199]
3	**181**	N/A	DAST, CH_2Cl_2, –70 °C to rt	42	[200]
4	**182**[a]	*trans*	PyFluor (pyridine-2-sulfonyl fluoride), DBU, toluene, rt	63–75	[201]
5	**183**[a]	*trans*	PyFluor, DBU, toluene, rt	77	[201]
6	**184**[a]	*trans*	DAST, CH_2Cl_2, –70 °C to rt	N/A	[202]
7	**185**	N/A	$(MeOCH_2CH_2)_2NSF_3$, CH_2Cl_2, –70 °C to rt	N/A	[203]
8	**186**	*trans*	DAST, CH_2Cl_2, rt	14	[204]
9	**187**	*trans*	DAST, CH_2Cl_2, 0 °C	5	[205]

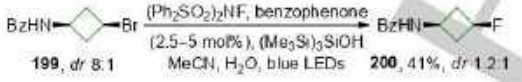
10	**188**	N/A	DAST, CH_2Cl_2, 0 °C	25	[206]
11	**189**[b]	*cis*	DAST, CH_2Cl_2, rt	7	[195]
12	**190**	*cis*	DAST, CH_2Cl_2, 0 °C to rt	37	[207]
13	**191**[b]	*trans*	DAST, CH_2Cl_2, –78 °C to rt	63	[76]
14	**192**[b]	*cis*	DAST, CH_2Cl_2, –78 °C to rt	59	[76]
15	**193**	*trans*	DAST, CH_2Cl_2, –78 °C to rt	30	[76]
16	**194**	*cis*	DAST, CH_2Cl_2, –78 °C to rt	8	[76]
17	**195**	–	py·HF, 0 °C	24	[208]

[a] Both racemate and (1*R*,3*S*)-enantiomer of the compound were synthesized [b] Racemate [c] Ar = 2,3,4,5,6-pentamethylphenyl



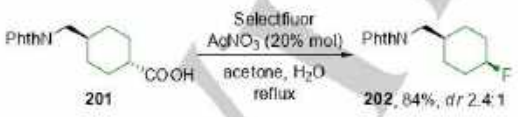
Scheme 83. Photoredox deoxyfluorination of functionalized cyclohexanols

The same group reported photoredox fluorination of (cyclo)alkyl-bromides, in particular, cyclobutane derivative **199** (Scheme 84).[209] Again, diastereoselectivity of the process was low.



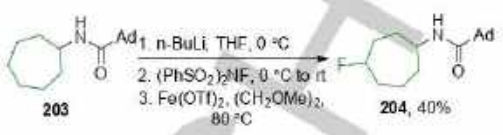
Scheme 84. Photoredox fluorination of bromide **199**

Silver-catalyzed decarboxylative fluorination of carboxylic acids already mentioned above (see Schemes 45 and 46) was also applied to cyclohexane derivative **201** (Scheme 85).[165]

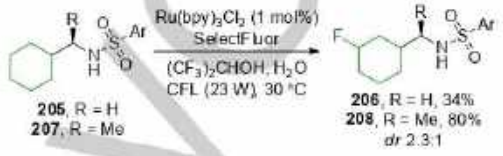


Scheme 85. Decarboxylative fluorination of amino acid derivative **201**

Fluorination at the non-activated C–H bonds. Some of the "remote" *N*-directed fluorinations discussed above for the case of β-fluorocycloalkyl building blocks (Schemes 43 and 44) can be also applicable for the preparation of γ- and δ-counterparts. Indeed, δ-fluorocycloheptylamine derivative **204** was obtained by Fe-catalyzed intramolecular fluorination in 40% yield (Scheme 86).[163] Also, γ-fluorocyclohexyl derivatives **206** and **208** were formed in 34% and 80% yield, respectively, in the Ru-catalyzed photoredox fluorination reaction (Scheme 87).[164] The latter method did not work, however, for the synthesis of the corresponding δ-fluorocyclohexylamine derivative. In both cases, initial formation of *N*-centered radical was postulated, followed by [1,5] H-shift and further reaction with the fluorine source (see also Scheme 16).

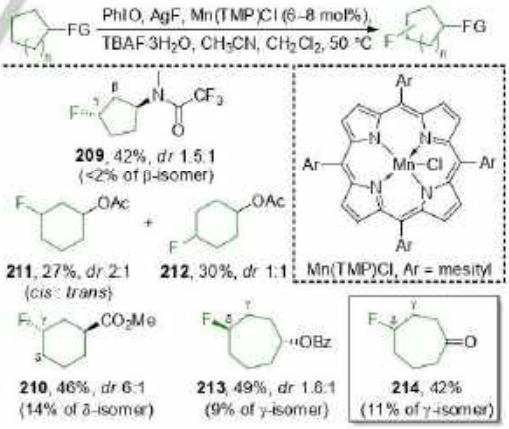


Scheme 86. Remote fluorination of amide **203** (Ad – 1-adamantyl)



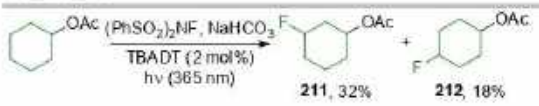
Scheme 87. Remote fluorination of sulfonamides **205** and **207** (Ar = 4-MeOC6H4)

Other radical fluorinations were site-selective but non-directed and governed by both electronic and steric factors. In particular, Groves and co-workers reported oxidative Mn-catalyzed C–F fluorination of cyclopentane, cyclohexane, and cycloheptane derivatives (Scheme 88). It was found that the process was significantly hampered by electron-withdrawing substituents (which in fact also ensured monofluorination). Also, low to moderate diastereoselectivity was observed.[210] A close variation of this method was used for the late-stage ^{18}F labelling of various substrates, mostly of the cyclopentane series.[211]



Scheme 88. Non-directed Mn-catalyzed C–H fluorination (relative configurations are shown)

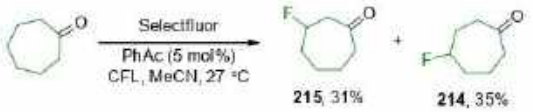
A related method was described by Britton and co-workers in 2014; they relied on the decatungstate photocatalysis.[212] Again, low regioselectivity was achieved for cyclohexylacetate as the substrate (Scheme 89).



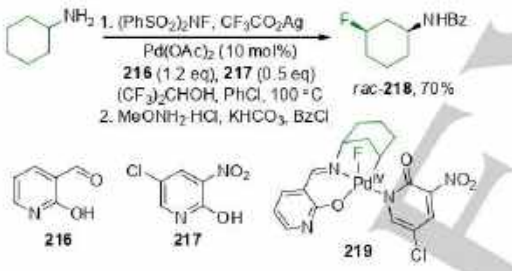
Scheme 89. Non-directed photocatalytic C–H fluorination promoted with tetrabutylammonium decatungstenate (TBATD)

Another photocatalytic method was applied to cycloheptanone; again, virtually no regioselectivity was observed (Scheme 90).[213]

A mechanistically different process was described by Yu and co-workers in 2020.[214] Their method included Pd-catalyzed γ-fluorination of unprotected primary amines (Scheme 91). The reaction involved palladacycle **219** (a simplified representation is given for clarity purposes) as the key intermediate. Notably, cyclohexylamine was γ-fluorinated with 70% yield and good regio- and stereoselectivity.



Scheme 90. Non-directed photocatalytic C–H fluorination promoted with acetophenone



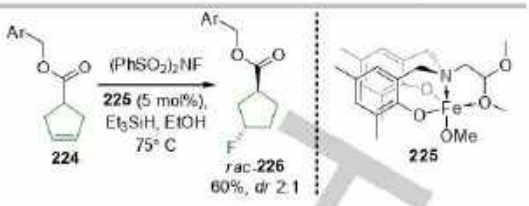
Scheme 91. Pd-catalyzed γ-fluorination of cyclohexylamine

Other fluorinative methods. Baran and co-workers reported electrophilic α-C–H-fluorination of cyclobutane-derived sulfone **221**, in turn obtained by strain-release amination of bicyclo[1.1.0]butane **220** (Scheme 92).[215] After removal of the sulfone moiety, 3-fluorocyclobutylamine derivative **223** was obtained.



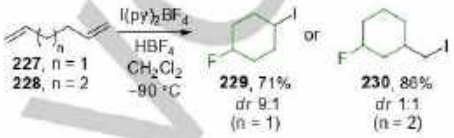
Scheme 92. Synthesis of 3-fluorocyclobutylamine derivative **223** via strain-release amination – electrophilic α-C–H-fluorination

Fe-catalyzed radical hydrofluorination of alkenes, including cyclopentene derivative **224**, was described by Ye, Li, and co-authors (Scheme 93).[216] As expected, the method had modest diastereoselectivity (*dr* 2:1).



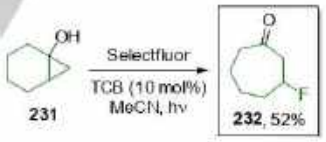
Scheme 93. Fe-catalyzed hydrofluorination of cyclopentene derivative **224**

Barluenga and co-workers described iodine-induced cyclizations of dienes **227** and **228** in the presence of HBF_4 (Scheme 94).[217] The method gave fluorinated cyclohexane derivatives **229** and **230** in 71% and 86% yield, respectively.



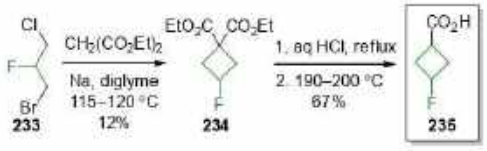
Scheme 94. Iodine-induced cyclizations of dienes **227** and **228** in the presence of HBF_4

Photocatalytic ring opening of bicyclic cyclopropanol **231** led to the formation of 3-fluorocycloheptanone (**232**) in 52% yield (Scheme 95; compare with Schemes 50 and 51).[218]



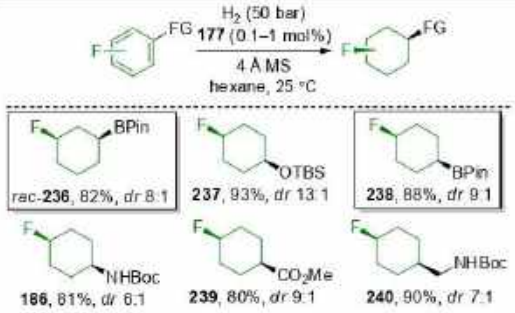
Scheme 95. Photocatalytic ring opening of bicyclic cyclopropanol **231** (TCB – 1,2,4,5-tetracyanobenzene)

Cyclizations and cycloadditions of fluorinated intermediates. A classical approach was applied to the synthesis of 3-fluoro-cyclobutanecarboxylic acid (**235**) a by Dolbier and co-authors.[219] Specifically, it included base-mediated reaction of 1-bromo-3-chloro-2-fluoropropane (**233**) with diethylmalonate (Scheme 96).



Scheme 96. Synthesis of 3-fluorocyclobutanecarboxylic acid (**235**) via malonate alkylation

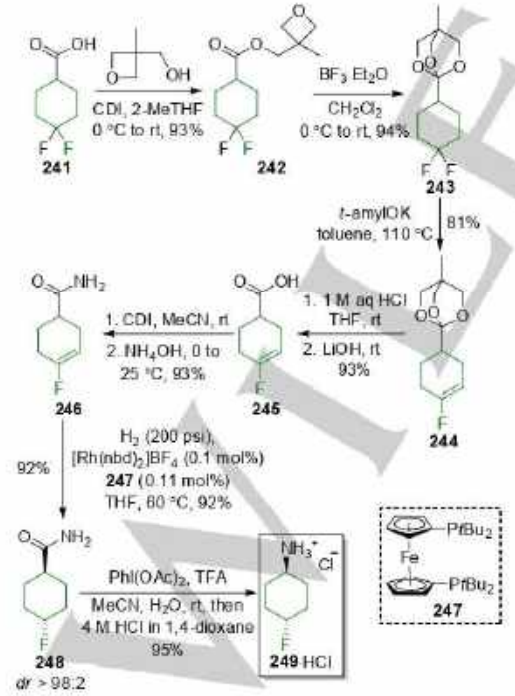
Transformations of compounds already containing the fluorinated cycloalkyl or related moiety. As it was mentioned above, non-selective chlorinations of fluorocyclobutane[190] and fluorocyclohexane[191] were reported; in our opinion, they are of little practical utility.



Scheme 97. Hydrogenation of γ- and δ-fluorinated arenes

Another approach also mentioned above – catalytic hydrogenation of fluorinated arenes (see Scheme 82) – is, on the contrary, highly promising; it has been successfully applied to the preparation of numerous fluorinated building blocks (Scheme 97).[192] Similar results (but somewhat lower diastereoselectivities) were obtained upon hydrogenation of functionalized *p*-fluorinated arenes using rhodium nanoparticles on molecularly modified silica as the catalyst.[220]

Recently, Leung and co-workers described a highly efficient multigram synthesis of *trans*-4-fluorocyclohexylamine (**249**) starting from highly accessible 4,4-difluorocyclohexanecarboxylic acid (**241**) (Scheme 98).[194] The key steps of the synthetic scheme included HF elimination, diastereoselective double bond hydrogenation, and Hoffmann amide rearrangement.



Scheme 98. Scalable synthesis of *trans*-4-fluorocyclohexylamine (**249**)

3. Synthesis of *gem*-difluorinated cycloalkyl building blocks

All 11 theoretically possible *gem*-difluorinated C_3–C_7 building block types have been reported to date, and all of them except cycloheptane derivatives were well-presented in the literature – better than any other fluorinated cycloalkyl derivatives (Figure 4). Enormous interest in *gem*-difluorocyclopropanes can be mostly addressed to their specific chemistry,[23,29,30] whereas even higher occurrence of 3,3-difluorocyclobutyl and 4,4-difluorocyclohexyl substituents can be related to their presence in the marketed drugs (see Figure 1).

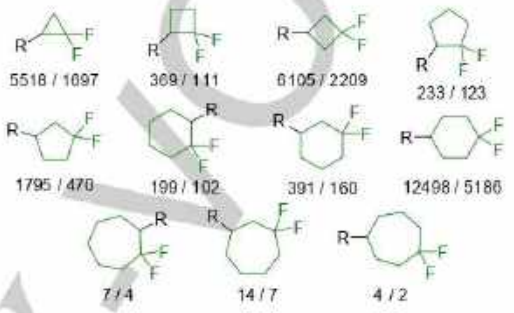
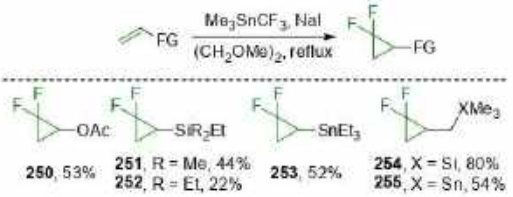


Figure 4. Number of compounds bearing *gem*-difluorinated C_3–C_7 cycloalkyl substituents / document referring to them in *Reaxys*® Database (accessed on 11-03-2022)

3.1. *gem*-Difluorocyclopropyl building blocks

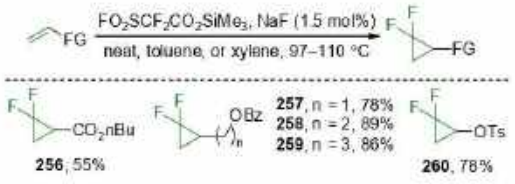
As mentioned above, synthesis of *gem*-difluorocyclopropanes has been reviewed comprehensively recently.[23] Therefore, we will briefly outline important works on the preparation of building blocks bearing the *gem*-difluorocyclopropyl moiety in this section. While a number of other methods exist, the title compounds were prepared almost exclusively via *gem*-difluorocyclopropanation of the appropriately functionalized alkenes or further transformations of the obtained adducts. The first application of this strategy to the synthesis of fluorinated building blocks was reported in 1967 by Seyferth and co-authors.[221] They prepared a number of functionalized *gem*-difluorocyclopropanes **250**–**255** by iodide-induced reaction of bromoethene and Me_3SnCF_3 (Scheme 99).



Scheme 99. Synthesis of *gem*-difluorocyclopropyl building blocks using the Me_3SnCF_3 – NaI system

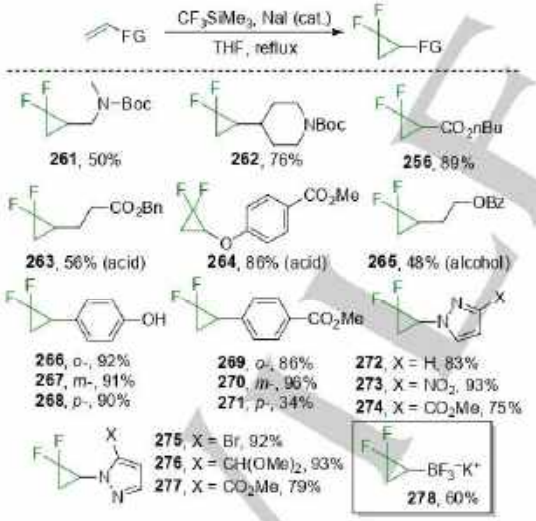
In 2004, Dolbier and co-workers applied trimethylsilyl fluorosulfonyldifluoroacetate (TFDA), a convenient reagent for the *gem*-difluorocyclopropanation, for the same reason (Scheme 100).[222] Later, this method was used to obtain several

sulfonates including tosylate **260**.[223] A related reagent, methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (MDFA), was also used to synthesize compounds **256** and **257** and gave comparable yields.[224]



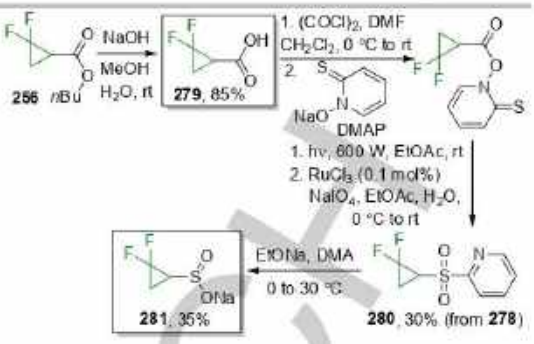
Scheme 100. Synthesis of *gem*-difluorocyclopropyl building blocks using trimethylsilyl fluorosulfonyldifluoroacetate (TFDA)

Perhaps the most important advancement in this area was made by Prakash, Hu, and co-workers in 2011.[225] They proposed CF_3SiMe_3, a highly accessible bulk reagent, for the *gem*-difluorocyclopropanation and demonstrated that NaI promoted this process efficiently. The original Prakash – Hu protocol was applied mainly to (functionalized) styrenes. In our group, we have shown that a "slow addition" modification of the original method allows extending the substrate scope significantly. In particular, *N*-Boc-protected amines,[226,227] esters,[227,228] phenols,[228] trifluoroborates,[229] and functionalized pyrazole derivatives[230] were compatible with the reaction conditions (Scheme 101). The reaction was shown to follow a complex anionic chain mechanistic pathway.[231]



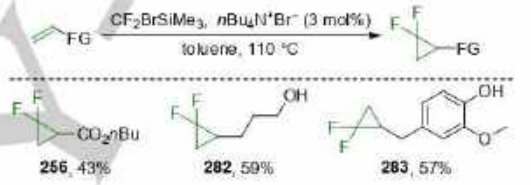
Scheme 101. Synthesis of *gem*-difluorocyclopropyl building blocks using the CF_3SiMe_3 – NaI system

All the intermediates shown in Scheme 101 were transformed into the corresponding building blocks (i.e. amines, carboxylic acids, alcohols, etc.) via obvious deprotection step and/or further standard organic chemistry reactions. As an example of less common transformations, synthesis of sulfinate **281** via the radical decarboxylation according to Baran and co-workers can be outlined (Scheme 102).[232]



Scheme 102. Synthesis of carboxylic acid **278** and sulfinate **281**

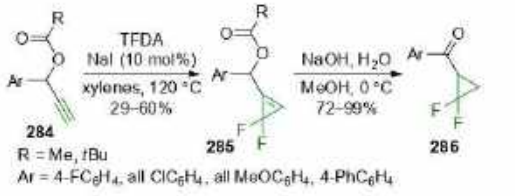
Hu and co-authors explored $CF_2BrSiMe_3$ – $nBu_4N^+Br^-$ system as a more reactive (but less accessible) alternative to the Ruppert – Prakash reagent (Scheme 103).[233] The method does not give a significant advantage compared to those obtained later using the "slow addition protocol" for the CF_3SiMe_3 – NaI system; however, it can be considered due to the safety reasons.



Scheme 103. Synthesis of *gem*-difluorocyclopropyl building blocks using the $CF_2BrSiMe_3$ – $nBu_4N^+Br^-$ system

Very recently, a $BrCF_2CO_2Et$ – $nBu_4N^+Br^-$ *gem*-difluorocyclopropanation system was successfully applied to the synthesis of ester **256** (and carboxylic acid **278** after the subsequent hydrolysis).[234] Hundreds of kilograms of the target compound were delivered successfully by the developed protocol. Furthermore, classical resolution with (*R*)-*N*-benzyl-α-methylbenzylamine was also developed to obtain compound **278** as a pure enantiomer.

An interesting rearrangement was used to obtain aryl(*gem*-difluorocyclopropyl)ketones **286** (Scheme 104).[235] It occurred upon treatment of cyclopropenes **285** (in turn obtained by reaction of alkyne **284** with TFDA) with a base.



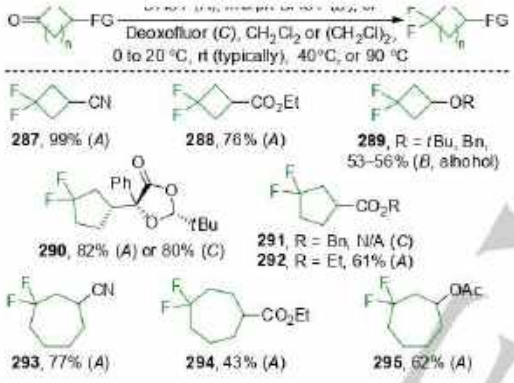
Scheme 104. Synthesis of *gem*-difluorocyclopropyl building blocks using the $CF_2BrSiMe_3$ – $nBu_4N^+Br^-$ system

3.2. Other *gem*-difluorocycloalkyl building blocks

The C_4–C_7 *gem*-difluorocycloalkyl building blocks were typically obtained by deoxofluorination of the corresponding ketones. Other approaches include:

- fluorinative ring expansions;
- other fluorinative methods;
- cyclizations and cycloadditions of fluorinated intermediates;
- transformations of alicyclic compounds already containing the CF_2 moiety.

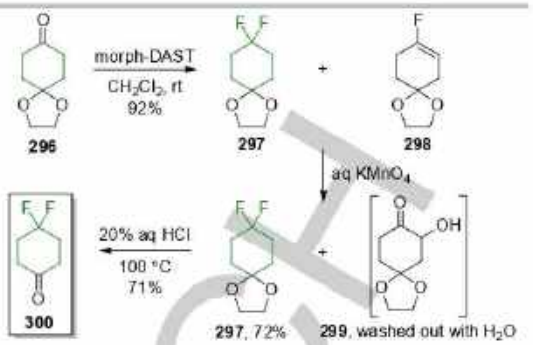
Deoxofluorination of functionalized alicyclic ketones. This method is of excellent utility for the preparation of γ,γ- and δ,δ-difluorinated cyclobutyl,[236,237] cyclopentyl,[238–240] and cycloheptyl[241] building blocks (Scheme 105). Diethylaminosulfur trifluoride (DAST)[235–239,241] was typically the reagent of choice; morpholinosulfur trifluoride (morph-DAST)[237] or bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor)[238,240] were also used.



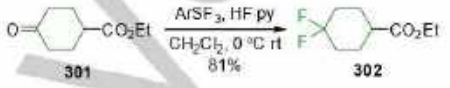
Scheme 105. Synthesis of γ,γ- and δ,δ-difluorinated cyclobutyl, cyclopentyl, and cycloheptyl building blocks via ketone deoxofluorination

In the case of γ,γ- and δ,δ-difluorinated cyclohexyl derivatives, the standard conditions (DAST or morph-DAST) give mixtures of the target and HF elimination products that are difficult to separate.[242,243] Some works relied on the oxidative work-up to remove the unsaturated by-product[242,243] (see an example in Scheme 106). Another approach relied on the reagent alteration. In particular, industrial optimization of the 4,4-difluorocyclohexanecarboxylic acid synthesis involved the use of *N*-aryl-substituted DAST analogs like Ph_2NSF_3 (the full details were not disclosed in the original patent).[244] Umemoto and co-workers showed that their 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride reagent gave ester **302** in 81% yield with less 1% of the elimination by-product (Scheme 107).[73] In our group, we have used XTal-Fluor-E – $Et_3N{\cdot}3HF$ system for the deoxofluorination of ketoester **303**; *gem*-difluoro derivative **304** contained only trace amounts of the elimination by-product at these conditions (Scheme 108).[239]

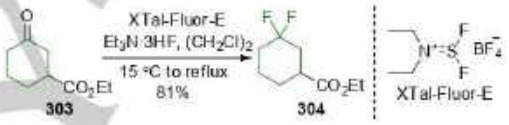
In the case of β,β-difluorinated cycloalkyl building blocks, deoxofluorination with typical reagents like DAST was problematic for the ketones bearing alkoxycarbonyl[245] or phthalimide[246] moieties. Nevertheless, we have found that the standard conditions gave satisfactory results for acetates **305** (Scheme 109) and trifluoroacetamides **307** (Scheme 110).[239,247]



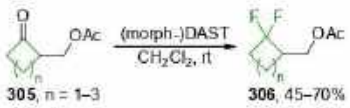
Scheme 106. Deoxofluorination of cyclohexanone derivative **296** with morph-DAST (similar results were obtained with ketoester **301**)



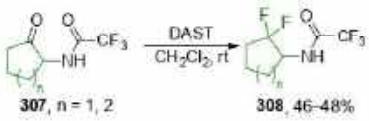
Scheme 107. Deoxofluorination of cyclohexanone derivative **296** with $ArSF_3$ (Ar = 4-*tert*-butyl-2,6-dimethylphenyl)



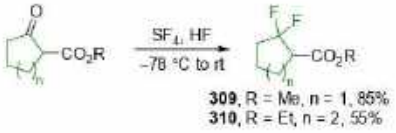
Scheme 108. Deoxofluorination of cyclohexanone derivative **296** with XTal-Fluor-E – $Et_3N{\cdot}3HF$



Scheme 109. Deoxofluorination of acetates **305** with (morph-)DAST



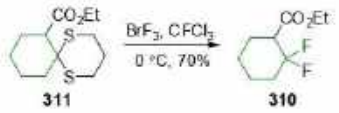
Scheme 110. Deoxofluorination of trifluoroacetamides **307** with DAST



Scheme 111. Deoxofluorination of cyclic β-keto esters with SF_4 – HF

Later, Trofymchuk and co-authors demonstrated that direct deoxofluorination of β-keto esters is possible using SF_4 – HF; the method worked for cyclopentane and cyclohexane, but not cycloheptane derivatives (Scheme 111).[248] Also, fluorination of

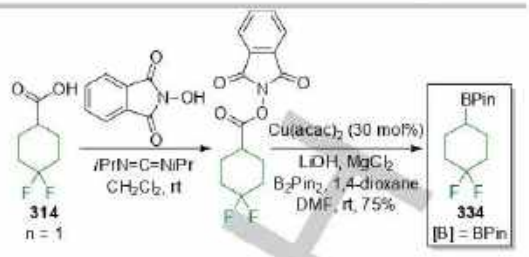
1,3-dithiane X with BrF_3 was reported to give ester **311** in 70% yield (Scheme 112).[240]



Scheme 112. Fluorination of 1,3-dithiane **311** with BrF_3

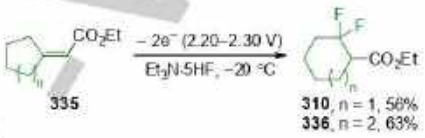
The synthetic intermediates shown in Schemes 105–112 were used to obtain a number of building blocks using common organic chemistry transformations (Figure 5), including:

- *gem*-difluorocycloalkanecarboxylic acids **312** (starting from **306**, n = 1–3,[239,247] **309**, **310**[248]), **313** (from **287**,[236] **288**,[237] **293**,[241] **304**[239]), and **314** (from **294**,[241] **302**[242,244]);
- *gem*-difluorocycloalkylamines **315** (from **312**, n = 1–3[239,247]), **316** (from **313**, n = 1–4[237,239,241]), and **317** (from **314**, n = 1,[250] 2[241]);
- (*gem*-difluorocycloalkyl)methanols **318** (from **306**, n = 1–3[239,247]), **319** (from **288**[237]), and **320** (from **302**[251]);
- (*gem*-difluorocycloalkyl)methylamines **321** (from **318**, n = 1–3[239,247]), **322** (from **319**[237]), and **323** (from **320**[252]);
- *gem*-difluorocycloalkanols **324** (from **289**[237] and **295**[241]) and **325**[253];
- *gem*-difluorocycloalkanones **326** (from **324**, n = 1,[237] 4[241]);
- sulfonyl chlorides **327** (from **318**, n = 1[247]) and **328** (from **319**[237]);
- carboxylic acid **329** (from **320**);[254]
- *gem*-difluorocycloalkylbromides **330** (from **312**, n = 1[247]) and **331** (from **313**, n = 1[237]);
- boronic esters or trifluoroborates **332** (from **330**[247]), **333** (from **333**[237] or **313**, n = 1[255]), and **334** (from **314**, n = 1[255–261]). In the latter case, decarboxylative borylation, a relatively novel transformation type, was used (see Scheme 113 for a randomly selected example[259]).



Scheme 113. Decarboxylative borylation of carboxylic acid **314** (n = 1)

Fluorinative ring expansions. This approach is especially attracting for the preparation of β,β-difluorinated cycloheptyl and cyclobutyl building blocks, although it was also used to obtain cyclohexane derivative **310**. In particular, Hara and co-workers reported electrochemically induced fluorinative ring expansion of cycloalkylideneacetates **335** giving fluorinated esters **310** and **336** (Scheme 114).[262]



Scheme 114. Electrochemically induced fluorinative ring expansion of cycloalkylideneacetates **335**

"Difluorohomologation" of cyclic ketones[28] is a useful approach to the synthesis of 2,2-difluorocycloalkanones (*e.g.*, **339**). The reaction sequence includes *gem*-difluorocyclopropanation of silyl enol ether **337** followed by base-promoted cyclopropane ring opening. Amii and co-authors used $BrCF_2CO_2Na$ at 150 °C for the first step;[263] in our recent work, we relied on the CF_3SiMe_3 – NaI system (Scheme 115).[241]

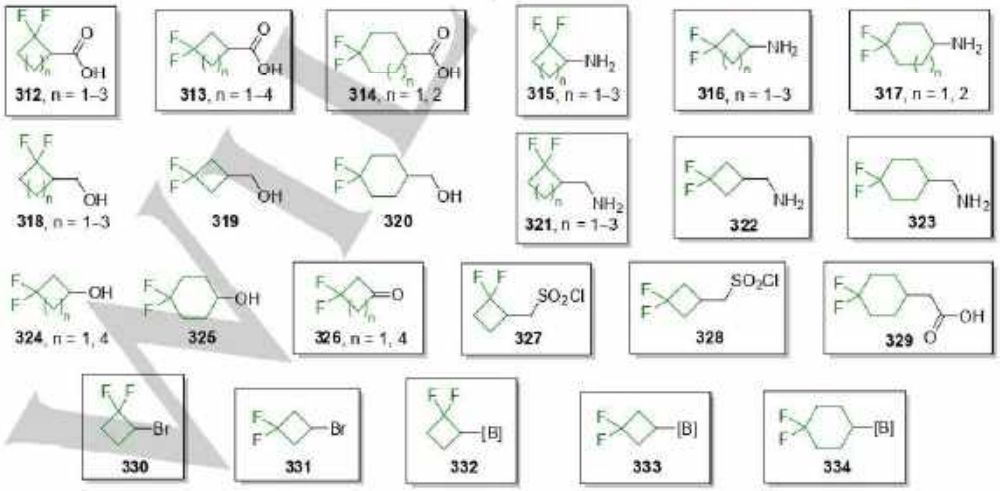
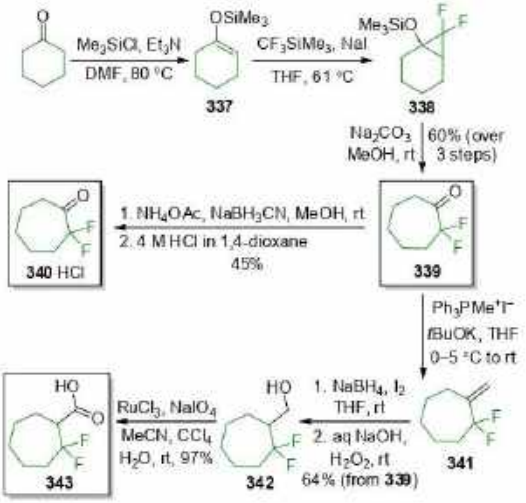


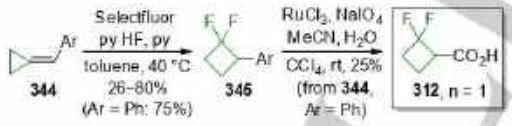
Figure 5. *gem*-Difluorocycloalkyl building blocks prepared via the deoxofluorination ([B] = boropinacolate (BPin), borocatecholate (BCat), or $BF_3^-K^+$)



Scheme 115. "Difluorohomologation" of cyclohexanone

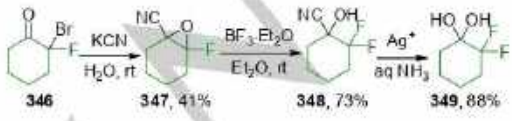
Compound **339** was the key intermediate in the preparation of several other building blocks, i.e. amine **340**, alcohol **342**, and carboxylic acid **343**.

Very recently, Li and co-workers described a Selectfluor – HF·py-mediated Wagner – Meerwein-type rearrangement of methylenecyclopropanes **344** leading to β,β-difluorinated arylcyclobutanes **345** (Scheme 116).[264] Apart from various functionalized aromatic derivatives, the method was also used to obtain building blocks **312**, **315**, and **318** (n = 1) via Ru-catalyzed oxidation of the phenyl moiety. This reaction sequence was much shorter than that reported previously by our group.[247]



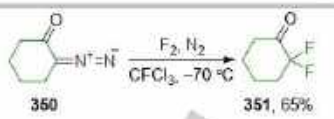
Scheme 116. Synthesis of β,β-difluorinated cyclobutanes via the Wagner – Meerwein-type rearrangement

Other fluorinative methods. In 1970, Cantacuzène and Leroy described synthesis of 2,2-difluorocyclohexanone as hydrate **349** via BF_3·Et_2O-induced ring opening of epoxide **347** (Scheme 117).[265]



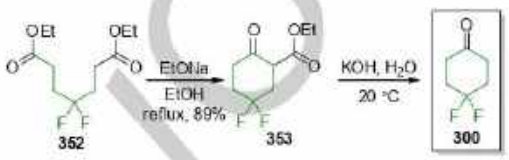
Scheme 117. Synthesis of 2,2-difluorocyclohexanone hydrate (**349**) via fluoride-induced ring opening of epoxide **347**

Patrick and co-workers reported fluorination of α-diazoketone **350** with diluted gaseous F_2 providing free 2,2-difluorocyclohexanone (**351**) (Scheme 118).[266]



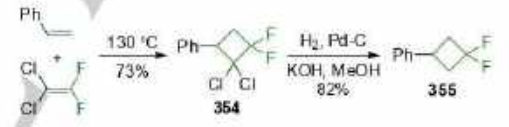
Scheme 118. Synthesis of 2,2-difluorocyclohexanone (**351**) via fluorination of diazo ketone **350**

Cyclizations and cycloadditions of fluorinated intermediates. The Dieckmann condensation of *gem*-difluorinated diester **352** was the earliest approach to 4,4-difluorocyclohexanone (**300**) reported by Roberts and co-workers in 1968 (Scheme 119).[267]



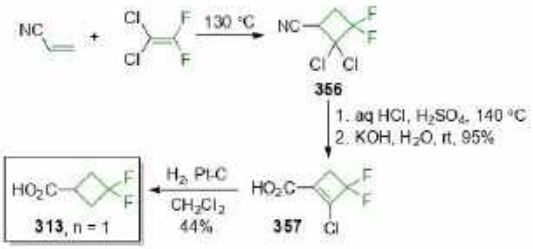
Scheme 119. Synthesis of 4,4-difluorocyclohexanone (**300**) via the Dieckmann condensation

Early synthesis of 1,1-difluoro-3-phenylcyclobutane (**355**) relied on [2+2] cycloaddition of styrene and 1,1-dichloro-2,2-difluoroethylene (Scheme 120).[268] Further modifications of **355** (i.e., bromination or nitration – reduction) allowed for the preparation of some aromatic building blocks bearing a γ,γ-difluorocyclobutyl moiety.[269]



Scheme 120. Synthesis of 1,1-difluoro-3-phenylcyclobutane (**355**) via [2+2] cycloaddition

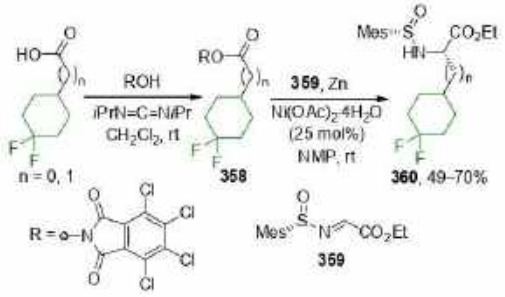
Later in 1987, similar approach was used by Dolbier and co-workers for the synthesis of 3,3-difluorocyclobutanecarboxylic acid (**313**, n = 1) (Scheme 121).[270] Obviously, this method has been replaced by newer one based on the deoxofluorination.



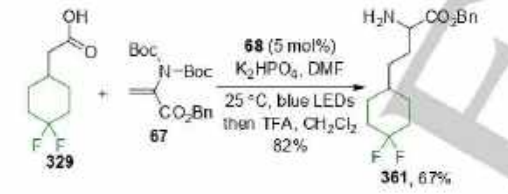
Scheme 121. Synthesis of 3,3-difluorocyclobutanecarboxylic acid (**313**, n = 1) via [2+2] cycloaddition

Transformations of alicyclic compounds already containing the CF_2 moiety. Many of these reactions have already been discussed above (see Figure 5 and the accompanying

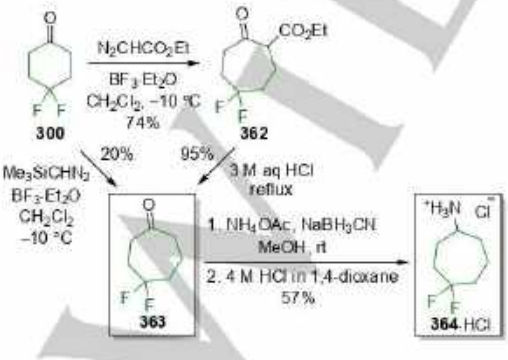
discussion). It should be noted that 4,4-difluorocyclohexyl-substituted building blocks have been often used as model substrates in recent studies describing the development of novel synthetic methodologies. Apart from decarboxylative borylations (see Scheme 113), decarboxylative synthesis of amino acid derivatives can be outlined. For example, in 2018, Baran and co-authors reported a diastereoselective Ni-catalyzed reaction of redox-active esters **358** with sulfinimide **359** giving amino acid derivatives **360** (Scheme 122).[271] Later in 2021, an organo-photocatalytic version of this reaction was reported by Kärkäs and co-workers.[272] Also, visible-light-mediated organocatalytic decarboxylative conjugate addition of compound **329** to dehydroalanine derivative **67** (Scheme 24) was applied to the synthesis of amino ester **361** (Scheme 123).[70]



Scheme 122. Synthesis of *gem*-difluorocycloalkyl-substituted amino acid derivatives **360** via Ni-catalyzed decarboxylative radical addition (NMP – *N*-methylpyrrolidone, Mes – mesityl)



Scheme 123. Synthesis of amino acid derivative **361** via conjugate addition to dehydroalanine derivative **67**



Scheme 124. Synthesis of δ,δ-difluorocycloheptyl building blocks via the ring expansion

Another important reaction category of this section includes ring expansions of *gem*-difluorocycloalkyl substituents. This method was used for the synthesis of δ,δ-difluorocycloheptyl building blocks, i.e. 4,4-difluorocycloheptanone (**363**)[157,241] and 4,4-difluorocycloheptylamine (**364**) (Scheme 124).[241]

4. Synthesis of other fluorinated cycloalkyl building blocks

Unlike mono- and *gem*-difluorinated cycloalkyl building blocks, other difluorinated cycloalkyl counterparts were presented in the literature scarcely (Figure 6). In particular, the synthesis was covered only for 1,2-difluorocyclopropyl, 1,2- and 3,4-difluoro-cyclopentyl, 1,2-, 2,3-, 2,4-, 2,6-, and 3,4-difluorocyclohexyl, and 1,2-difluorocycloheptyl derivatives (although in most cases, non-functionalized compounds were reported).

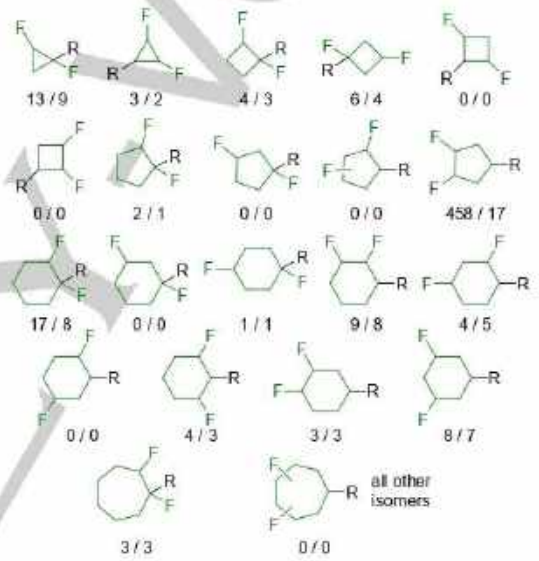


Figure 6. Number of compounds bearing other difluorinated C_3–C_7 cycloalkyl substituents / document referring to them in *Reaxys*® Database (accessed on 12-03-2022)

Synthesis of polyfluorinated cycloalkyl building blocks was also documented in the literature (Figure 7). Two categories can be outlined here: compounds with perfluorinated or almost fully fluorinated cycloalkyl substituents that were described somewhere in the middle of XX century, and vicinally polyfluorinated cyclohexane derivatives reported relatively recently (mostly by O'Hagan and co-workers). While the latter were already considered or even used for early drug discovery purposes, the former ones were historically filtered out by most structural alerts and largely ignored by medicinal chemists. However, with increased interest in previously neglected chemotypes,[22] fluorine-rich cycloalkyl substituents may find their application in drug discovery in the nearest future. Other chemotypes somewhat better presented in the literature are 2,2,3-trifluorocyclopropyl, 2,2,3,3-tetrafluorocyclopropyl, and 2,2,3,3-tetrafluorocyclobutyl derivatives.

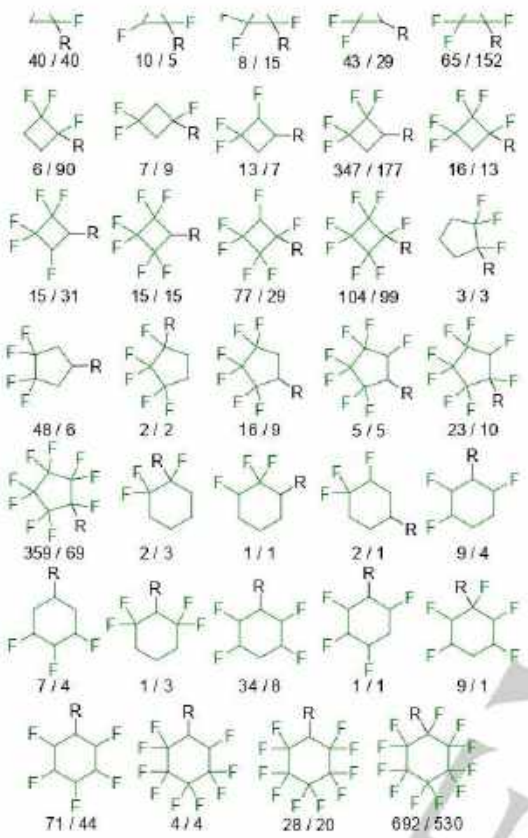
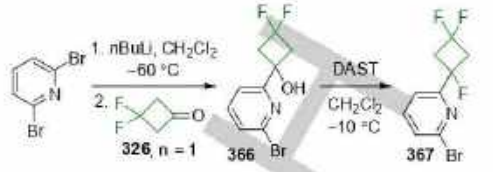


Figure 7. Number of compounds bearing tri- and polyfluorinated C_5–C_7 cycloalkyl substituents / document referring to them in *Reaxys*® Database (only compounds with documented synthetic approaches are shown) (accessed on 12-04-2022)

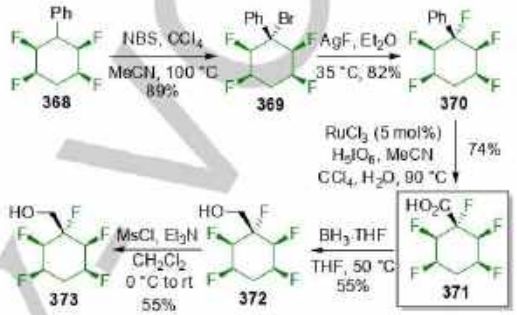
The following approaches were used to synthesize compounds shown in Figures 6 and 7:

- nucleophilic substitution with fluoride (including deoxy- and deoxofluorination);
- epoxide and cyclic sulfite ring opening with fluoride (also in tandem with nucleophilic substitution with fluoride);
- cycloalkene 1,2-difluorination;
- other fluorinations;
- cyclopropanations of fluorinated alkenes;
- [2+2] cycloadditions with perhalogenated ethylenes;
- hydrogenation of polyfluorinated arenes;
- addition to the double bond of perfluoroalkenes;
- other transformations of fluorinated compounds.

Nucleophilic substitution with fluoride. This approach can be used with already fluorinated substrates to introduce a remaining fluorine atom. This was the case with 1,3,3-trifluorocyclobutyl derivative **367** (Scheme 125),[273] as well as 1,2,3,5,6-pentafluorocyclohexyl derivative **370** used to obtain several building blocks **371–373** (Scheme 126; see Scheme 135 for the synthesis of precursor **368**);[274] see also the next section.

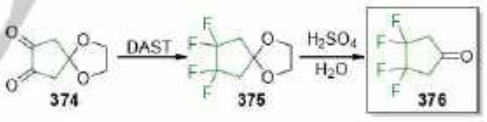


Scheme 125. Synthesis of 1,3,3-trifluorocyclobutyl derivave **367** (the yields were not provided in the original document)

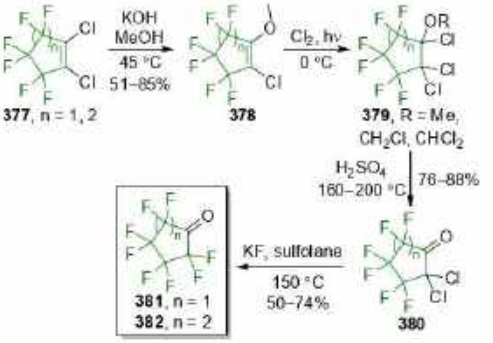


Scheme 126. Synthesis of 1,2,3,5,6-pentafluorocyclohexyl building blocks

Also, deoxofluorination of 1,2-dione **374** was proposed as an approach to the synthesis of 3,3,4,4-tetrafluorocyclopentyl-substituted building block **376** (Scheme 127).[275]

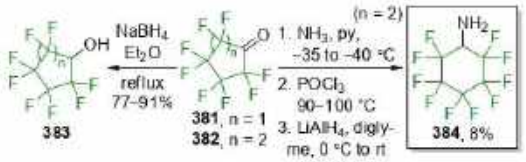


Scheme 127. Synthesis of 3,3,4,4-tetrafluorocyclopentyl-substituted building block **376** (no experimental details were given in the original publication)

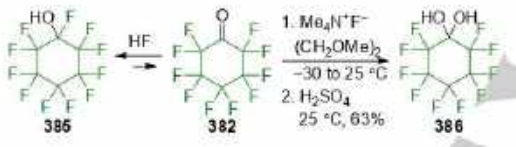


Scheme 128. Synthesis of perfluorinated ketones **381** and **382** via nucleophilic substitution

Nucleophilic chloride – fluoride exchange was the last step in the reaction sequence used to obtain perfluorinated ketones **381** and **382** starting from pehalogenated alkenes **377** (Scheme 128).[276] Compounds **381** and **382** were used to obtain some other building blocks including alcohols **383**[276] and amine **384**[277] (Scheme 129). Interestingly, ketone **382** gave adduct with $Me_4N^+F^-$ that was transformed hydrate **386** upon treatment with concentrated H_2SO_4 (so that dehydration of H_2SO_4 formally occurred) (Scheme 130).[278] Moreover, even **382** itself was capable of dehydrating H_2SO_4. In the presence of HF, formation of unstable undecafluorocyclohexanol (**385**) was observed from **382**. The compound could be isolated below –30 °C but was stable under its own vapor pressure even at ambient temperature.



Scheme 129. Synthesis of 1-H-octafluorocyclopentyl- and 1-H-decafluorocyclohexyl building blocks



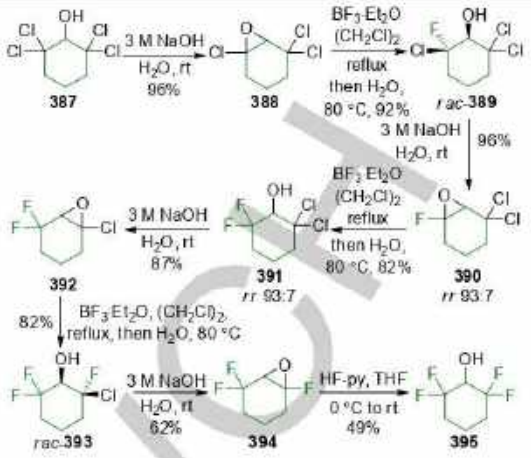
Scheme 130. Some other transformations of perfluorocyclohexanone (**382**)

Epoxide or cyclic sulfate ring opening with fluoride (also in tandem with nucleophilic substitution with fluoride). A series of fluoride-induced epoxide ring openings and base-promoted re-formations were used to obtain 2,2,6,6-tetrafluorocyclohexanol (**395**) starting from 2,2,6,6-tetrachlorocyclohexyl counterpart **387** (Scheme 131).[279,280] The overall result of this sequence is formal nucleophilic chloride – fluoride exchange.

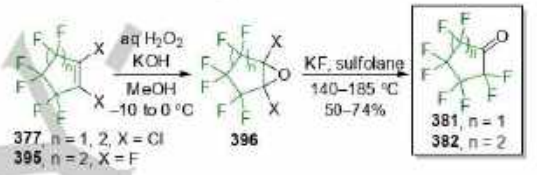
An alternative (and much shorter) approach to perfluorocycloalkanones **381** and **382** was also based on nucleophilic epoxide ring opening.[276] In this case, epoxidation of alkenes **377** or **396** was followed by reaction with KF (Scheme 132); with **377** as the starting material, nucleophilic substitution also occurred at the last step.

A general approach to the vicinally fluorinated cycloalkane derivatives includes fluoride-induced epoxide ring opening followed by direct or indirect nucleophilic fluorination at the OH group formed. In 2009, Simpson and Zhao applied this method for the preparation of diastereomeric amino acid derivatives **402** and **405** (Schemes 133 and 134).[281] In these examples, the epoxide ring opening and deoxyfluorination steps were spaced apart in the synthetic scheme (at the first and the last steps, respectively).

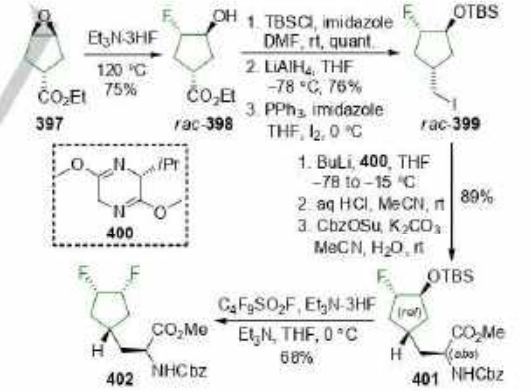
In a recent work, multigram synthesis of building block **406** by a one-pot difluorination of epoxide **397** was described (Scheme 135).[282] This procedure was shown to be superior over several other methods and was used on up to 300 g of **397**. Alcohol **407** was also synthesized.



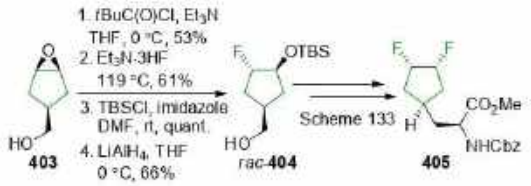
Scheme 131. Synthesis of 2,2,6,6-tetrafluorocyclohexanol (**395**) (*rr* – regioisomer ratio)



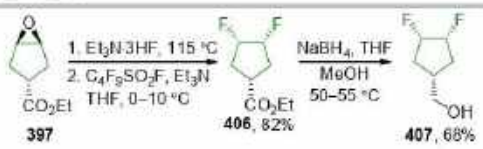
Scheme 132. Synthesis of perfluorinated ketones **381** and **382** via epoxide ring opening



Scheme 133. Synthesis of amino acid derivative **402**

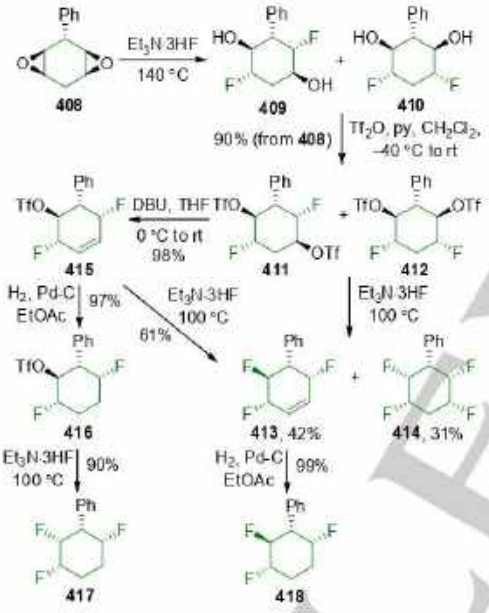


Scheme 134. Synthesis of amino acid derivative **405**



Scheme 135. Scalable synthesis of 3,4-difluorocyclopentyl building blocks

The above strategy was exploited extensively by O'Hagan and co-workers for the synthesis of all-*cis* fluorinated cyclohexanes. In particular, reaction of bis-epoxide **408** with $Et_3N{\cdot}3HF$ gave a mixture of diols **409** and **410** that was triflated and then subjected to reaction with $Et_3N{\cdot}3HF$ again (Scheme 136).[283] As a result, products **413** and **414** were obtained.

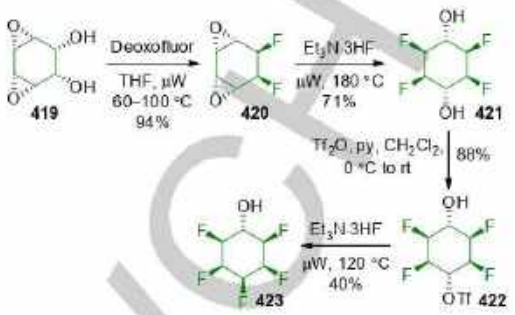


Scheme 136. Synthesis of 2,3,5,6-tetrafluorocyclohexyl derivative **414**, 2,3,5-trifluorocyclohehyl derivatives **417** and **418** (relative configurations are shown)

Later, it was shown that if triflates **411** and **412** were fluorinated separately, they gave **413** and **414**, respectively, as the only products with improved yields.[284] The stereochemistry of **413** was addressed to the participation of phenonium ions; to avoid this, elimination was performed with triflate **411**. Further hydrogenation of alkene **415** followed by fluorination gave all-*cis*-2,3,5-trifluorocyclohexyl derivative **417**, whereas hydrogenation of **413** gave diastereomer **418**.

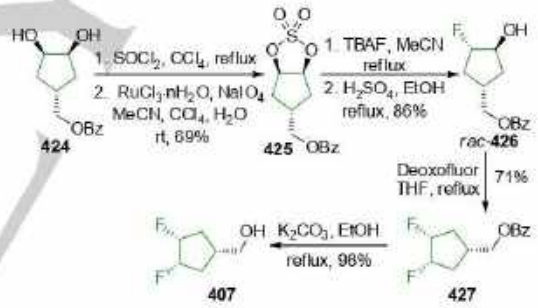
A possibility of modification at the phenyl ring of the obtained products was demonstrated.[283,285] In particular, iodination of **414** was the key step in the synthesis of amino acids and peptides bearing an all-*cis*-2,3,5,6-tetrafluorocyclohexyl substituent.[286] Unfortunately, oxidation of the phenyl ring to install the COOH moiety did not work, but the unwanted side reactions could be blocked by introducing methyl group or fluorine atom at the α position (see Scheme 126).[274,287]

The above methodology was used to obtain alcohol **423**, an intermediate in the synthesis of all-*cis*-hexafluorocyclohexane (Scheme 137).[288] Analogously, all-*cis*-2,3-difluorocyclohexyl-substituted derivatives were prepared.[285]



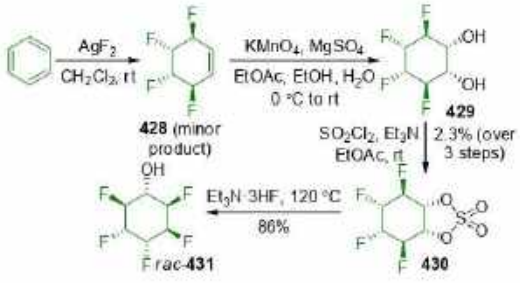
Scheme 137. Synthesis of 2,3,4,5,6-pentafluorocyclohexanol **423**

Apart from epoxides, cyclic sulfates (easily obtainable from the corresponding 1,2-diols) were used as the synthetic equivalents of *cis*-vicinal difluorocycloalkane moieties; it seems that this methodology is less preferable though. In particular, an earlier approach to the compound **407** included ring opening of sulfate **424** followed by deoxyfluorination (Scheme 138).[282]



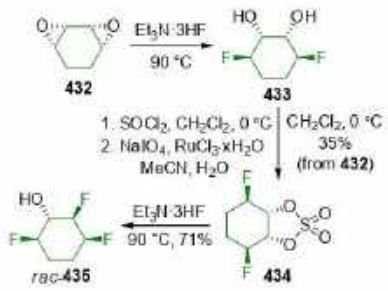
Scheme 138. Synthesis of alcohol **407** via cyclic sulfate ring opening

Also, a diastereomer of the compound **423**, alcohol **431**, was prepared via ring opening of bicyclic sulfate **430** (Scheme 139).[289] As in the case of **423**, compound **431** was an intermediate in the synthesis of 1,2,3,4,5,6-hexafluorobenzene.



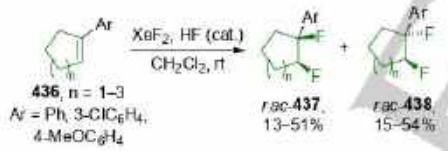
Scheme 139. Synthesis of 2,3,4,5,6-pentafluorocyclohexanol **431**

Synthesis of 2,3,6-trifluorocyclohexanol **435** included both epoxide and cyclic sulfate ring opening steps (Scheme 140).[290] Again, compound **435** was an intermediate in the synthesis of all-*cis*-1,2,3,4-tetrafluorocyclohexane.



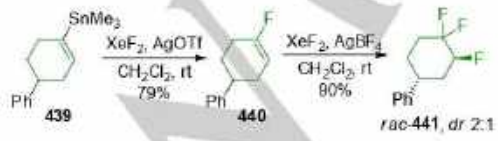
Scheme 140. Synthesis of 2,3,6-pentafluorocyclohexanol **435**

Cycloalkene 1,2-difluorination. Since both epoxides and 1,2-diols used as the starting materials in the previous sections are often obtained from the corresponding cycloalkenes, direct 1,2-fluorination of the latter compounds could be a convenient and straightforward approach to vicinally di- and polyfluorinated cycloalkyl derivatives. Early reports on such transformations relied on the use of XeF_2 and catalytic amounts of HF (Scheme 141).[291] The reaction lacked sufficient diastereoselectivity, with *cis* : *trans* ratio varied from 1:4.2 to 2.5:1 depending on the ring size and the substituent, and likely involved formation of carbocationic intermediates.



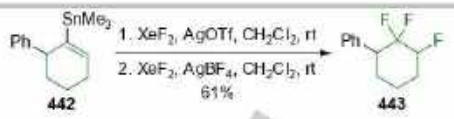
Scheme 141. Cycloalkene 1,2-difluorination with XeF_2

A modification of this process involved reaction of vinyl fluoride **440** (in turn prepared by fluorination of vinyl stannane **439**) with XeF_2 – $AgBF_4$ (Scheme 142).[292] Direct one-step transformation of **439** into trifluoride **441** was also possible but with lower yield (51%). Analogously, 2,2,3-trifluorocyclohexyl derivative **443** was obtained (Scheme 143).



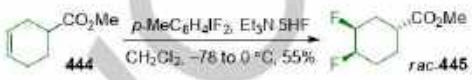
Scheme 142. Synthesis of 3,4,4-trifluorocyclohexyl derivative **441**

Unfortunately, in all three examples described above, no further functionalization of the obtained products to obtain the corresponding building blocks was performed.



Scheme 143. Synthesis of 2,2,3-trifluorocyclohexyl derivative **443**

In 1998, Hara and co-workers described diastereoselective 1,2-*syn*-difluorination of cyclohexene derivative **444** with iodotoluene difluoride – $Et_3N{\cdot}5HF$ (Scheme 144).[293] A slightly modified version of this protocol was evaluated for the synthesis of cyclopentane derivative **406**, however, it did not work (possibly due to the improper stereochemistry of the desired product).[282]



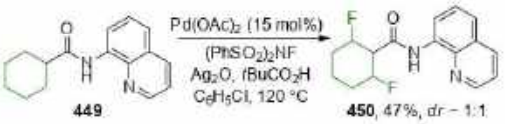
Scheme 144. Synthesis of 3,4-difluorocyclohexyl derivative **445**

One more related protocol for the diastereoselective alkene 1,2-difluorination was described by Jacobsen and co-authors in 2016.[294] It involved the use of py·9HF as the fluorination reagent, MCPBA as the oxidant, and aryl iodide **447** as the catalyst (Scheme 145). Notably, *anti* difluorination was observed in this case.



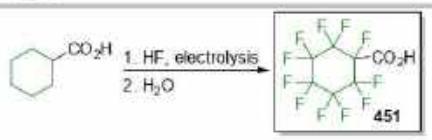
Scheme 145. Synthesis of 3,4-difluorocyclohexyl derivative **445**

Other fluorinative methods. Directed Pd-catalyzed C–H fluorination of amide **449** resulted in the formation of 2,6-difluorocyclohexanecarboxylic acid derivative **450** (Scheme 146).[295]



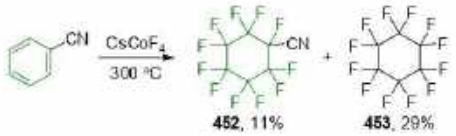
Scheme 146. Synthesis of 2,6-difluorocyclohexanecarboxamide **450**

Perfluorocycloalkanecarboxylic acids (in particular, perfluorocyclohexanecarboxylic acid, **451**) can be obtained by electrolysis of the corresponding non-fluorinated acids by electrolysis in liquid HF (Scheme 147).[296] Benzoic acid is also a suitable substrate to obtain compound **451** under these conditions.[297] This method is of industrial significance. Electrolytic perfluorination of some other substrates, e.g. cyclopentylmethyl acetate, was reported, providing the corresponding perfluorocycloalkanecarboxylic acid derivatives in low yield.[298]



Scheme 147. Synthesis of perfluorocyclohexanecarboxylic acid (**451**)

Alternatively, fluorination of benzonitrile with $CsCoF_4$ was applied to obtain perfluorinated nitrile **452** together with dodecafluorocyclohexane (**453**) (Scheme 148).[299]

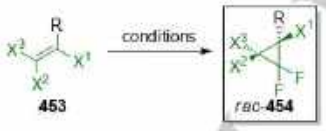


Scheme 148. Synthesis of perfluorocyclohexanecarbonitrile (**452**)

Compounds **451** and **452** were used to obtain some other building blocks containing the undecafluorocyclohexyl moiety, namely, *cyclo*-$C_6F_{11}Br$, *cyclo*-$C_6F_{11}I$ (by Hunsdiecker reaction of **451**),[300] or *cyclo*-$C_6F_{11}CH_2NH_2$ (by reduction of **452** with $LiAlH_4$).[299]

Cyclopropanations of fluorinated alkenes. All *vic*-di- and polyfluorinated cyclopropyl derivatives were synthesized via the cyclopropanation of the corresponding fluorinated alkenes. If the CF_2 moiety was present in the target structure, one of the protocols for the *gem*-difluorocyclopropanation was typically used at the key step (Table 6).

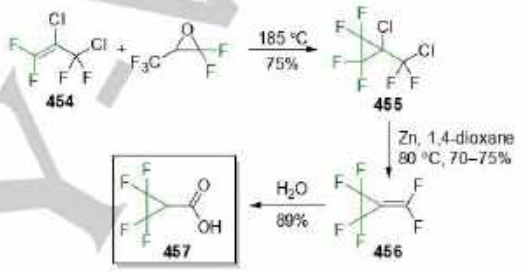
Table 6. Synthesis of polyfluorinated cyclopropanes via *gem*-difluorocyclopropanation



#	$X^1/X^2/X^3$	R	Conditions	Yield, %	Ref
1	F/F/F	Cl	difluorodiazirine, 150–160 °C	85	[301]
2	F/F/F	CN		68	[301]
3	F/F/H	Cl	hexafluoropropene epoxide, 200 °C	75[a]	[302]
4	F/H/F	Cl		80[a]	[302]
5	F/F/F	CO_2Me	hexafluoropropene epoxide, 225 °C	15	[303]
6	F/F/F	Cl, Br, CH_2CH_2Br	hexafluoropropene epoxide, 180–190 °C	63–92	[304] [305]
7	H/F/F	aryl[b]	$ClCF_2CO_2Na$, diglyme, 180 °C	34–57	[306]
8	F/F/F	aryl[b]	$ClCF_2CO_2Na$, diglyme, 180 °C	53–93	[307]
9	F/F/H	Ph, PhC_6H_4	CF_3SiMe_3, NaI, THF, reflux	40–48	[308]

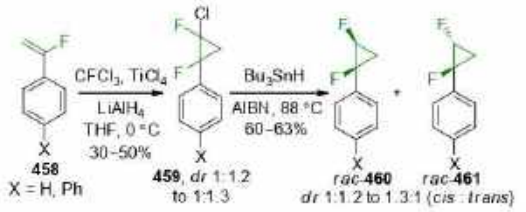
[a] Product slowly isomerized to other stereoisomer. [b] Including 3- and/or 4-BrC_6H_4.

An alternative approach to 2,2,3,3-tetrafluorocyclopropyl derivatives (including carboxylic acid **XXX**) was described by Smart in 1974.[309,310] It included *gem*-difluorocyclopropanation of 2,3-dichlorotetrafluoropropene (**454**), reductive dechlorination, and hydrolysis of the resulting strained alkene **456** (Scheme 149). Some other building blocks were obtained from **457** including primary alcohol (by reduction with borane) and primary bromide (by further Appel bromination).[310]



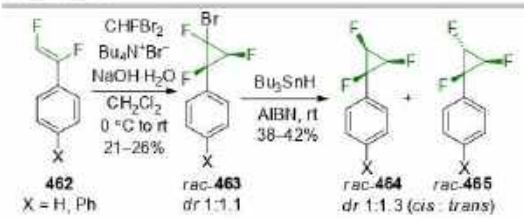
Scheme 149. Synthesis of 2,2,3,3-tetrafluorocyclopropanecarboxylic acid (**457**)

Other di- and trifluorinated cyclopropanes were described in a recent paper by O'Hagan and co-workers.[308] Thus, 1,2-difluorocyclopropyl derivatives **460** and **461** were obtained from monofluorinated styrenes **458** via chlorofluorocyclopropanation and reductive dechlorination (Scheme 150).



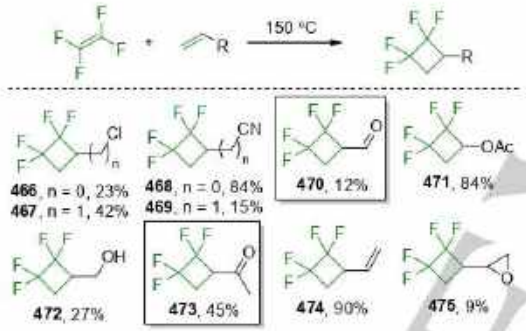
Scheme 150. Synthesis of 1,2-difluorocyclopropyl derivatives **460** and **461**

Analogously, 1,2,3-trifluorocyclopropanes **464** and **465** were obtained from α,β-difluorostyrenes **462** (Scheme 151; see also Table 6, Entry 9).[308] A more efficient method was developed for the preparation of **465**; it involved the use of $CHFI_2$ instead of $CHFBr_2$ for the cyclopropanation (38% and 75% yields for the first and the second steps, respectively). However, only **465** could be obtained using this sequence; the second iodide diastereomer that should lead to **464** underwent cyclopropane ring opening upon the deiodination.



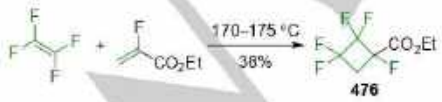
Scheme 151. Synthesis of 1,2,3-difluorocyclopropyl derivatives **464** and **465**

[2+2] cycloadditions with perhalogenated ethylenes. Formal [2+2] cycloaddition of monosubstituted alkenes and tetrafluoroethylene is an old but general approach to 2,2,3,3-tetrafluorocyclobutyl derivatives. The first detailed report describing the scope of this method was published in 1949 (Scheme 152).[311] In later works, synthesis of some other important 2,2,3,3-tetrafluorocyclobutyl (= R^F) building blocks was reported, e.g. R^FBr (from vinyl bromide),[312] $R^FCH_2NH_2$[313] and R^FCOOH[314] (from **468**), $R^FCH_2CH_2OH$ and $R^FCH_2CH_2Br$ (from **474**).[315]

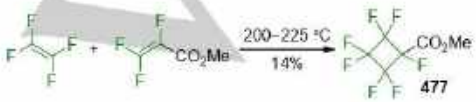


Scheme 152. Synthesis of 2,2,3,3-tetrafluorocyclobutyl derivatives

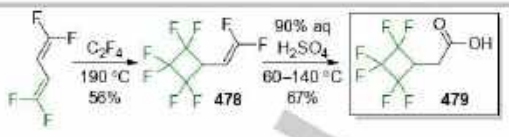
If the second component of the reaction was also fluorine-containing alkene, penta-, hexa-, and heptafluorocyclobutyl derivatives could be obtained. In particular, the method worked with α-fluoroacrylate (Scheme 153)[316] and trifluoacrylate (Scheme 154).[303] An adduct with 1,1,4,4-tetrafluorobutadiene (compound **478**) was used to obtain carboxylic acid **479** bearing a 2,2,3,3,4,4-hexafluorocyclobutyl moiety (Scheme 155).[317] Analogously, an adduct with methyl trifluorovinyl ether (compound **480**) was an intermediate in the synthesis of perfluorocyclobutanone (**481**) (Scheme 156).[318]



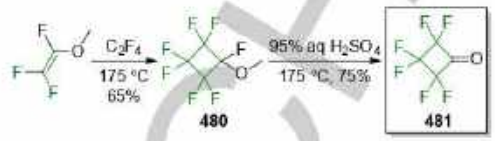
Scheme 153. Synthesis of 1,2,2,3,3-pentafluorocyclobutyl derivative **476**



Scheme 154. Synthesis of perfluorocyclobutyl derivative **477**

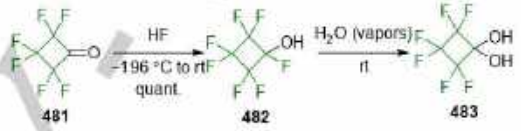


Scheme 155. Synthesis of (2,2,3,3,4,4-hexafluorocyclobutyl)acetic acid (**479**)



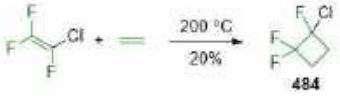
Scheme 156. Synthesis of perfluorocyclobutanone (**481**)

As in the case of perfluorinated cyclohexanone **382** (Scheme 130), compound **481** was prone to the reversible formation of hydrate **483** and HF adduct **482** that hydrolyzed to **483** even by traces of water (Scheme 156).[319]

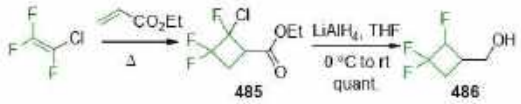


Scheme 157. Synthesis of perfluorinated cyclobutanols

Chlorotrifluoroethylene is another perhalogenated ethylene derivative that was used for the synthesis of polyhalogenated cyclobutyl-substituted building blocks. In particular, its reaction with ethylene gave chloride **484** bearing a 1,2,2-trifluorocyclobutyl moiety (Scheme 158),[312] whereas adduct with ethyl acrylate (compound **485**)[314] was transformed into alcohol **486** with a 2,2,3-trifluorocyclobutyl substituent (Scheme 159).[320]

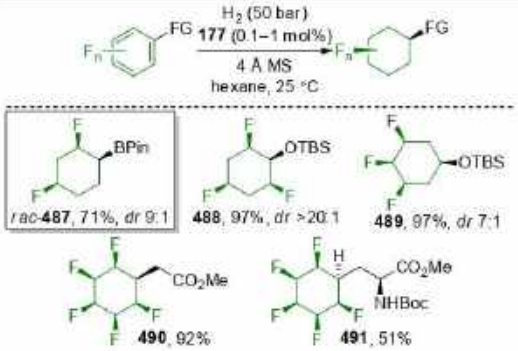


Scheme 158. Synthesis of 1,2,2-trifluorocyclobutyl derivative **484**



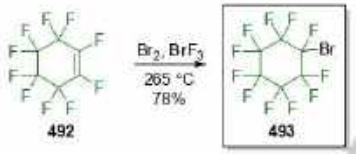
Scheme 159. Synthesis of 2,3,3-trifluorocyclobutyl derivative **486**

Hydrogenation of polyfluorinated arenes. This method has already been mentioned above for the synthesis of monofluorinated cyclohexane derivatives (Schemes 82 and 97); it was also applicable for their more fluorinated counterparts (Scheme 160).[192] [321] 2,3,4,5,6-Pentafluorocyclohexyl (= R^F) derivatives **490** and **491** were used to obtain several other building blocks via the standard functional group transformations, e.g. alcohol $R^FCH_2CH_2OH$, aldehyde R^FCH_2CHO, amine $R^FCH_2CH_2NH_2$, bromide $R^FCH_2CH_2Br$, or azide $R^FCH_2CH_2N_3$.[321]



Scheme 160. Hydrogenation of di- and polyfluorinated arenes

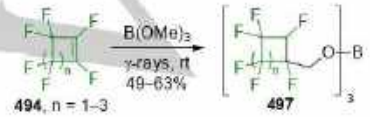
Addition to the double bond of perfluoroalkenes. Some examples involving the use of perfluorinated (or perhalogenated) alkenes to obtain polyfluorinated cycloalkyl derivatives were already mentioned above (see Schemes 128 and 132). In this section, direct 1,2-addition reactions leading to the formation of functionalized derivatives are discussed. In particular, this method was used for the synthesis of undecafluorocyclohexyl bromide (**493**) including reaction of decafluorocyclohexene (**492**) with $BrF_3 – Br_2$ (Scheme 161).[322]



Scheme 161. Synthesis of perfluorocyclohexyl bromide

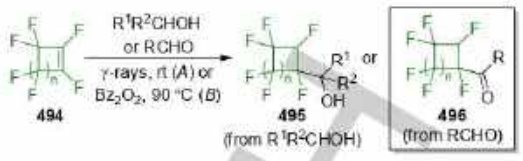
Radical addition of alcohols and aldehydes to perfluorocycloalkenes **494** promoted either with γ-rays or benzoyl peroxide initiation (Table 7).[323,324] Although the first method sometimes gave higher yields and diastereoselectivities of the products, it is obviously of lesser practical significance due to the safety reasons. The approach was also used for the synthesis of boron derivatives **497** (Scheme 162).[325]

Synthesis of hexa- and heptafluorocyclopentanones commenced with the addition-elimination of alkoxide to the double bond of perfluorocyclohexene (**494**, n = 2). Further hydrolysis of adduct **498** gave heptafluorocyclopentanone that existed as enol **499** (Scheme 163). Upon treatment with aqueous HCl, **499** gave the corresponding hydrate; its formation was reversible. Reduction of **498** with $LiAlH_4$ and further hydrolysis led to the formation of hexafluorocyclopentanone (**501**) that existed predominantly in the ketone form (ketone : enol = 74:26 after the reaction, 87:13 after reaching equilibrium). In both cases, 5% of the HF elimination by-product were also observed in the product.

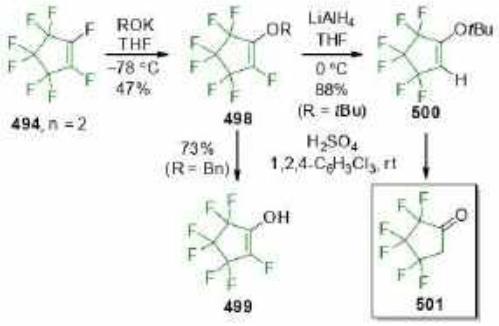


Scheme 162. Synthesis of perfluorinated boron derivatives **455**

Table 7. Radical addition of alcohols and aldehydes to perfluorocycloalkenes



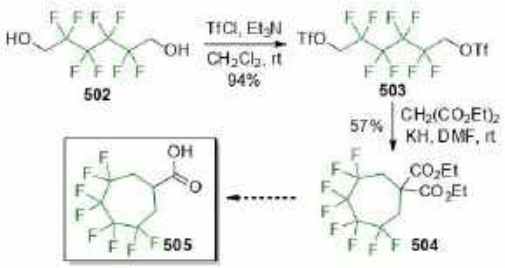
#	n	Reagent, R^1R^2CHOH or RCHO	Yield, % (*dr*, *trans* : *cis*)	
			method *A*	method *B*[324]
1	1	CH_3OH ($R^1 = R^2 = H$)	85 (5:1)[323] 85 (8.7:1)[324]	57 (5:1)
2	1	C_2H_5OH (R^1 = Me, R^2 = H)	70 (2.6:1)[323]	–
3	1	nC_3H_7OH (R^1 = Et, R^2 = H)	67 (1.8:1)[323]	–
4	1	$(CH_3)_2CHOH$ ($R^1 = R^2$ = Me)	80 (5:1)[323]	–
5	1	CH_3CHO (R = Me)	25 (4:1)[323] 67 (3.4:1)[324]	88 (2.6:1)
6	1	C_2H_5CHO (R = Et)	62 (5.1:1)[323]	–
7	1	nC_3H_7CHO (R = *n*Pr)	76 (4.8:1)[323]	–
8	2	CH_3OH ($R^1 = R^2$ = H)	68 (1:1)[324]	64 (1.4:1)
9	2	CH_3CHO (R = Me)	81 (1:1.2)[324]	49 (1:1.6)
10	3	CH_3OH ($R^1 = R^2$ = H)	79 (1:1.4)[324]	67 (1:2.6)
11	3	CH_3CHO (R = Me)	89 (0:1)[324]	87 (1:20)



Scheme 163. Synthesis of polyfluorinated cyclopentanones

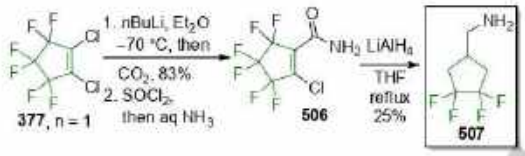
Other transformations of fluorinated compounds. Reaction of ditriflate **503** with malonate anion led to intermediate **504** that

is one step from 3,3,4,4,5,5,6,6-octafluorocyclohexanecarboxylic acid (**505**), not done by the authors though (Scheme 164).[326]



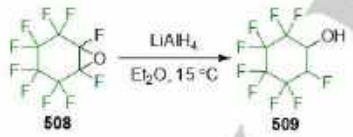
Scheme 164. Synthesis of polyfluorinated cycloheptane derivative **504**

Perhalogenated cyclopentene derivative **377** (n = 1) was the starting material for the synthesis of 3,3,4,4-tetrafluorocyclopentyl building blocks, in particular, amine **507** (Scheme 165).[327–329]



Scheme 165. Synthesis of (3,3,4,4-tetrafluorocyclopentyl)methylamine (**507**)

Also, perfluorinated epoxide **508** (see Scheme 132) was used for the preparation of polyfluorinated cyclohexanol **509** (Scheme 166).[330]



Scheme 166. Synthesis of polyfluorinated cyclohexanol **509**

5. Key in vitro properties of fluorinated cycloalkyl derivatives

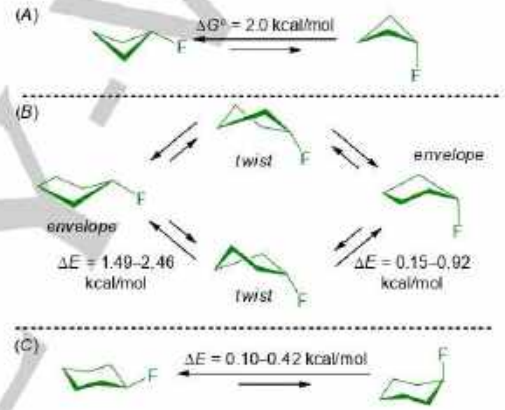
As mentioned in the Introduction, fluorination can affect the compound's physicochemical properties such as acidity/basicity, lipophilicity, or solubility, alter its metabolism, provide additional weak non-covalent interactions possibilities, and have some conformational effects. Whereas for acyclic aliphatic compounds, most of these properties were studied more or less thoroughly,[13,14,335,340,391–398] similar results for the fluorinated cycloalkyl derivatives are scarce. Herein, studies specially designed to reveal some of the above aspects, as well as results mentioned in mainly synthetic works, are covered. Examples, where modification of the compound's properties was a part of medicinal chemistry optimization, are discussed in the next section.

5.1. Conformational properties

Recently, a comprehensive review on the conformations of fluorinated saturated rings was published by Naiorukh and co-workers.[30] Therefore, we will outline only most important features in this section, as well as some recent works not covered by the previous authors.

Studies of monofluorinated cycloalkanes (C_4–C_8) showed that their conformational behavior follows that of the parent hydrocarbons, with (pseudo)equatorial position of the fluorine atom being slightly more preferable (Scheme 167).[341–343] However, this preference is easily modulated by additional fluorine atom(s) and/or the substituent (i.e., the functional group). The following factors should be taken into account (Figure 8):

- steric 1,3-diaxial repulsion (*A*);
- dipole minimization (*B*);
- solvation (*C*);
- hyperconjugation (*D*);
- charge-dipole or coulombic interactions (*E*).



Scheme 167. Conformational equilibria of monofluorinated cycloalkanes (calculated energy differences are given for the gas phase)

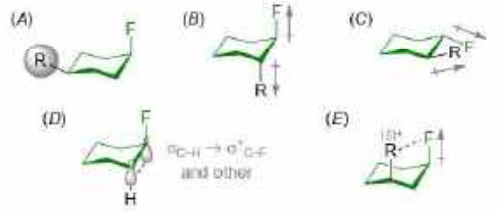


Figure 8. Factors affecting conformations of fluorinated cycloalkyl derivatives

For example, axial conformer of 2-fluorocyclohexanone is slightly more preferable in gaseous phase due to the hyperconjugation, while the equatorial conformer with higher net dipole moment prevails in polar solvents (Scheme 168).[344] The diequatorial conformer dominated for *trans*-2-fluorocyclohexanecarbonitrile[76] and *trans*-2-fluorocyclohexanol (Figure 9).[345] The latter fact was partially addressed to the O–H···F interaction, albeit the steric effects also favor this substituent disposition. For *cis*-2-fluorocyclohexanol,[346] *cis*-2-fluorocyclohexanecarbonitrile,[76] and *cis*-2-fluorocyclohexylamine,[347] the conformers with

axial position of the fluorine atom prevailed according to the calculations (although the difference was small), which was addressed to the hyperconjugation effects.



Scheme 168. Conformational equilibria of 2-fluorocyclohexanone

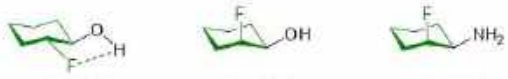
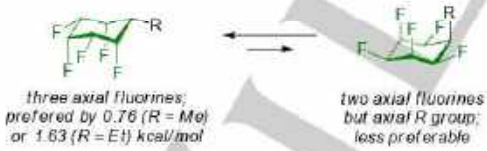


Figure 9. Preferable conformers of 2-fluorocyclohexyl derivatives

The energy differences between the conformers can increase in the vicinally polyfluorinated systems due to the repulsing 1,3-diaxial orientation of the C–F dipoles. Thus, for all-*cis*-1,3,5-trifluorocyclohexane, the all-equatorial conformer is favorable by 3.45–3.60 kcal/mol.[348] For the more fluorinated all-*cis*-derivatives, the 1,3-diaxial fluorine orientation cannot be avoided (Figure 10),[274,283] which leads to the increased "Janus phase" molecule polarization (see also further sections).[288,290,349] Interestingly, for all-*cis*-2,3,4,5,6-pentafluorocyclohexyl derivatives, the dominant conformer was defined by the equatorial position preference of the alkyl substituent, even for the smallest methyl group (Scheme 169).[350]



Figure 10. Conformations of tetra- and pentafluorinated cyclohexyl derivatives



Scheme 169. Conformational equilibria of all-*cis*-2,3,4,5,6-pentafluorocyclohexyl derivatives

Obviously, the fluorine effects illustrated in Figure 8 can also define conformation of the functional substituent attached to the cycloalkyl moiety. In particular, orthogonal orientation was preferable for the phenyl ring and the α-C–F bond in the molecule of **511**, which can be addressed to a small hyperconjugative interaction (Figure 11).[307] Also, antiperiplanar orientation of the α-C–F and C=O bonds was characteristic of amide **512**; $\sigma_{C-F} \rightarrow \pi^*_{C=O}$ or N–H…F interactions may be responsible for that. The observed conformation of amide **510** was addressed to the N–H…F contact (Figure 10).[274]

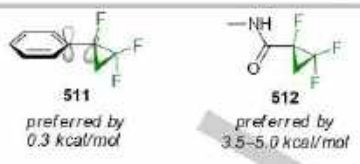


Figure 11. Conformations of 1,2,2-trifluorocyclopropyl derivatives

An interesting effect was observed for *gem*-difluorocyclohexyl derivatives **513–515**.[351] Whereas the methoxy group preferably adopted equatorial position in the case of **514** (as for the parent cyclohexyl methyl ether), axial orientation prevailed for the two remaining representatives (Figure 12). The effect was even more pronounced for the corresponding tetra- and hexafluorinated derivatives (with two and three CF2 moieties). It can be addressed to the C–F and C–OMe dipole repulsion or 1,3-diaxial C–H…OMe stabilizing interaction for **514** and **513**/**515**, respectively.

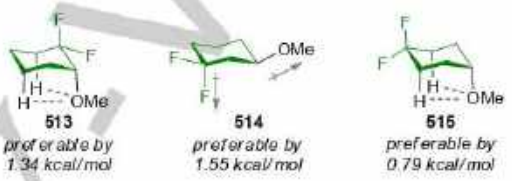
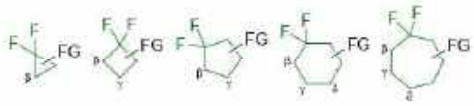


Figure 12. Conformations of gem-difluorocyclohexyl derivatives

5.2. Acidity/basicity

A few months ago, a comprehensive experimental study of the pK_a values for *gem*-difluorocycloalkanecarboxylic acids and *gem*-difluorocycloalkylamines was published by our group (Table 8).[247,352]

Table 8. pK_a values for gem-difluorocycloalkanecarboxylic acids and gem-difluorocycloalkylamines (H_2O, 21 °C)



#	Ring size	FG position	pK_a, FG = COOH	pK_a, FG = NH_2[a]
1	3	no CF_2	4.60±0.02	8.76±0.06
2	3	β	3.25±0.03	–[b]
3	4	no CF_2	4.50±0.05	9.86±0.08
4	4	β	3.62±0.05	7.20±0.02
5	4	γ	4.02±0.02	8.37±0.03
6	5	no CF_2	4.69±0.06	10.52±0.07

7	5	β	3.76±0.04	7.54±0.01
8	5	γ	3.98±0.09	8.83±0.03
9	6	no CF_2	4.85±0.04	10.58±0.06
10	6	β	3.81±0.04	7.45±0.09
11	6	γ	4.18±0.03	9.12±0.02
12	6	δ	4.32±0.02	9.45±0.03
13	7	no CF_2	5.08±0.06	10.69±0.08
14	7	β	3.78±0.05	8.13±0.02
15	7	γ	4.09±0.05	9.35±0.03
16	7	δ	4.36±0.04	9.57±0.11

[a] For the conjugated acid [b] Could not be determined due to instability of the free base

It was found that the impact of *gem*-difluorination on the acidity/basicity of the corresponding carboxylic acids and amines is very similar within the cycloalkane and acyclic series and defined almost exclusively by the CF_2 group position, i.e. in line with the inductive effect of the fluorine atoms. The following rule of thumb was established: upon introducing the CF_2 moiety into the cycloalkyl building block, the pK_a value decreases by 1.1±0.2 (β isomer), 0.7±0.2 (γ isomer), 0.5±0.2 (δ isomer) for carboxylic acids, and 2.8±0.2 (β isomer), 1.4±0.3 (γ isomer), 0.9±0.4 (δ isomer) for primary amines.

5.3. Lipophilicity and solubility

The impact of fluorination on the lipophilicity of the cycloalkyl-substituted derivatives received attention in recent works, still, it is far from complete understanding. A major contribution in this area was done by O'Hagan and co-workers. In particular, they measured Log*P* values for many di- and polyfluorinated phenylcyclopropanes (Figure 13).[307,308] In all cases studied, the lipophilicity of the compound decreased upon the fluorination. The effect was especially pronounced for the derivatives bearing a CHF moiety, showing that these fragments are significantly polarized. The all-*cis*-1,2,3-trifluorocyclopropyl derivative was the most hydrophilic – an example of "facially polar cycloalkyl compounds. In general, the CF_2-substituted derivatives were more lipophilic (but still less than the parent hydrocarbon).

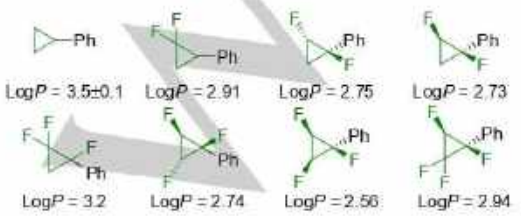


Figure 13. Log*P* values for fluorinated phenylcyclopropanes (relative configurations are shown)

Recently, Linclau and co-workers reported a Log*P* analysis of fluorinated cyclopropylmethanols (Figure 14).[353] In this series, the fluorination resulted in decreased lipophilicity in all cases except *gem*-difluorocyclopropyl derivative, where the Log*P* value did not change. In all examples, the relative Log*P* decrease was smaller upon the fluorination than for the corresponding acyclic counterparts, which was addressed to the hybridization state of the partially unsaturated cyclopropane carbon atoms.

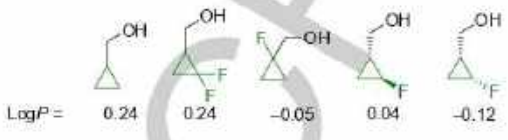
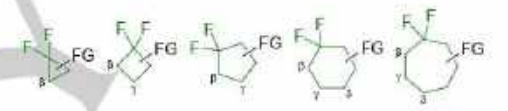


Figure 14. Log*P* values for fluorinated phenylcyclopropanes (relative configurations are shown)

In our work on the C_3–C_7 *gem*-difluorocycloalkyl building blocks cited above, a comprehensive analysis of lipophilicity and aqueous solubility was also provided for the model amide derivatives (Table 9).[247,352]

Table 9. Log*P* and S_w values for amides derived from *gem*-difluorocycloalkanecarboxylic acids and *gem*-difluorocycloalkylamines (21 °C)



Ring size	FG position	FG = C(O)NHPh		FG = NHC(O)Ph	
		Log*P*	S_w, g/L	Log*P*	S_w, g/L
3	no CF_2	1.92±0.01	0.97±0.01	1.29±0.01	3.91±0.03
3	β	2.07±0.01	0.99±0.03	1.51±0.01	0.78±0.02
4	no CF_2	2.26±0.03	0.359±0.004	1.95±0.01	0.82±0.02
4	β	2.03±0.01	0.73±0.01	1.70±0.01	0.451±0.002
4	γ	2.26±0.01	0.066±0.002	1.94±0.01	0.231±0.002
5	no CF_2	2.68±0.01	0.046±0.001	2.23±0.01	0.276±0.02
5	β	2.25±0.01	0.48±0.01	1.87±0.02	0.218±0.006
5	γ	2.50±0.02	0.121±0.001	2.02±0.01	0.348±0.002
6	no CF_2	2.88±0.12	0.038±0.007	2.72±0.02	0.059±0.001
6	β	2.50±0.01	0.067±0.001	2.16±0.01	0.153±0.003
6	γ	2.72±0.04	0.077±0.035	2.31±0.01	0.101±0.003
6	δ	2.63±0.01	0.038±0.017	2.32±0.02	0.036±0.002

7	no CF_2	3.24±0.03	0.022±0.001	3.03±0.01	0.026±0.001
7	β	2.90±0.01	0.060±0.003	2.56±0.02	0.066±0.007
7	γ	3.03±0.02	0.094±0.011	2.57±0.02	0.042±0.001
7	δ	2.95±0.01	0.032±0.001	2.50±0.02	0.076±0.002

It was found that *gem*-difluorination of the cyclopropyl derivatives resulted in increased lipophilicity (Δ*Log*P ~ 0.2). Initially, we addressed this effect to partial sp^2-like hybridization of the carbon atoms in the cyclopropane ring. However, a comparison of our results with those obtained by O'Hagan's and Linclau's groups (Δ*Log*P = –0.6 and 0, respectively; see above) shows that the situation is far more complex. Indeed, the Δ*Log*P value (and even sign) seems to depend on the nature of the substituent attached to the (fluorinated) cycloalkyl moiety. Hence, simple additive schemes of the lipophilicity prediction should be applied with great caution here.

For other model cycloalkyl-derived amides, the lipophilicity either decreased or did not change upon *gem*-difluorination, typically demonstrating the following order for different isomers: β < δ ≤ γ. This effect was least pronounced for the cyclobutane series, with Δ*Log*P ≈ –0.24 and 0 for the β- and γ-isomers, respectively. For the C_5–C_7 homologs, the Δ*Log*P was –(0.38±0.04) for β-isomers, –(0.18±0.02) for γ-isomers, and –(0.27±0.03) for δ-isomers with FG = C(O)NHPh, and about –0.4…–0.5 – for most amides with FG = NHC(O)Ph except the cyclopentane derivative having Δ*Log*P = –0.21. Again, these results demonstrate that the Δ*Log*P value depends not only from the structure of the *gem*-difluorocycloalkyl moiety but also from the nature of the substituent attached, thus questioning the validity of simple additive schemes for the lipophilicity prediction.

Interestingly, a different order of lipophilicity was observed for the acyclic series: δ < γ < β. In other words, acyclic β isomers had considerably lower *Log*P decrese upon the *gem*-difluorination as compared to their cyclic counterparts. This effect can be easily explained by a vector analysis of functional group dipole moments.[335]

Even more complex trends were observed for the compounds' aqueous solubility. While higher *Log*P values were typically related to lower aqueous solubility, this correlation was modest (R^2 = 0.69). A possible explanation might include the effects of numerous crystal packing forces, including weak interactions enabled by fluorine atoms. In most cases, the CF_2-bearing amides were more soluble than their non-fluorinated counterparts but there were noticeable exceptions (e.g. some cyclopropyl and cyclobutyl derivatives).

Finally, O'Hagan and co-workers studied lipophilicity of vicinally polyflorinated cyclohexyl-substituted derivatives.[321,354] They found that a substantial *Log*P decrase was observed for tri-, and tetra-, and pentafluorinated phenylcyclohexanes compared to the parent hydrocarbon and even to biphenyl (Figure 15). This can be mostly addressed to the enormously high dipole moment of such all-*cis* compounds: for 1,2,3,4- and 1,2,4,5-tetrafluorocyclohexanes, μ = 4.91 D and 5.24 D, respectively,[355] 2,3,4,5,6-pentafluorocyclohexyl derivatives – μ ~ 5.5 D;[350] 1,2,3,4,5,6-hexafluorocyclohexane – μ = 6.2 D.[288] These extraordinary properties resulted in naming such systems as "Janus face" or facially polarized cycloalkanes.[356] An explanation refers to a substantial fraction of axially placed fluorine atoms, as well as significant polarization of the opposite axial C–H bonds (see also Figure 10 and Scheme 168).

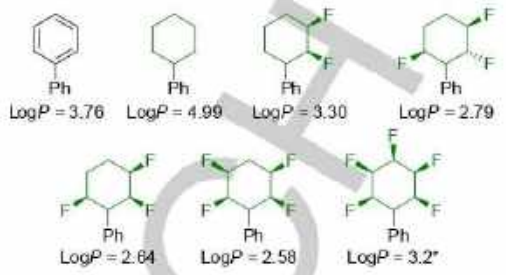
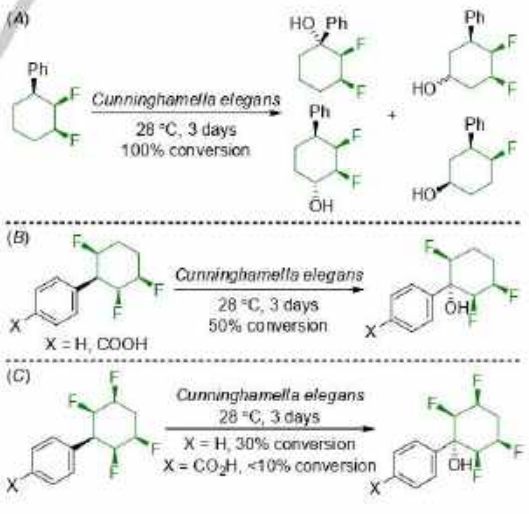


Figure 15. Log*P* values for fluorinated phenylcyclohexanes (relative configurations are shown; * – the value is extrapolated)

5.4. Metabolic stability

In our recent work, we have evaluated microsomal stability of model *N*-benzoyl-(*gem*-diflurocycloalkyl)amines (Table 9, FG = NHC(O)Ph).[352] It was found that compounds from both fluorinated and non-fluorinated series had low intrinsic clearance. Hence *gem*-difluorination either did not decrease the metabolic stability of the compounds or even slightly improved it (up to three-fold for cyclopentyl derivative).

O'Hagan and co-workers studied metabolic properties of their all-*cis* di-, tri-, and tetrafluorocyclohexyl derivatives.[354] They have found that incubation of the corresponding derivatives with *Cunninghamella elegans*, a well-established fungi model for drug metabolism, over three days resulted in cytochromic hydroxylation (Scheme 169). The compound's metabolic stability improved significantly upon increasing the fluorination degree.



Scheme 169. Metabolic transformations of all-*cis*-di-, tri-, and tetrafluorocyclohexyl derivative

5.5. Weak non-covalent interactions

It is now widely recognized that fluorinated moieties can participate in a number of weak interaction types[15–19,357–359] that can potentially increase the compound's affinity to the corresponding biological target and hence lead to higher potency and selectivity. These include hydrogen bonds and similar contacts (C–F…H and F–C–H…X), multipolar interactions (mainly C–F…C=O), halogen bonding (C–F…X), etc. (for biologically relevant systems, X = O or N).

Monofluorinated cycloalkanols were widely used as the model systems to assess intramolecular hydrogen bonding. In particular, Abraham and co-authors determined a 0.8 kcal/mol attraction energy for the C–F…H–O bond in the diequatorial conformer of *trans*-2-fluorocyclohexanol (Figure 9).[345] Using a combination of microwave spectroscopy and quantum chemical calculations, Møllendal and co-workers found that the rotamer of (1-fluorocyclopropyl)methanol with an intramolecular hydrogen bond was at least 1 kcal/mol more stable (Figure 16, *A*).[60] According to Basso and co-authors, nearly 2.6–3.0 kcal/mol were required to be broken by a rotation for the two most stable conformers of *cis*-2-fluorocyclohexanol in the gaseous phase (Figure 16, *B*).[345] Similar results were obtained by Rosenberg for a larger set of fluorinated alcohols (Figure 17).[360] Only for *cis*-3-fluorocyclobutanol, the corresponding interaction was found to be destabilizing (although for all *cis*-3-fluorocycloalkanols, an unfavorable (pseudo)diaxial conformation should be achieved first for the hydrogen bond formation).

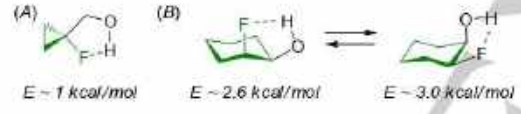


Figure 16. Intramolecular C–F…H–O hydrogen bonds in (1-fluorocyclopropyl)-methanol and *cis*-2-fluorocyclohexanol

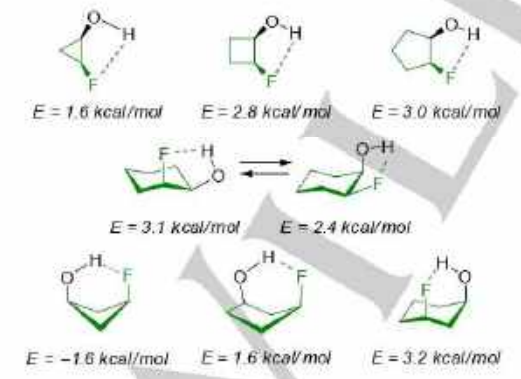


Figure 17. Intramolecular C–F…H–O hydrogen bonds in fluorinated alcohols as determined by Rosenberg

A capability of the fluorine atom of *cis*-2-fluorocyclohexanol to participate in intermolecular hydrogen bonds with the solvent (i.e., methanol) was demonstrated for a gaseous phase; in the solution, such interactions were neglectable.[346]

Linclau and co-workers assessed the so-called hydrogen-bond acidity for the hydroxyl group of cyclohexanol, *cis*- and *trans*-2-fluorocyclohexanol, and 2,2-difluorocyclohexanol.[92] They found that monofluorinated derivatives were less acidic (by 0.20 and 0.01 pK_a units, respectively), which was addressed to the intramolecular hydrogen bond compensating or even overcoming the fluorine electronegativity effect. On the contrary, the *gem*-difluorinated derivative was by 0.31 pK_a unit more acidic. In this case, intramolecular contacts are not enough to override the increased O–H bond polarization.

A number of interesting non-covalent interactions were identified for the vicinally polyfluorinated cyclohexanes. In particular, all-*cis*-1,2,3,4,5,6-hexafluorocyclohexane demonstrated strong C–F…H–C bonds in the solid state (*ca.* 2.40 Å), which resulted in unusually high melting point of the compound (208 °C).[288] For a dimer in gaseous phase (having a different intermolecular contact pattern though), an interaction energy of 8.2 kcal/mol was predicted (Figure 18, *A*).[361]

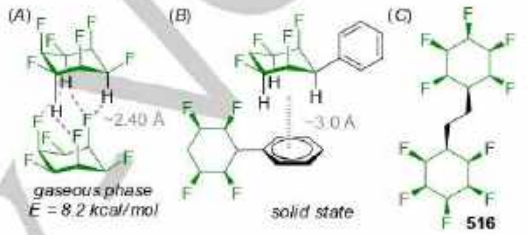


Figure 18. Intermolecular contacts for vicinally polyfluorinated cyclohexanes

Similar intermolecular contacts were observed for all-*cis*-1,2,3,4- and all-*cis*-1,2,4,5-tetrafluorocyclohexanes.[200,355] For phenyl derivative **414**, one more interesting interaction was identified in the crystalline state, namely, C–H…π interaction (ca. 3.0 Å) (Figure 18, *B*).[283] Also, axial C–F…H–C interactions were very strong for all-*cis*-2,3,4,5,6-pentafluorocyclohexyl derivatives, with the H…F distance reaching 2.27 Å in one of the examples.[350] In particular, compound **516** (Figure 18, *C*) had three such contacts (2.46–2.54 Å) per one ring pair and hence remained solid even at 300 °C.

Further examples of weak non-covalent interactions involving fluorinated cycloalkyl moieties are given in the next section as a part of medicinal chemistry optimization stories.

6. Biologically active derivatives of fluorinated cycloalkyl building blocks

6.1. Enzyme inhibitors

The most renowned representative of enzyme inhibitors bearing a fluorinated cycloalkyl moiety is ivosidenib (AG-120), a mutant isocitrate dehydrogenase 1 (IDH1) inhibitor approved by FDA in 2018.[362] Point mutations at the arginine-132 residue in the active site of the enzyme lead to its undesirable activity resulting in accumulation of D-2-hydroxyglutatrate. This oncometabolite blocks normal cellular differentiation and causes oncogenic transformations. Selective inhibition of the mutant enzyme is an obvious approach to this cancer type treatment.

Discovery of ivosidenib commenced from high-throughput screening campaign that resulted in discovery of an initial hit **517** (Figure 19).[363] Initial SAR studies were aimed at improving the compound's potency and selectivity and led to AGI-5198. This

compound had poor metabolic stability, with both cyclohexyl and imidazole rings susceptible towards microsomal oxidation. Replacement of the cyclohexyl substituent with the 3,3-difluorocyclobutyl moiety appeared to be beneficial; this modification was kept though the rest of the study. Further optimization allowed addressing this issue and also further increase the potency. However, the resulting compound AGI-14100 already bearing the moiety appeared to be a potential cytochrome P450 (CYP) 3A4 inducer. Final modifications were focused on the eastern part of the molecule and eventually led to AG-120 (Ivosidenib). Further related IDH1 inhibitors with the 3,3-difluorocyclobutyl moiety were also developed.[364]

Another compound with the 3,3-difluorocyclobutyl moiety that reached the clinical stage is IPN60090, a selective glutaminase-1 (GLS-1) inhibitor.[365] GLS-1 is an enzyme converting glutamine to glutamate; it is a promising therapeutic target in glutamine-dependent tumors. The starting point in the discovery of IPN60090 was compound **519** known previously from an Elan patent (Figure 20).[366] Isosteric replacements of heterocycles accompanied by other minor modifications led to patent-free compound **520**. Further optimization of these series was aimed at improving metabolic stability and physicochemical properties (i.e., aqueous solubility). These goals were achieved by removing the pyridine ring in the northern part of the molecule and modifications in the southern part, respectively. These alterations led to compound **523** bearing the 3,3-difluorocyclobutyl fragment (along with some other analogs lacking this moiety). Adding the fluorine atom into the tetramethylene linker resulted in IPN60090 being slightly more potent. It should be noted that both **523** and IPN60090 were not the most active compounds in the series (e.g., compound **524**); they were selected for further stages based on their favorable physicochemical properties.

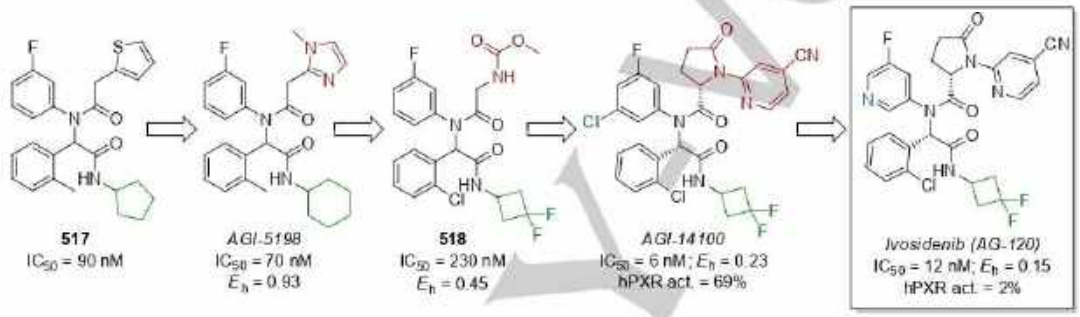


Figure 19. Discovery of Ivosidenib (AG-120) (E_h – microsome stability recorded as the hepatic extraction ratio in human liver microsomes; hPXR act. – cytochrome P450 3A4 inducing potential measured in the human pregnane X receptor activation screen at 1 μM)

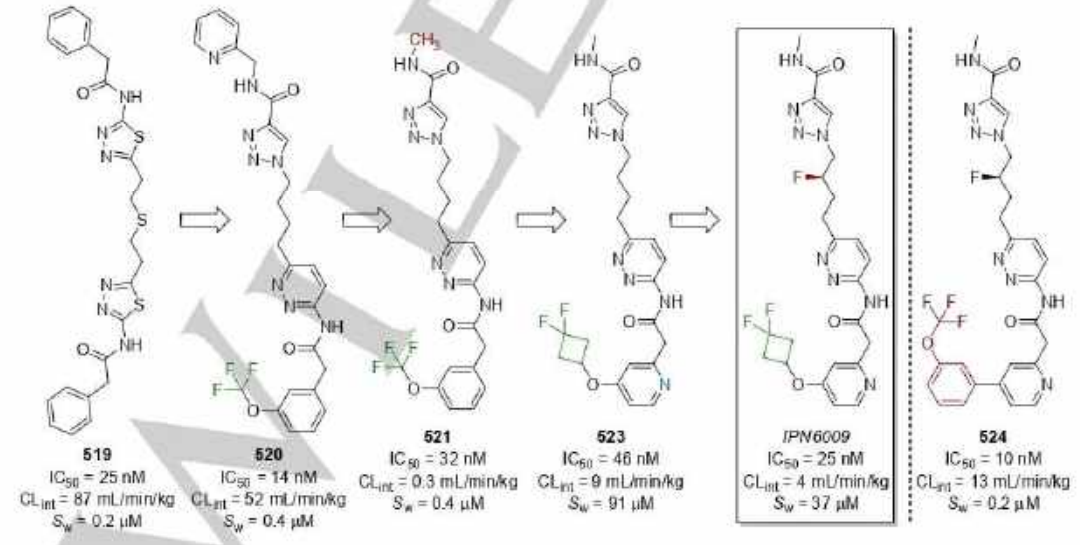


Figure 20. Discovery of IPN60090 (CL_{int} – human liver microsomal intrinsic clearance, mL/min/kg protein; S_w – kinetic aqueous solubility in 0.1 M phosphate buffer at pH = 7.4 and rt)

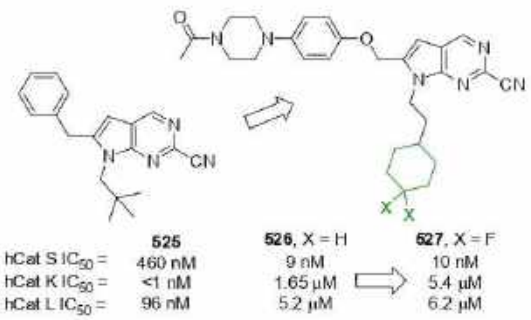


Figure 21. Discovery of compound **527** (hCat – human cathepsin)

All other optimized compounds in this section had a 4,4-difluorocyclohexyl motif. In a search for new inhibitors of cathepsin S, a promising protease target for the reversal of neuropathic pain, compound **526** with in vivo activity in mice was discovered through computer-assisted modeling studies (Figure 21).[367] The compound had high potency and selectivity against other cathepsins (K and L). Further optimization was aimed at additional improvement of this selectivity and resulted in compound **527**. It was suggested that the *gem*-difluorinated moiety fit better into a larger binding pocket of cathepsin S.

Discovery of NMS-P118, a selective poly(ADP-ribose) polymerase-1 (PARP-1) inhibitor with antitumor activity, commenced from the HTS campaign that identified compounds **528** and **529** as the promising starting points (Figure 22).[368] Both compounds lacked selectivity against the PARP-2 isoform and had modest activity in cells. X-Ray crystal structure was obtained for a complex of **529** with enzyme; it revealed that the ω-methoxypropyl side chain did not participate in significant interactions and might be a target for modifications. Optimization of this moiety resulted in piperidine derivative **530** having an excellent PARP1/PARP2 selectivity and high cellular activity.

Unfortunately, compound **530** had negligible bioavailability in mice (<1%). Therefore, a slightly different series starting with related compound **531** was studied in order to obtain derivatives with better ADME profile; in particular, extensive replacements of the benzyl moiety were done. They led to compound **532** containing a 4,4-difluorocyclohexyl moiety. This compound had an excellent aqueous solubility, low metabolic clearance, reasonable plasma protein binding (PPB), and partially regained high cellular activity. Further SAR around the isoindoline moiety identified even more potent derivative NMS-P118 that demonstrated in vivo antitumor activity in mice models.

X-Ray diffraction studies showed that the 4,4-difluorocyclohexyl moiety of NMS-P118 occupied an induced pocket in the binding site of the enzyme and participated in hydrophobic interactions. Furthermore, one of the fluorine atoms of the CF_2 moiety formed a multipolar contact with the backbone C=O group of phenylalanine-897 residue. It was envisaged that the 4,4-difluorocyclohexyl substituent had a better fit for PARP1 pocket that for PARP2, thus being at least partially responsible for the observed selectivity.[369]

Fluorinated analogs of Perhexiline, a cardiovascular drug introduced into the market almost 50 years ago and then withdrawn in 1988 due to hepato- and neurotoxicity, were developed to overcome the metabolic oxidation issue of the parent compound.[251] It was found that *gem*-difluorinated compound **533** had much improved half-life both in vitro and in a mouse model (Figure 23). Meanwhile, it retained activity against carnitine palmitoyltransferase 1 (CPT-1), an enzyme involved into mitochondrial uptake of long chain fatty acids, the major biological target of Perhexiline. Notably, 4,4-difluorination at both cyclohexyl rings resulted in loss of the activity; meanwhile, 3,3-difluorinated and 4-monofluorinated analogs of **533** did not gain or even had decreased metabolic stability.

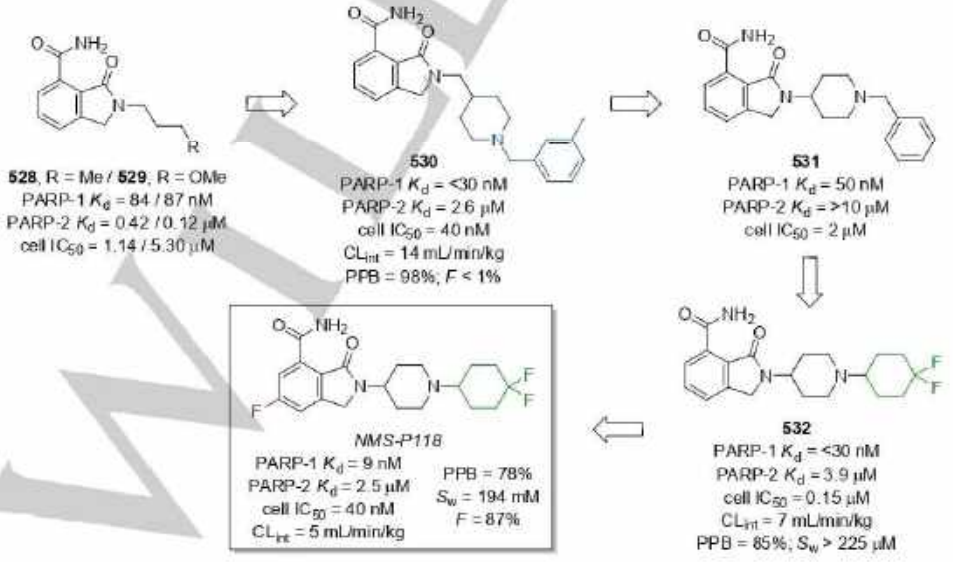


Figure 22. Discovery of NMS-P118 (CL_{int} – human liver microsomal intrinsic clearance; PPB – plasma protein binding; *F* – oral bioavailability in rats at 10 μM; S_w – aqueous solubility at pH = 7)

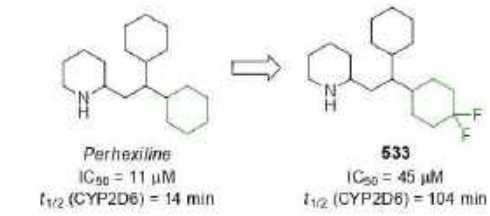


Figure 23. Compound **533**, a fluorinated perhexiline analog

Similar idea was behind the design of fluorinated analogs of Emixustat, a potent retinoid isomerase (RPE65) inhibitor.[370] The parent compound was evaluated in clinical trials as for use in several retinopathies (i.e. as an ophthalmologic agent) but failed due to rapid clearance. ***gem***-Difluorinated analog **534** had slightly improved potency and allowed for nearly two-fold increase of concentration in eyes upon administration as compared to Emixustat.

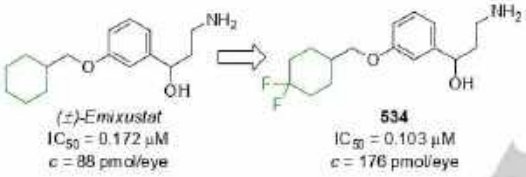


Figure 24. Compound **534**, a fluorinated emixustat analog (c – concetration at 3 h after intraperitoneal administration)

6.2. GPCR ligands

Chemokine receptor 5 (CCR5) ligands. The most prominent example from these series is Maraviroc (UK-427857, approved by), a marketed anti-HIV agent approved by FDA in 2007.[371–378] Maraviroc acts an antagonist of human C-C motif chemokine receptor 5 (CCR5). This biological target is used by the virus to facilitate insertion of its fusion protein into the host cell lipid bilayer. Discovery of Maraviroc started with an HTS campaign that revealed two structurally similar hits, UK-107543 and UK-179645, used as the starting points of the optimization program (Figure 25). To decrease CYP2D6 inhibition and lipophilicity of UK-107543, some structural features of UK-179645 were incorporated into its molecule, which gave compound **535**. Further two-step optimization was performed around its core and eventually led to highly potent derivative **537**.

Unfortunately, compound **537** appeared to be a potent human ether a-go-go related gene (hERG) inhibitor. This issue can be addressed by decreasing the compound's lipophilicity; however, the hydrogen bonding potential should not be increased significantly since it would lead to low membrane permeability. Modifications of the benzimidazole moiety allowed identification of compound **538** with improved properties; still, it had some activity against hERG. Replacing the cyclobutyl ring with cyclopentyl moiety slightly increased the compound's potency and, more importantly, diminished hERG inhibition (likely due to a steric clash with the ion channel); however, metabolic stability was decreased dramatically. Therefore, other replacements were evaluated at this position, and the 4,4-difluorocyclohexyl group worked perfectly, finally leading to Maraviroc discovery.

Crystal structure of a CCR5 – Maraviroc complex showed that one of the fluorine atoms formed hydrogen bonds with hydroxyl groups of threonine-195 and -259 residues, thus contributing slightly into the binding affinity.[374]

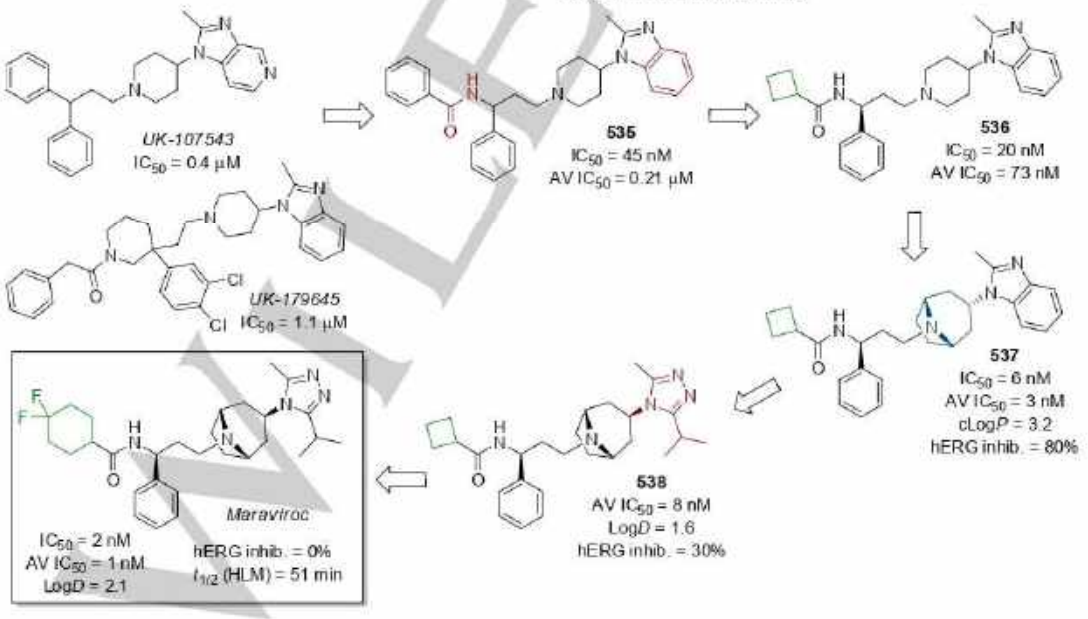


Figure 25. Discovery of Maraviroc (AV IC_{95} – the concentration required to inhibit replication of HIV into PM-1 cells by 50%; hERG inhib. – hERG inhibition at 0.3 μM; HLM – human liver microsomes)

Since the Maraviroc discovery, thousands of papers were published on its various aspects. In some of them, further CCR5 antagonists bearing 3,3-difluorocyclbutyl or 4,4-difluorocyclohexyl moieties were proposed [375–382] None of them repeated the success of the original drug so far.

Metabotropic glutamate receptor (mGluR) ligands. mGluRs are classical drug discovery targets involved into numerous central nervous system disorders. Several compounds with *gem*-difluorocycloalkyl moiety can be mentioned here. Thus, attempted scaffold hopping of mGluR5 positive allosteric modulator **539** led to less potent derivative **540** with improved physico-chemical characteristics (Figure 26).[383] Compound **542** was an outcome of optimization of another mGluR5 positive allosteric modulator **541** aimed at reducing glutathione reactivity (Figure 27).[384] In this case, the main goal was achieved through the scaffold modification, while the 3,3-difluorocyclobutyl moiety likely played a minor part.

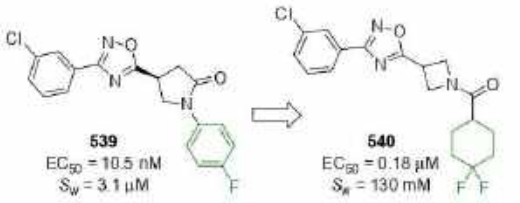


Figure 26. Design of mGluR5 positive allosteric modulator **540** (S_w –solubility in 25 mM phosphate buffer – DMSO)

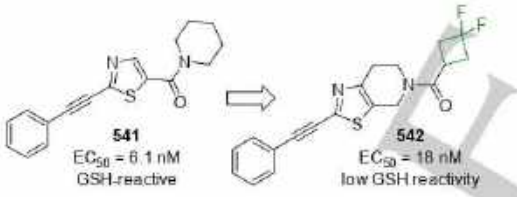


Figure 27. Design of mGluR5 positive allosteric modulator **542** (GSH – glutathione)

A somewhat related alkyne derivative BMS-955829 was the starting point in the discovery of another 3,3-difluorocyclobutyl-substituted mGluR5 positive allosteric modulator **545** (Figure 28).[385] In this case, the optimization was aimed at avoiding metabolic oxidation of BMS-955829 – the main reason of the compound's hepatotoxicity in dogs. Replacement of the phenyl ring with cyclobutyl moiety allowed achieving this goal with most activity retained; however, the compound's microsomal stability diminished significantly. Fluorination appeared to be fruitful to fix this issue; further modifications of resulting compound **544** led to derivative **545**. Although all of the above improvements were done at the expense of potency, the latter compound was active in mouse novel object recognition test but showed no glutathione conjugation via oxidation.

A very potent mGluR2 positive allosteric modulator **547** was reported.[386] It was stated that its design originated from the template of compound **546** (Figure 29).[387] Thus, the *gem*-difluorocyclopropyl moiety was used as an isosteric replacement for a *tert*-butyl substituent.

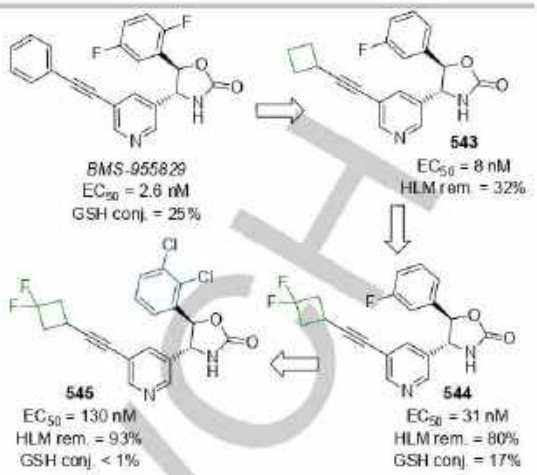


Figure 28. Design of mGluR5 positive allosteric modulator **546** (HLM rem. – % of the compound remaining after incubation with human liver microsomes; GSH conj. – % of the compound susceptible to glutathione conjugation via metabolic oxidation)

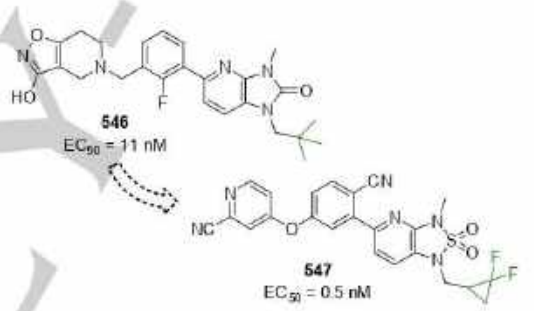


Figure 29. Discovery of mGluR2 positive allosteric modulator **547**

The discovery of VU6001376, a positive allosteric modulator of mGluR4 and a potential agent to treat Parkinson's disease, started with a high-throughput screening campaign more than a decade ago.[388] After a multistep optimization of the initial hits, compound **550** was identified together with some other close analogs (Figure 30).[389] The compound was able to reverse haloperidol-induced catalepsy (HIC) in a preclinical rodent model. However, it suffered from modest potency, high cytochrome CYP1A2 inhibition, and significant clearance in rats. Minor alterations to the scaffold of **550** led to compound **551** with much-improved potency but largely retained ADME issues. Further modifications included switching to the amide series. Among many compounds tested, derivatives with the CF_2 moiety included into a saturated carbo- or heterocyclic ring demonstrated higher activity, which was addressed to the probable participation of the *gem*-difluoro group in the receptor binding. Among such compounds, VU6001376 was revealed to be optimal as a potent and selective mGluR4 ligand with good DMPK properties in rats and sufficient activity in the HIC model.

Muscarinic receptor ligands. Muscarinic acetylcholine receptors are other classical GPCRs involved into numerous disorders. For example, their M_5 subtype is an important target for anticholinergic bronchodilators; apart from respiratory disorders, its antagonists can be also used to treat urinary tract disorders and

irritable bowel syndrome. Thus, 3,3-difluorocyclopentyl-substituted M_3 antagonist series was discovered upon optimization of the lead structure **552** aimed at improving metabolic stability (Figure 31).[390] 3-Fluorocyclopentyl derivatives were also evaluated for that reason but did not show any improvement. Interestingly, (1*R*) enantiomer **553** appeared to be more potent, and this configuration was kept for the next SAR studies. As a result, compound **554** was discovered; however, it was susceptible to metabolic *N*-dealkylation. Further optimization led to derivative **555**.[391] In a later work, RBx 343E48F0 derived from the same scaffold was characterized in a preclinical study as a bronchodilator.[392]

The discovery of M_4 positive allosteric modulator **559** with potential antipsychotic activity commenced from high-throughput screening hit **556** (Figure 32).[393] Compound **556** was susceptible to P-glycoprotein (P-gp) efflux. This problem was eliminated by introduction of the quinoline moiety instead of the aryl group. SAR of the *N*-substituent at the pyrazole moiety of **557** revealed several cyclopentyl derivatives amenable for further optimization, including 1-fluorocyclopentyl-substituted compound **558**. Selectivity studies showed that compound **559** is optimal; furthermore, it showed promising pharmacokinetics in rats.

Opioid receptor-like 1 (ORL1) ligands. ORL-1, also called nociceptin receptor, was discovered based on its homology to the classical opioid receptors in 1994. It is likely involved in regulating several biological systems and considered as a target for potential anesthetic development.[394] A group of Japanese scientists identified pyrazole **560** as ORL-1 antagonist by sample collection screening (Figure 33).[395] While having sub-micromolar activity, compound **560** also showed strong binding to hERG. An extensive SAR showed that the potency can be

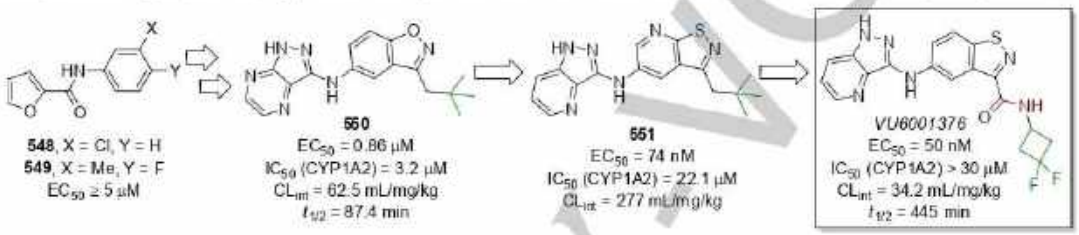


Figure 30. Discovery of VU6001376, a mGluR4 positive allosteric modulator (CL_{int} – rat liver microsomal intrinsic clearance; $t_{1/2}$ – half-life in rat cassette intravenous screening)

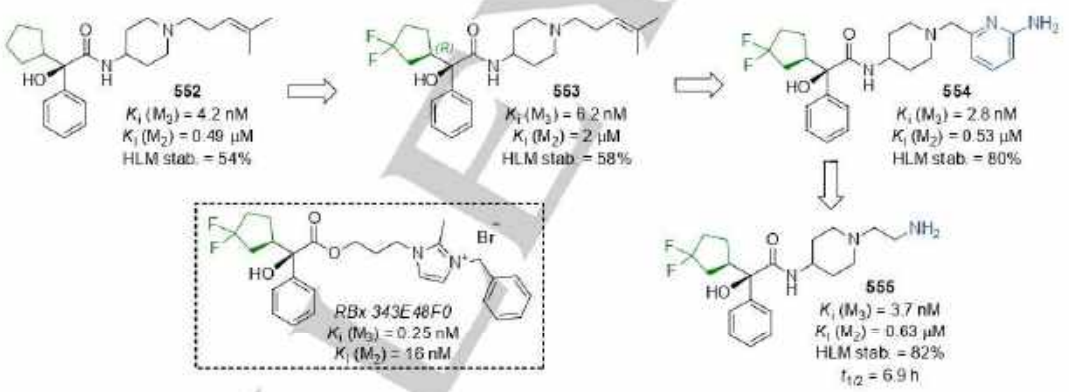


Figure 31. 3,3-Difluorocyclopentyl-substituted M_3 antagonists (HLM stab. – % of the compound remaining after a 30-min exposure to human liver microsomes; $t_{1/2}$ – half-life after intravenous administration in dogs)

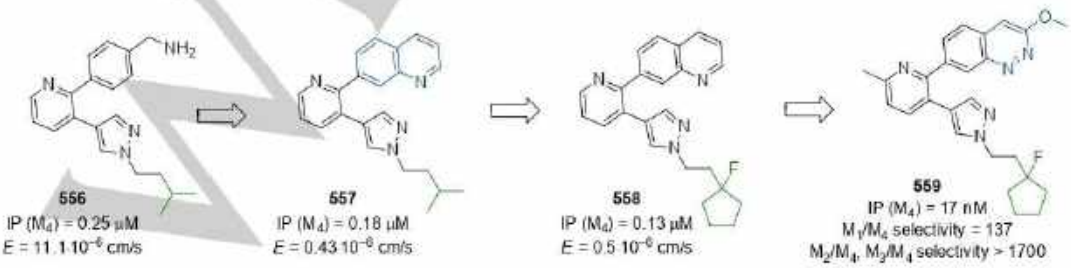


Figure 32. Discovery of M_4 positive allosteric modulator **559**

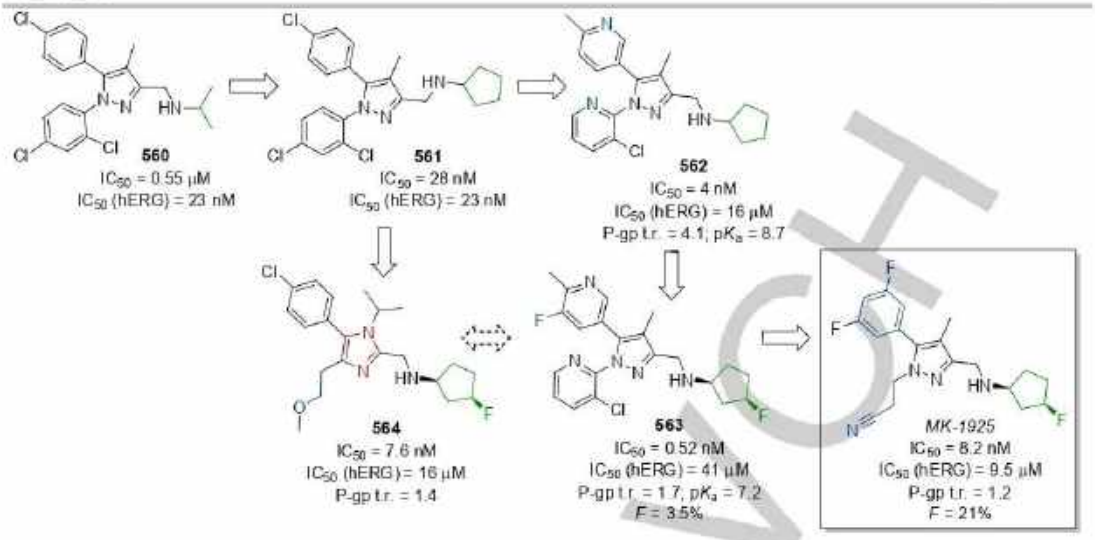


Figure 33. Discovery of ORL-1 antagonists (P-gp t.r. – human P-glycoprotein transport ratio; *F* – oral bioavailability in rats; relative configurations are shown)

increased by introducing the *N*-cyclopentyl moiety on the eastern side of the molecule. Meanwhile, hERG activity can be suppressed by replacing aryl groups with pyridine rings. The resulting compound, **562**, was very potent and had low hERG activity but was prone to human P-glycoprotein (P-gp) efflux. This effect was strongly related to the compound's pK_a. Adding two fluorine atoms lowered the basicity, diminished the P-gp efflux, and even improved the potency. Moreover, compound **563** had low activity against μ and κ opioid receptors.

Apart from 3-fluorocyclopentyl moiety in **563**, other fluorinated cyclopentyl moieties (i.e., 2-fluoro- and 3,3-difluoro-) were evaluated; however, the corresponding derivatives were less potent. This might be considered as indirect evidence of fluorine participation in receptor binding.

Since compound **563** had a poor pharmacokinetics profile in rats, it was further optimized. As a result, MK-1925 was discovered.[396] Alternative optimization studies led to imidazole **564** that did not get further development.[397]

Sphingosine-1-phosphate (S1P) receptor ligands. Agonists of these receptors have been considered as immunosupressants. Selectivity to $S1P_1$ receptor over other subtypes (especially $S1P_3$) was shown to be important. In a study by Merck scientists, compound **565** was identified as a result of initial lead structure optimization (Figure 34).[398] In this work, compounds with 3,3-difluorocyclopentyl moiety were also evaluated but were slightly less potent. Later, two additional series were developed starting from the structure of **565**, and in both of them, 3,3-difluorocyclopentyl derivatives **568**[399] and **570**[400] were among the best ones in terms of both high potency and reasonable pharmacokinetics in rats.

Bradykinin receptor ligands. Bradykinin B_1 receptors are involved in peripheral and central nervous systems and are promising biological targets for treating chronic pain and inflammation. Two B_1 selective antagonists **574** and **577** bearing a 4,4-difluorocyclohexane motif were discovered starting from the same lead structure **572** (Figure 35). In turn, compound **572** was identified after multistep optimization of high-throughput screening hit **571** including several interesting isosteric replacements (out of scope of this review).[401–403]

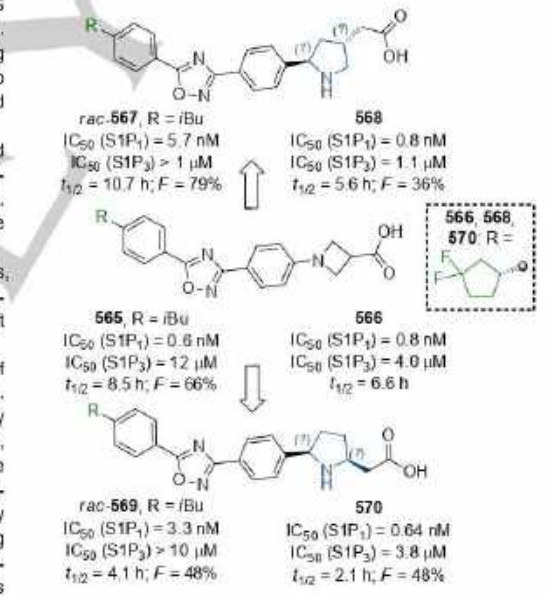


Figure 34. Design of selective $S1P_1$ agonists (for **569** and **570**, only relative configuration of the substituents at the pyrrolidine ring is established; $t_{1/2}$ and *F* were measured in rat models)

Compound **572** had one major metabolism pathway (i.e., oxidation at the methyl group) providing a major active metabolite and hence was at risk of potential drug-drug interactions. Therefore, the discovery of **574** was aimed at compounds that had several alternative clearance pathways.[240] Namely, a five- or six-membered ring was introduced as an additional metabo-

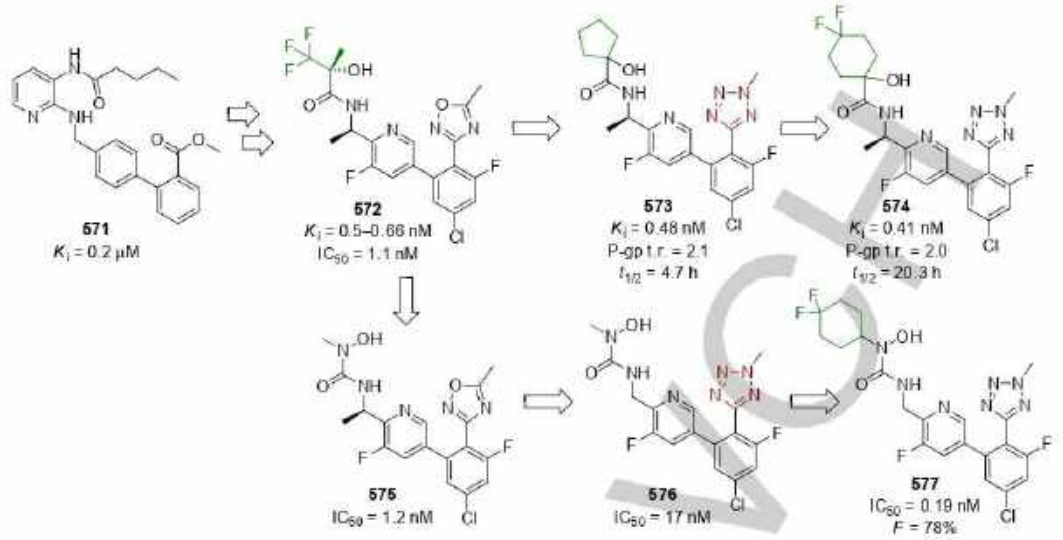


Figure 35. Discovery of B_1 selective antagonists (P-gp t.r. – human P-glycoprotein transport ratio; $t_{1/2}$ – half-life time in dogs; *F* – oral bioavailability in rats)

lism site instead of the $CF_3(CH_3)C$ moiety. Also, 1,2,4-oxadiazole was replaced with *N*-methyltetrazole to provide inactive metabolite upon *N*-demethylative oxidation.

Among the analogs tested, cyclopentane derivative **573** was potent and was not P-gp substrate; however, it had relatively shorter half-life time in dogs. Therefore, CF_2-substituted analogs were studied, and cyclohexane derivative **574** was found to be optimal.

In another study, hydroxyureas was proposed as a replacement for α-hydroxyamide moiety in the molecule of **572** that would reduce the number of chiral centers.[404] SAR around compound **575** showed that most structural moieties found by the previous authors were optimal. Meanwhile, replacing the *N*-methyl group in the resulting derivative **576** with larger (cyclo)alkyl moieties improved the compound's potency. The best result was (again) achieved with 4,4-difluorocyclohexyl moiety. Homology modeling of the receptor – **577** complex suggested that this moiety is likely engaged in efficient interactions with the side chains of isoleucine-117 and phenylalanine-302 residues. Indeed, the non-fluorinated cyclohexyl analogue of **577** was much less active (IC_{50} = 3.9 nM).

Cannabinoid receptor ligands. Cannabinoid receptor subtype 1 (CB_1) antagonists are potential anti-obesity drugs, whereas subtype 2 (CB_2) is a therapeutic target to treat pain and inflammation. Thus, Rimonabant, a CB_1 inverse agonist, passed clinical studies but was not approved by FDA in 2007 due to an increased risk of psychiatric disorders. The side effects were addressed to the inverse agonist activity, and efforts were put into switching to a neutral antagonist. Using the scaffold hopping approach, diarylpyrazine derivatives, e.g., **578,** were identified (Figure 36).[405] Further modifications led to compound **579** which still had the inverse agonist activity.[406] Nevertheless, thioamide **580** was a true neutral antagonist, and it retained the anorexic effect in mice. The role of the *gem*-diflurinated substituent in this study is unclear, but it seems to improve the compound's potency.

CB_2 agonist **581** also bearing the 4,4-difluorocyclohexyl moiety was disclosed in a patent as the most potent in the series studied (Figure 37).[407] Again, the role of the CF_2 moiety is unclear, but compound **581** and its analogs were more active than the corresponding counterparts with CH_2, O, or SO_2 moieties at the same position.

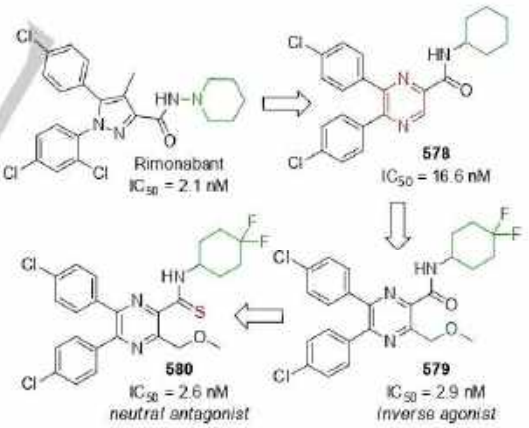


Figure 36. Discovery of neutral CB_1 antagonist **580**

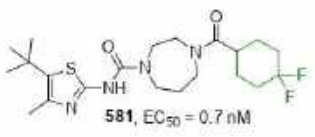


Figure 37. CB_2 agonist **581**

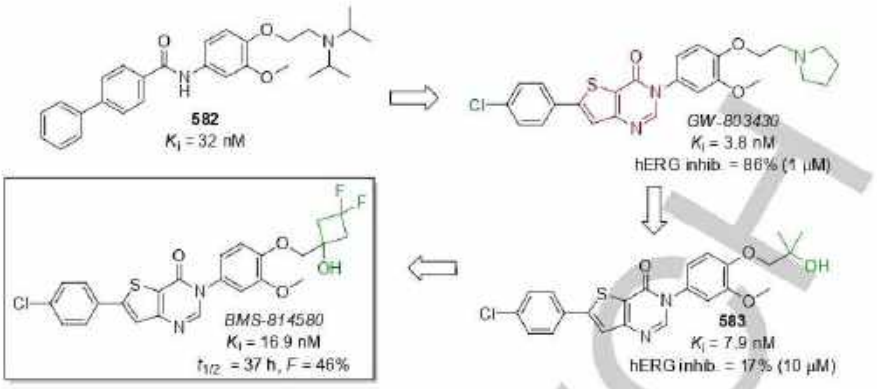


Figure 38. Discovery of BMS-814580 ($t_{1/2}$ and *F* were measured in cynomolgus monkeys)

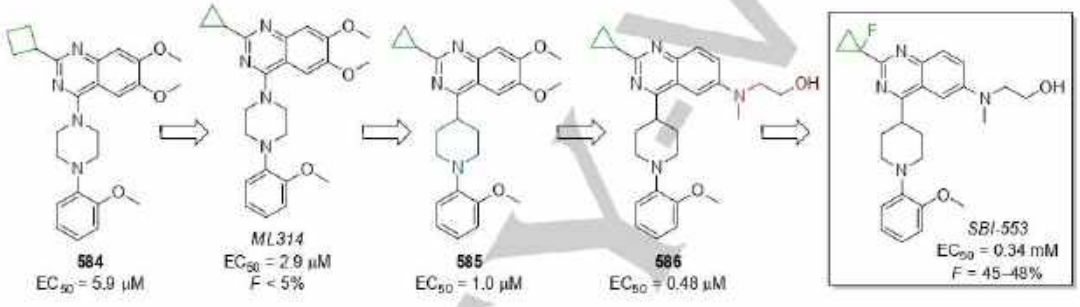


Figure 39. Discovery of SBI-553, a NTR1 allosteric modulator (*F* – oral bioavailability in rodents)

Melanin concentrating hormone receptor 1 (MCHR1) ligands. MCHR1 is one more therapeutic target for potential anti-obesity drugs. The discovery of BMS-814580, its potent orally active inhibitor,[408] was a long journey starting from high-throughput screening hit **582** (Figure 38).[409] The compound was identified by GlaxoSmithKline researchers; later, they optimized it into GW-803430.[410] The main issue with this series was hERG activation due to the presence of a basic lipophilic moiety. Bristol-Myers Squibb scientists suggested its replacement with a non-basic side chain, which led to the discovery of compound **583**.[411] This derivative was potent and had a good pharmacokinetics profile but demonstrated a hepatotoxic effect upon prolonged administration in rats due to metabolic oxidation at one of the methyl groups. Therefore, the dimethylcarbinol moiety was subjected to the replacement studies. It was found that 3,3-difluorocyclobutanol residue worked well: the metabolic stability was improved, while other important properties were only slightly affected. It should be noted that BMS-814580 (as well as several other compounds in the study) was dosed as a phosphate prodrug in the preclinical studies to increase its solubility.

Neurotensin receptor 1 (NTR1) ligands. NTR1 is widely expressed throughout the central nervous system and implicated in a number of its disorders. Apart from applications in this area, its ligands were also considered potential anticancer agents. The discovery of SBI-553, a biased allosteric modulator of NTR1,[412] commenced from high-throughput screening hit **584** (Figure 39).[413] Hit-to-lead optimization led to ML314 that was potent but had very low bioavailability in rodent models. Further SAR was focused on metabolically problematic sites but also allowed improving the compound's potency and eventually led to 1-fluorocyclobutyl derivative SBI-553. The compound had high clearance but high distribution volume and good bioavailability in rodents. Notably, the 1-fluorocyclobutyl homolog of SBI-553 was even slightly more potent (EC_{50} = 0.27 μM), while the non-fluorinated cyclobutyl derivative (EC_{50} = 1.0 μM) was less active than **586**. These results demonstrate the importance of the α-fluorine atom to the allosteric site binding.

Glucagon-like peptide-1 receptor (GLP-1R) ligands. GLP-1R is a well-validated biological target for type 2 diabetes. High-throughput screening campaign around this target revealed hit **587** derived from natural product-like 3,4,5,6-tetrahydro-1*H*-1,5-epiminocazocino[4,5-*b*]indol-4(11*H*)-one scaffold (Figure 40).[414] Hit expansion was performed in an attempt to find simpler analogs, which led to much more potent positive allosteric modulator **588** bearing a 4,4-difluorocyclohexyl motif. According to the induced fit docking model, this moiety was located in a hydrophobic pocket near the tyrosine-241 residue of the receptor. The modeling results were used for structure-based optimization and led to compound **589** having excellent activity, high selectivity, and reasonable ADME properties in vitro. Unfortunately, it had a poor pharmacokinetics profile in vivo due to extensive efflux in liver. This issue could be addressed by co-administration of an efflux transporter inhibitor, rifampicin: under these conditions, nearly 100% bioavailability of **589** was reached, and glucose level was lowered efficiently in mice models.

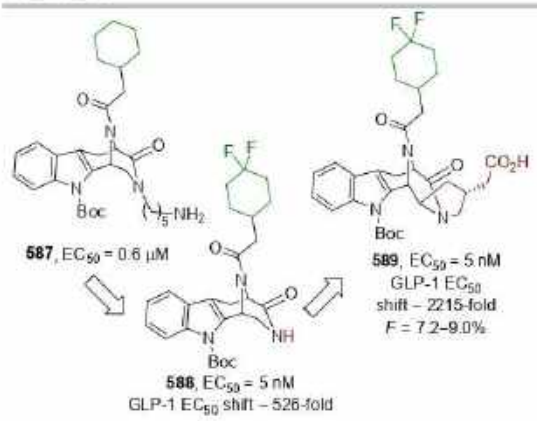


Figure 40. Discovery of GLP-1R positive allosteric modulator **589** (GLP-1(9-36)NH_2 fragment EC_{50} shift at 3 μM of the modulator is given; *F* – oral bioavailability in rodents)

Smoothened (Smo) ligands. The hedgehog signaling pathway is an important development pathway that seems to be aberrantly reactivated in several human tumors. Smoothened (Smo) is one of its key receptors, so that its antagonists can inhibit the signal transduction efficiently and are therefore potential anticancer agents. In a high-throughput screening campaign aimed at the discovery of Smo antagonists, several structurally similar hits **590–592** were identified (Figure 41). Extensive SAR studies around each fragment of their molecules followed by combining the optimal substituents led to compounds **594** and **595**. The latter was one of the most potent antagonists in the series while showing somewhat improved metabolic stability.

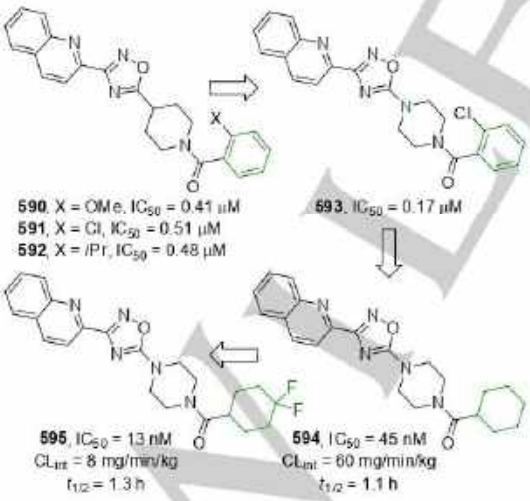


Figure 41. Discovery of Smo antagonist **595** (CL_{int} – intrinsic human liver microsomal clearance; $t_{1/2}$ – half-life time in rat models)

The impact of the CF_2 moiety on the binding affinity in the discovered series was not apparent. Thus, in *N*-methylbenzimidazole isosteres of the **594**/**595** pair at the quinoline ring, the non-fluorinated cyclohexyl derivative was more potent (IC_{50} = 3 nM vs 7 nM, respectively).

6.3. Kinase ligands

Kinases have been among the most popular biological targets in recent decades. Every year, several antitumor agents – kinase inhibitors – are approved by FDA, with other therapeutic applications being also found. It is not surprising therefore that the fluorinated cycloalkyl compounds have found their place among the kinase ligands as well. In particular, 4,4-difluorocyclohexyl derivative **599** was identified as an interleukin-2 inducible T-cell kinase (Itk) inhibitor and a potential agent to treat inflammatory diseases.[415] Its discovery started with screening hit **596** (Figure 42). SAR around this molecule led to lead compounds **597** and **598** that were potent and selective Itk inhibitors but rapidly metabolized in human liver microsomes. Introducing the *gem*-difluorinated moiety improved metabolic stability and led to compound **599**.

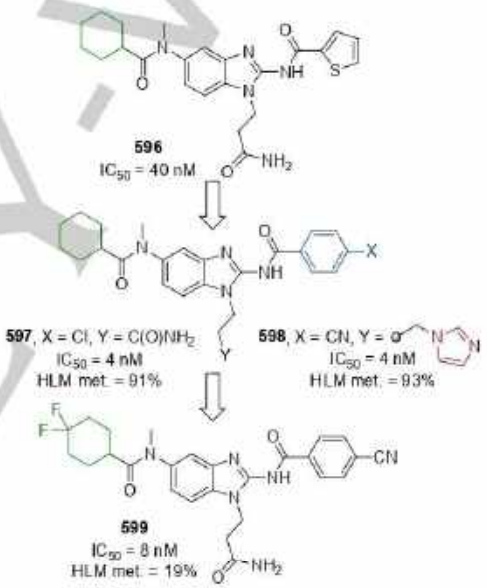


Figure 42. Discovery of Itk inhibitor **599** (HLM met. – % of the compound that metabolized after explosion to human liver microsomes)

Another 4,4-difluorocyclohexyl-substituted derivative **603** was developed as an inhibitor of *c*-Jun *N*-terminal serine/threonine protein kinases (JNK) and a tool for Huntington's disease.[416] A combination of molecular docking into the structure of JNK3 and in vitro screening led to discovery of hit **600** (Figure 43). Being guided by X-Ray diffraction data for the complex of **600** with JNK3, introducing a secondary amine function into the molecule of **600** was proposed. As a result, compound **601** with nanomolar activity against JAK3 was identified. It was also active against JNK1 and JNK2 isoforms; nevertheless, binding to protein p38α was also observed. SAR around the pyrazole ring led to compound **602** that retained pan-JNK activity but was not active against p38α. Unfortunately, compound **602** had moderate to high P-gp efflux. To address this, reducing the number of hydrogen bond donors was reduced; another round of

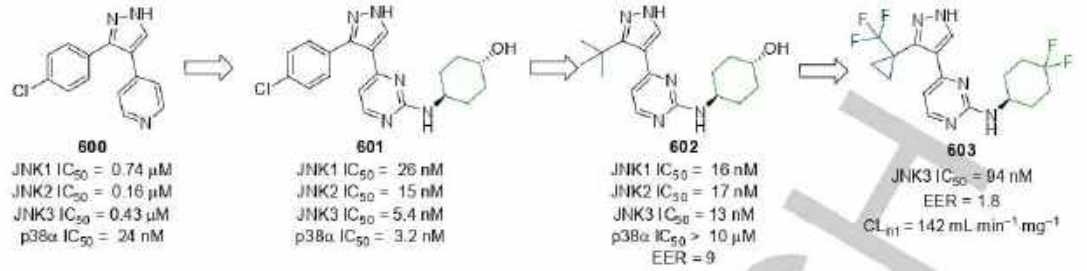


Figure 43. Discovery of pan-JNK inhibitor **603** (EER – P-gp-mediated efflux, CL_{int} – mouse microsomal intrinsic clearance)

SAR led to a series of compounds including derivative **603**. This compound was optimal in terms of biological properties, including those obtained in animal models, and the highest metabolic stability in the series studied (although still not sufficient for further development).

3,3-Difluorocyclobutyl moiety appeared to be essential in transforming growth factor-β type 1 receptor (THF-β1R) inhibitors potentially useful for addressing fibrotic diseases and malignant tumors.[417] This study used THF-β1R inhibitor LY-3200882 as the starting point, in turn, optimized from the structure of Galunisertib – an experimental anticancer drug whose development was discontinued in 2020 (Figure 44). SAR around the pyrazole moiety revealed compound **605** having a two-fold enhanced cellular potency relative to LY-3200882. Next, variation of the substituent in the pyridine ring was performed; while some more potent compounds were identified, they had poorer in vitro pharmacokinetic characteristics. Therefore, compound **604** was progressed into preclinical studies and showed promising results there. Importantly, the 3,3-difluorocyclobutyl moiety was important for both compound's potency and metabolic stability. The use of this moiety as an isosteric replacement of tetrahydropyran confirmed by predicted binding mode overlay can be also stressed out.

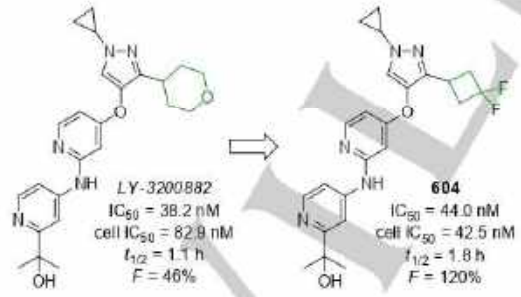


Figure 44. Discovery of THF-β1R inhibitor **604** ($t_{1/2}$ and *F* were determined at 10 mg/kg dose after oral administration in mice)

All other kinase inhibitors discussed in this section had either β-fluoro- or *gem*-difluorocyclopropyl moiety in their structure. Thus, Non-receptor tyrosine-protein kinase 2 (TYK2) inhibitor **60X**, a potential agent for treating psoriasis and inflammatory bowel diseases, contained the residue of cis-2-fluorocyclopropanecarboxylic acid.[418] Its design commenced from high throughput screening hit **605** that was optimized to lead **606** through a structure-based hit to lead campaign aimed mainly at increasing potency (Figure 45).[419] SAR exploration around the phenyl and cyclopropane rings was aimed at increasing TYK2/JAK selectivity and led to compounds **607** and **608**, respectively. Combining their structural features gave preclinical candidate **609** with cytokine interferon-γ (IFNγ) suppressing activity and good pharmacokinetics in mouse models. X-Ray diffraction studies showed that in the complex with enzyme, the fluorine atom of **609** had short contacts with arginine-901 and leucine-903 side chains, thus being important for the observed selectivity.

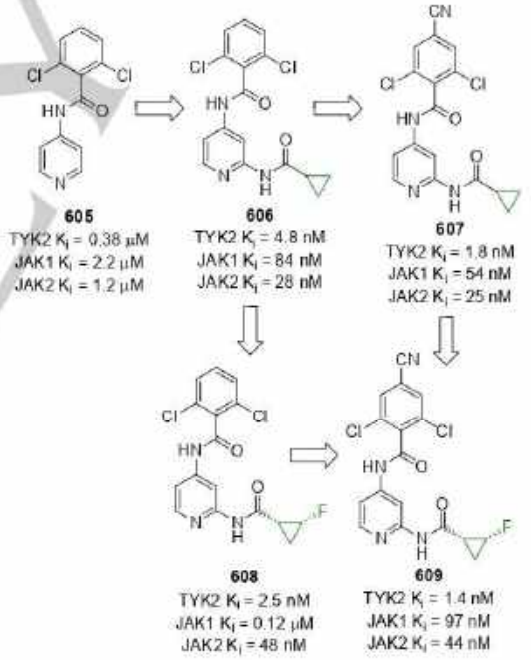


Figure 45. Discovery of TYK2 inhibitor **609**

Another TYK2 inhibitor **613** addressed non-catalytic JAK homology 2 (JH2) domain of the enzyme.[420] It was discovered through optimization of initial hit **610** (Figure 46).[421] The first SAR studies resulted in increasing potency and led to compound **611**; however, it had low metabolic stability. Addressing this issue was based on decreasing the compound's lipophilicity while keeping good membrane permeability and eventually led

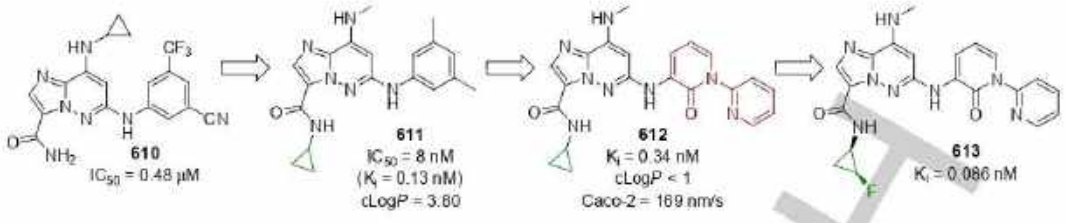


Figure 46. Discovery of TYK2 inhibitor **613**

to compound **612**. Adding fluorine atom to the cyclopropyl moiety of **612** gave highly potent inhibitor **613** with good pharmacodynamics and pharmacokinetic properties in vivo. A few additional highly potent compounds with (1*R*,2*S*)-2-fluorocyclopropyl moiety were also described in this work.

In a study on Bruton's tyrosine kinase (Btk) inhibitors, potential agents to treat chronic immune diseases, the importance of 2-fluorocyclopropyl moiety stereochemistry for the compound's biological action was demonstrated.[422] The work commenced from the structure of Fenebrutinib, a clinical-stage Btk inhibitor. Replacement of the arylaminopyridine side chain with amide was suggested in order to avoid potential issues with hepatotoxicity often encountered with electron-rich 1,4-disubstituted arenes, and cyclopropyl derivative **614** was identified (Figure 47). At this stage, the *cis*-2-fluoro-substituted analog of **614** was also found, being even slightly more potent. Further optimization included a variation of another side chain at the western part of the molecule using previously identified motifs that provided selectivity for Btk. These modifications resulted in compound **615** having slightly improved potency. Introducing the fluorine atom into the cyclopropane ring of **615** led to a series of stereoisomeric derivatives **616**, of which (*S*,*S*)-isomer appeared to be most active. Unfortunately, compound (*S*,*S*)-**616** demonstrated hERG activity; it was six times lower for its (*R*,*R*) isomer.

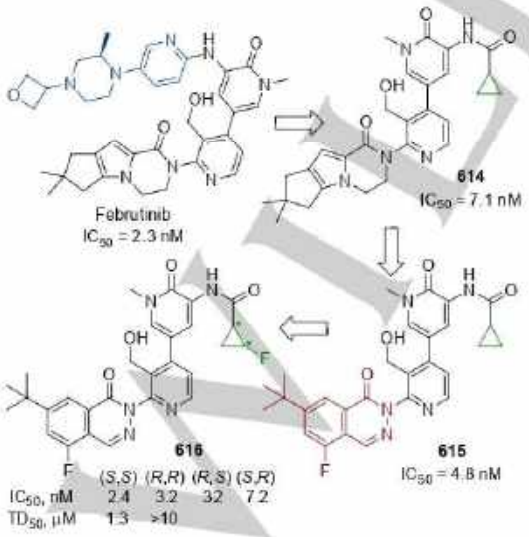


Figure 47. Discovery of TYK2 inhibitors **616** (TD_{50} – hERG IC_{50})

cis-2-Fluorocyclopropyl-substituted derivatives were found to be potent inhibitors of activated Abelson nonreceptor tyrosine kinase (c-Abl), a target that has a potential role in Parkinson's disease progression.[423] In particular, potent and selective compound **617** with in vivo activity in mouse models was identified as a result of SAR around the benzothiazole core (Figure 48). It had a two-fold higher potency compared to the non-fluorinated compound; also, all three other stereoisomers were less active. X-Rays diffraction studies revealed interactions of the cyclopropyl moiety with phenylalanine-336 side chain.

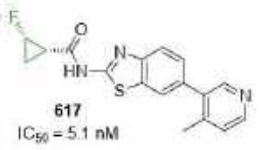


Figure 48. cAbl inhibitor **617**

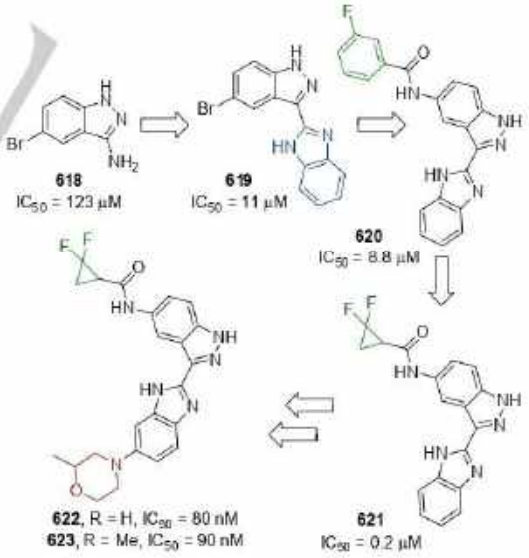


Figure 49. Discovery of PDK1 inhibitor **623**

Compound **623**, an inhibitor of phosphoinositide-dependent kinase-1 (PDK1) and a potential antitumor agent, was discovered through the fragment-based approach guided by X-Ray diffraction studies.[424] Among five initial fragment hits bea-

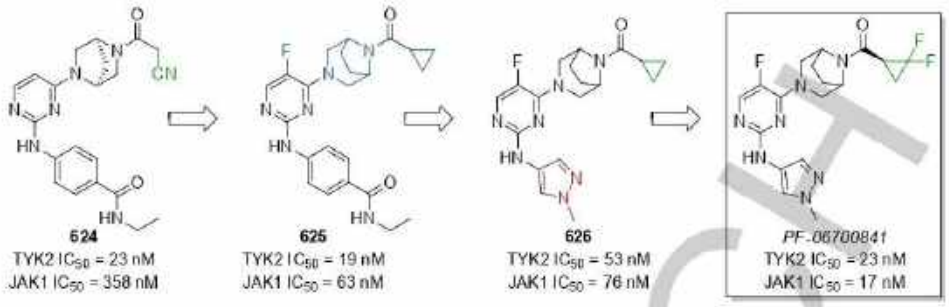


Figure 50. Discovery of TYK2 inhibitor **613**

ring an indazole moiety, compound **618** was not the most active but had promising growth vectors according to its binding mode (Figure 49). The evolution of fragment **618** led to compound **620**. Replacement of the 3-fluorophenyl moiety in the molecule of **620** with *gem*-difluorocyclopropane resulted in compound **621** with submicromolar potency. Further optimization gave compounds **622** and **623** that were progressed into animal studies. The latter compound had higher in vivo activity, likely due to better membrane permeability, and was moved to more advanced preclinical studies.

Discovery of PF-06700841, a dual inhibitor of TYK2 and JAK1 for the treatment of autoimmune diseases, included the optimization of lead structure **624** (Figure 50).[425] SAR around each part of the molecule led to cyclopropyl-containing derivative **626**. Adding two fluorine atoms resulted in potent compound PF-06700841; interestingly, (*S*) enantiomer was much more active than (*R*) isomer. As of 2018, the compound was in phase II clinical trials. X-ray diffraction studies showed the proximity of the *gem*-difluorine moiety to carbonyl oxygens of aspartate-1041 and asparagine-1028 residues of the biological target.

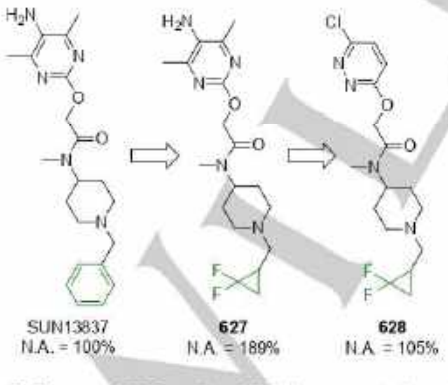


Figure 51. Discovery of FGFR modulator **628** (N.A. – neuroprotective activity at 10 μM)

Fibroblast growth factor receptor (FGFR) modulator **628** was discovered through optimization of SUN13837.[426] The latter compound was an attractive candidate for treating neurodegenerative diseases; however, its metabolic hydrolysis gave piperidine-derived diamine that induced phospholipidosis. Optimization of SUN13837 was aimed at reducing the tertiary amine basicity and eventually led to **628** that retained in vivo activity in mouse models (Figure 51).

Brain-penetrant and selective leucine-rich repeat kinase 2 (LRRK2) inhibitor **633**, a potential agent to treat Parkinson's disease, was discovered during optimization of aminoquinazoline series.[427] To eliminate possible blood – brain penetrance issues at early stages, in silico predictions were made together with in vitro studies to prioritize compounds. As a result of these efforts, early lead **629** was identified (Figure 52). This compound had high potency and predicted CNS permeability but poor selectivity against other kinases. Optimization of its structure was aimed at improving off-target selectivity, potency, pharmacokinetics (both in vitro and in vivo), and diminishing hERG inhibition, eventually leading to compound **630**. To address its poor pharmacokinetics in dogs, modifications at the pyrazole ring were performed. Negligible P-gp efflux was observed for *N*-difluoroethyl derivative **631**. Combination of the structural features of **630** and **631** led to *gem*-difluorocyclopropyl derivative **632** with much improved pharmacokinetics in rodent models. Final modifications were made around the potentially electrophilic oxetane moiety of **632** and included possible metabolic site blocking. As a result, compound **633** was obtained as a CNS-penetrant, potent, selective, and orally bioavailable pharmacological tool to study the role of LRRK2 in the pathogenesis of Parkinson's disease.

6.4. Ion channel and other transporter ligands

Nicotine acetylcholine receptors (nAChR) are classical ligand-gated ion channels characterized thoroughly as the CNS targets. In a study of 3,6-diazabicyclo[3.1.1]heptane series, TC-8831 was identified as a very potent ligands for human α4β2 and (to lesser extent) α6β2β3 nAChR isoforms (Figure 53).[428] Monofluorination at the cyclopropane ring of TC-8831 resulted in analogs with slightly improved potency (except (1*R*,2*S*)-**634**), whereas the *gem*-difluorination somewhat reduced the compound's activity.

In efforts to discover ligands for purinoreceptor P2X7 involved in diverse conditions associated with tissue damage and inflammation, lead compound **636** was taken from the literature and subjected to modifications (Figure 54).[429] As a result, 4,4-difluorocyclohexyl-substituted derivative **637** was identified; further SAR led to compound **638** having excellent cellular potency and good ADME properties but lacking promising in vivo activity in rodent models.

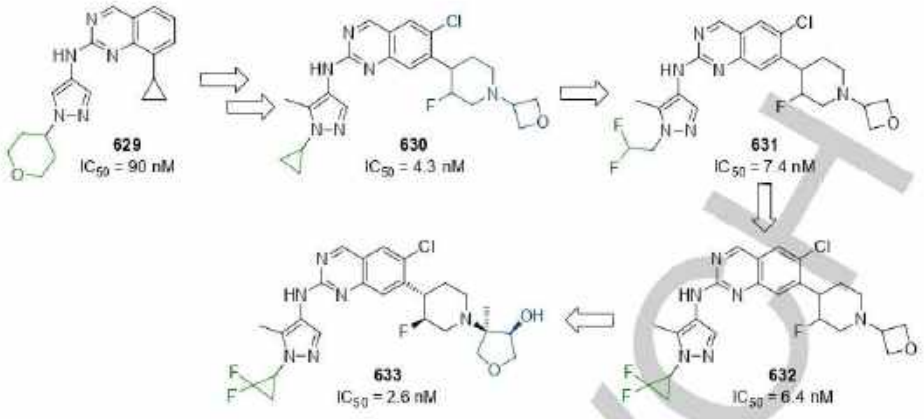


Figure 52. Discovery of LRRK2 inhibitor **633**

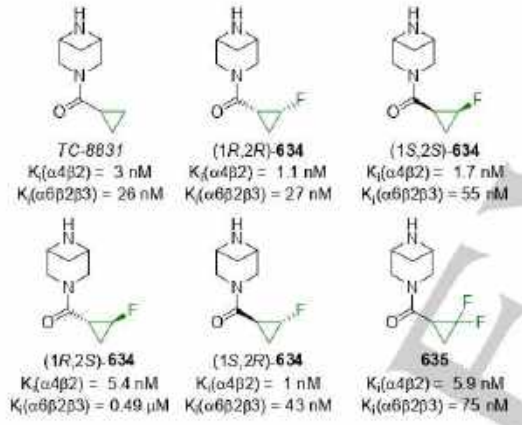


Figure 53. Fluorinated analogs of TC-8831, a nAChR ligand

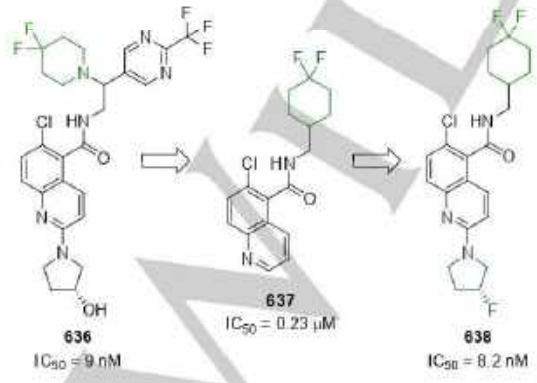


Figure 54. Discovery of P2X7 ligand **638**

Cholesteryl ester transfer protein (CETP) has been considered as a potential biological target to address atherosclerosis.

Compound **639** was identified as a screening hit in a campaign aimed at discovery of CETP inhibitors (Figure 55).[430] Early SAR around this hit identified urea lead **640**. Further optimization of this compound led to *gem*-difluorocyclopentyl derivative **641** with much improved potency and metabolic stability. Interestingly, all three regioisomeric *gem*-difluorocyclohexyl analogs of **641** were less potent (although still active). Later, it was found that a diastereomer of **641** with *R* configuration at the cyclopentyl moiety is seven times more potent than *S* diastereomer. Finally, (*R*)-**641** was active in mice models.

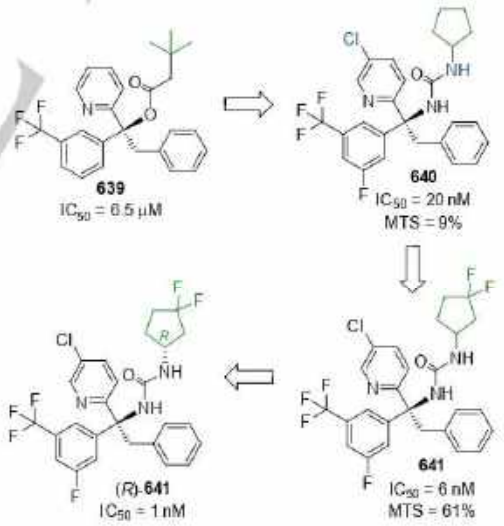


Figure 55. Discovery of CETP inhibitor (*R*)-**641** (MTS – % of the compound remaining after exposure to human liver microsomes at 3 μM)

To understand the structural requirements of ligands binding to a substrate-binding site of P-glycoprotein (P-gp) and their effect on modulating the ATPase function of this efflux pump, a series of analogs were prepared starting from lead compound **642**, a P-gp stimulator.[431] SAR around the eastern part of the molecule showed that compound **643** bearing a cyclohexylamide moiety

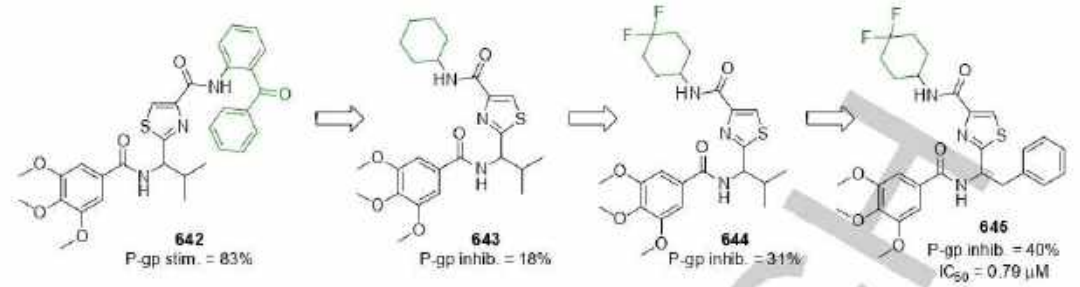


Figure 56. Discovery of P-gp inhibitor **645** (stim./inhib. – stimulation/inhibition at 0.5 μM)

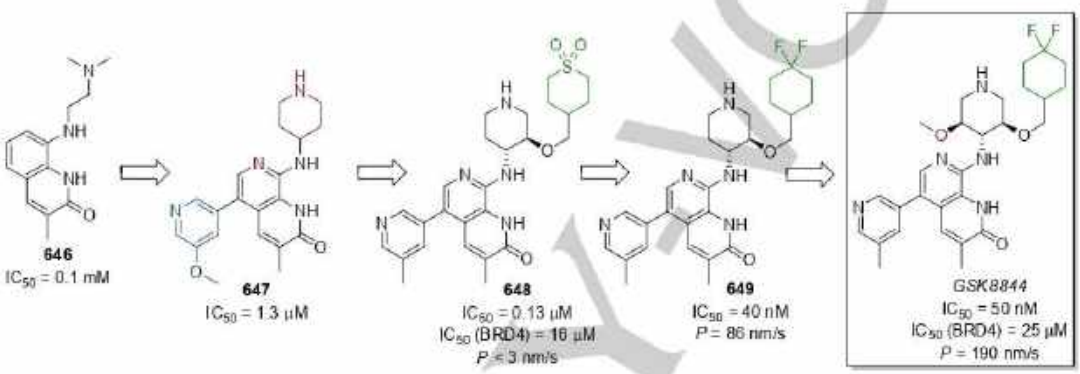


Figure 57. Discovery of ATAD2 inhibitor GSK8844 (*P* – artificial membrane permeability)

(Figure 56) was a weak P-gp inhibitor. Further SAR led to 4,4-difluorocyclohexyl derivaitves **644** and **645** with improved potency. A fit-induced homology model for the compound **645** suggested that the 4,4-difluorocyclohexyl moiety occupied a hydrophobic pocked formed by phenylalanine-335, phenylalanine-336, leucine-339, isoleucine-340, and phenylalanine-343 residues of the protein.

6.5. Other human protein ligands

ATPase family AAA domain containing protein 2 (ATAD2), an epigenetic reader, is related to several cancer types; its bromodomain is believed to be among the least druggable targets. In one of the studies aimed at discovery of its inhibitors, fragment-based approach was applied.[432] Starting with fragment hit **646**, initial lead structure **647** with micromolar potency but no selectivity against other bromodomains was identified (Figure 57). Its further structure-based optimization led to a selective submicromolecular inhibitor **648** bearing a sulfone moiety.[433] Unfortunately, compound **648** had low membrane permeability. Isosteric replacement of the sulfone moiety in the molecule of **648** with the CF_2 unit fixed this issue and led to a slightly more lipophilic compound **649** with much improved permeability.[434] Notably, the *gem*-difluoromethylene moiety retained the capability to form hydrogen bonds with guanidinium group of ATAD2 arginine-1077 residue characteristic of the sulfone group in **648**. Further modification included addition of the MeO group and led to GSK8844 with additionally improved selectivity and ADME characteristics as a probe to study ATAD2-related biological functions.

Further studies led to identification of two less potent ATAD2 inhibitors **650**[435] and **651**[436] with the same binding mode also bearing the *gem*-difluorocyclohexyl moiety (Figure 58).

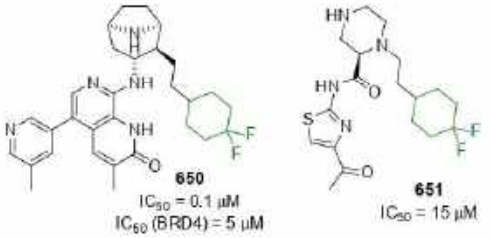


Figure 58. ATAD2 inhibitors **650** and **651**

Inhibitor of apoptosis proteins (IAPs) are crucial regulators of apoptosis overexpressed in several cancer cell types. An important approach to design of their antagonists is based on mimicking the terminal AVPI (alanine – valine – proline – isoleucine) binding motif of IAPs. Using the literature precedents, the structure of antagonist **652** was proposed that showed good activity against the X-chromosome-linked inhibitor of apoptosis protein (XIAP) and especially cellular IAP1 (cIAP1) (Figure 59).[437,438] Further optimization of **652** was aimed at improving potency (compound **653**) and then – bioavailability (compounds

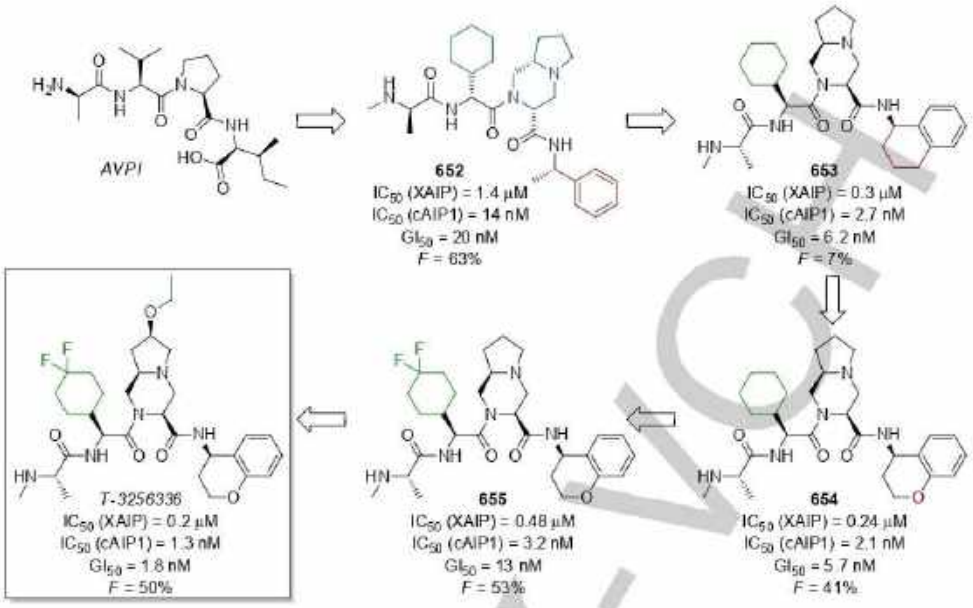


Figure 59. Discovery of AIPs antagonist T-3256336

654 and **655**). In particular, the *gem*-difluoromethylene moiety was introduced into the molecule of **655** to increase the compound's polarity and metabolic stability. Finally, SAR around the heterocyclic core led to compound T-3256336 with improved cellular potency, also showing antitumor activity in a xenograft model in mice.

Transcriptional enhanced associate domain (TEAD) transcription factors serve as the receptors for the downstream effectors of the Hippo pathway, in turn involved in cell proliferation. Blocking TEAD lipidation is a promising strategy for antitumor agent design. It was shown that compound **657** (obtained after optimization of initial hit **656**, Figure 60) binds to TEAD efficiently and prevents is palmitoylation, hence showing tumor stasis in a mouse xenograft model.[439] It was shown that the *gem*-difluorocyclohexyl moiety is involved into Van der Waals contacts in the lipidation site of TEAD.

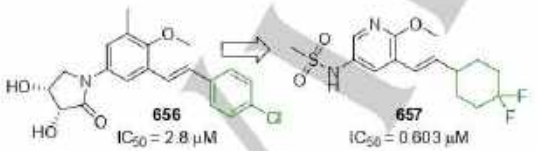


Figure 60. Discovery of TEAD lipidation antagonist **656**

6.6. Proteolysis targeting chimeras (PROTACs)

Proteolysis targeting chimeras (PROTACs) received much attention in recent years since targeted protein degradation has a great potential to modulate proteins difficult to target with conventional small molecules.[440] von Hippel–Lindau E3 ubiquitin ligase (VHL) is an important biological target involved into proteasome activation. Conjugation of VHL modulators with target ligands of interest is one of the major approaches to PROTAC design.

In a search for VHL ligands, the known VHL inhibitor VH032 was subjected to optimization leading to compound **659** bearing an α-fluorocyclopropyl moiety (Figure 61).[441] Importantly, introducing the fluorine atom (when going from **658** to **659**) increased both binding affinity and cellular potency. This was related to the conformational effect of the fluorine atom stabilizing the *anti* orientation of the C–F and C=O bonds.

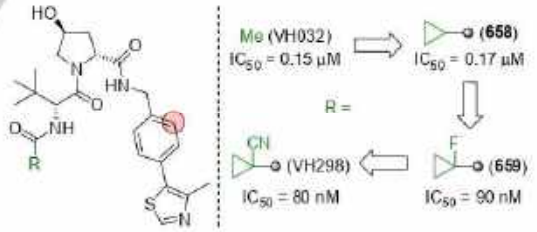


Figure 61. Discovery of VHL inhibitors **659** and VH298

Although the following optimization showed that replacing the fluorine atom with CN group led to a more potent compound (VH298), derivatives of **659** were still used in further works on the PROTAC design. In particular, highly active conjugates with cereblon,[442] androgen receptor,[443,444] bromodomain BRD7 and BRD9,[445] estrogen receptor α,[446] ligands were reported. It total, around 4% of the successful PROTACs based on the VHL ligands contained the structure of **659**.[447] The conjugation typically occurred through an ether linkage introduced into the *p*-phenylene group of the parent molecule (the position outlined by a red circle in Figure 61).

6.7. Antimicrobial agents

Fluoroquinolone antibacterial agents. Fluoroquinolones are well-known class of antibiotics acting through converting bacterial type II topoisomerases into cellular toxins.[448] Among them, compounds with *N*-1-cyclopropyl substituents were shown to possess outstanding antibacterial activity (e.g. widely used marketed drug Ciprofloxacin, Figure 62). Since such derivatives were shown to have side effects on CNS, fluorination at the cyclopropane ring was suggested to increase the compound's hydrophilicity and reduce brain penetration.[449] Extensive SAR around the central core was performed, including variation of the diamine fragment, substitution at the aromatic ring, and stereochemical configuration of the 2-fluorocyclopropyl moiety. It was found that *cis* isomers were considerably more potent than their *trans* counterparts.[449] On the contrary, altering the absolute configuration resulted in a two-fold difference in antibacterial activity at the most.[450] As a result, DU-6859a (Sitafloxacin) was discovered. The compound was introduced to market in Japan in 2008; however, it showed mild phototoxicity in Caucasian patients, which complicated its registration in many other countries.[451,452] Further studies resulted in discovery of many other potent antibacterial fluoroquinolones bearing the *cis*-2-fluorocyclopropyl moiety at the N-1 atom of the heterocyclic system, including clinical candidates DS21412020[453] and **660**.[454]

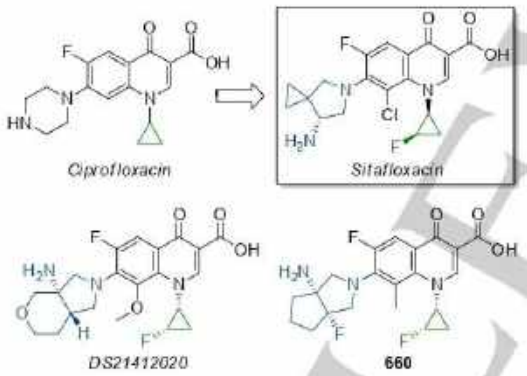


Figure 62. Fluoroquinolone antibiotics bearing a 2-fluorocyclopropyl moiety

Antimycobacterial agents. In two independent works published simultaneously, 2-mercaptoquinazolinones were identified as *Mycobacterium tuberculosis* type II NADH dehydrogenase inhibitors. In one of the studies, initial hit **661** was identified in the screening campaign (Figure 63).[455] SAR around the *N*-substituent showed that 4,4-difluorocyclohexyl derivative **662** retained activity of the parent compound and had similar pharmacokinetic profile, whereas 2,2- and 3,3-difluorinated isomers were less potent.

In another work, compound CBR-1825, a very close analog of **661**, was one of the validated hits discovered after the screening campaign and a variety of triage assays.[456] Its optimization led to CBR-1922 with much improved potency. Notably, the 4,4-difluorocyclohexyl moiety in the structure of CBR-1922 was important for the pronounced activity; its modifications resulted in less potent analogs.

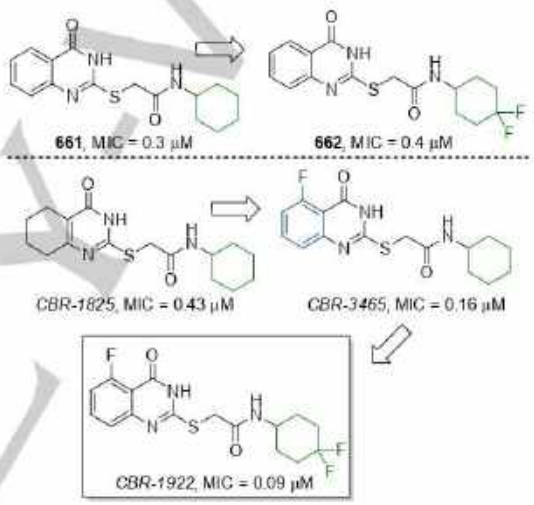


Figure 63. Discovery of antimycobacterial agents with 4,4-difluorocyclohexyl moiety

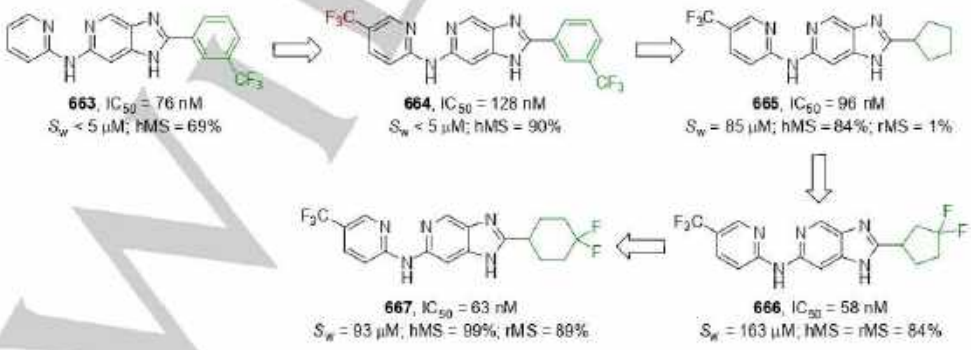


Figure 64. Discovery of antimalarial agent **667** (S_w – aqueous solubility at pH = 6.5; hMS and rMS – human and rat microsomal stability, respectively (% of the compound remaining after a 30-min exposure))

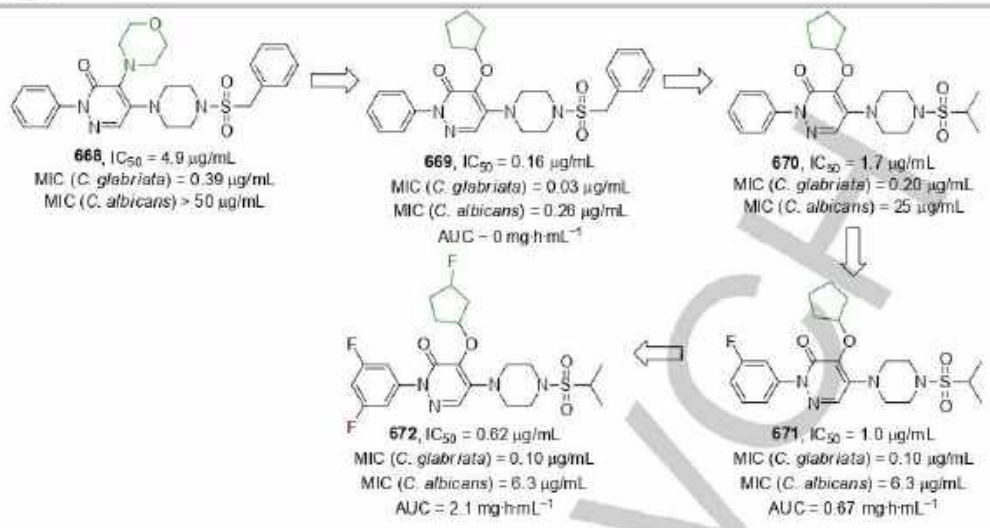


Figure 65. Discovery of antifungal agent **672** (AUC – area under pharmacokinetic curve (0–6 h) after the peroral administration of a 10 mg/kg dose in rat models)

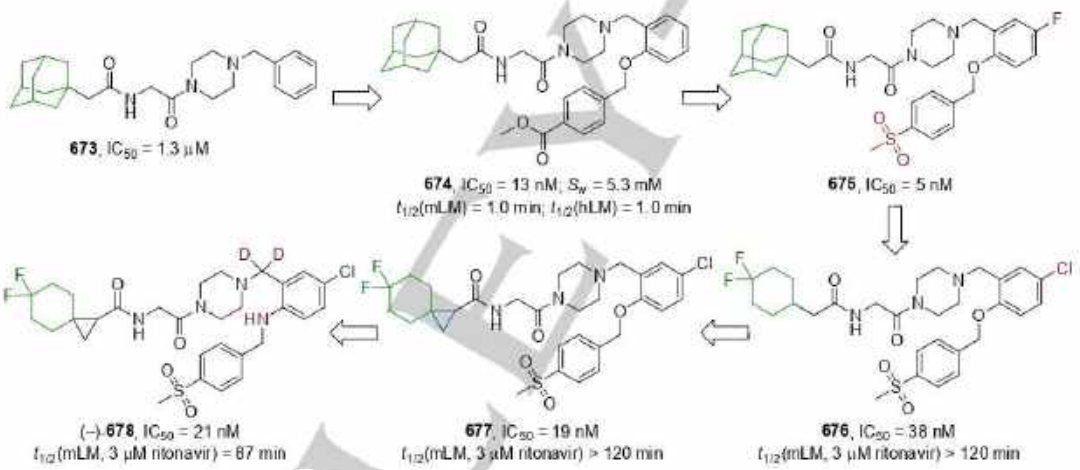


Figure 66. Discovery of antiviral agents **677** and **678** (m/hLM – mouse/human liver microsomes)

Antimalarial agents. Whole-cell phenotypic screening of an imidazopyridine library against the human malaria parasite, *Plasmodium falciparum*, followed by hit extension led to the discovery of compound **663** with high potency (Figure 64).[457] Initial SAR identified several analogs of **663** with similar activity (20–60 nM); all of them displayed poor metabolic stability, low aqueous solubility, and considerable cytotoxicity. Further optimization was aimed at eliminating these drawbacks. Thus, blocking one of the metabolic sites (2-aminopyridine moiety) by introducing the CF_3 group improved the metabolic stability (compound **664**). Replacing *m*-CF_3-phenyl group with the cyclopentyl substituent increased aqueous solubility but had a negative impact on the microsomal clearance (compound **665**). *gem*-Difluorination at the cyclopentane ring improved all the compound's characteristics including metabolic stability (compound **666**). Further optimization gave 4,4-difluorocyclohexyl derivative **667** that was progressed to rodent model studies together with its 2,5-difluorophenyl-substituted counterpart. Both compounds showed promising results in terms of *in vivo* pharmacokinetics and antimalarial efficacy.

Antifungal agents. High throughput screening identified compound **668** as an in vitro inhibitor of *Candida albicans* glucan synthase (Figure 65).[458] However, it lacked in vitro activity against some fungi strains and therefore required further optimization. Replacing morpholine ring with cyclopentyloxy substituent solved this problem but resulting compound **669** had zero bioavailability in rat models. Several sites were considered for the modification, and eventually, compound **671** was discovered with sufficient activity against *Candida glabrata*, *Candida albicans*, and *Aspergillus fumigatus*, as well as at least some bioavailability in rats. Further increasing the metabolic stability was based on the fluorination strategy. Interestingly, monufluorination (and not *gem*-difluorination) at the C-3 position of the cyclopentane ring resulted in optimal ADME properties in

this case. Compound **672** had also confirmed in vivo activity in rodent models.[459]

Antiviral agents. In a study towards the discovery of potent Ebola virus entry inhibitors, compound **673** was identified through high-throughput screening (Figure 66).[460] Its preliminary optimization led to compound **674** with nanomolar activity but modest aqueous solubility and very low microsomal stability. Further optimization was aimed mainly at addressing the latter issue (as well as diminishing the compound's lipophilicity) and eventually led to compounds **677** and **678** bearing the 4,4-difluorocyclohexane moiety as a part of spirocyclic system.[461]

Design of severe acute respiratory syndrome coronavirus 2 3C-like (SARS-CoV-2 3CL) protease inhibitors started with the structure of known antiviral dipeptide GC376 having covalent mechanism of action (Figure 67).[462] Replacement of the benzyl moiety with cyclohexane derivatives led to compound **679** with increased potency;[463] further structure-guided optimization led to even more active derivative **680**.[464] X-Ray diffraction studies showed that fluorine atoms of the 4,4-difluorocyclohexyl moiety is capable of forming short contacts with the backbone oxygen and nitrogen atoms of threonine-190 and alanine-191 residues of the protease, respectively.

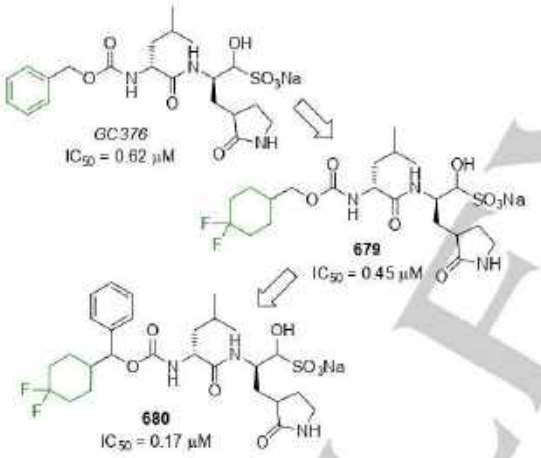


Figure 67. Discovery of antiviral agent **677** and **678** (m/hLM – mouse/human liver microsomes)

6.8. Positron emission tomography (PET) imaging agents

A very special use of fluorine in drug discovery that was not covered in any of the above sections is related to radioactivity of ^{18}F isotope ($t_{1/2}$ = 110 min). This allows using organofluorine compounds enriched with this isotope as tracers for positron emission tomography (PET) – a widely used diagnostics technique for visualizing metabolic processes and other physiological activities.[465] Due to the relatively short half-live, design of such tracers should take into account the necessity to introduce the ^{18}F atom at the last steps of the synthesis, which should be performed near the facility where the diagnosis itself takes place, preferably in an automated manner.[466] Of course, this is more feasible for the chemical biology studies where ^{18}F-labelled compounds are used as the tools.

For the case of cycloalkyl groups, nucleophilic fluorination of the appropriate substrates with a ^{18}F-fluoride source (e.g., $Bu_4N^{18}F$ or $K^{18}F$) is the method of choice. That is why monofluorinated cycloalkane (cyclobutane, cyclohexane) derivatives were used as PET tracers in all the previous studies. In any case, such compounds are somewhat beyond the scope of this review since their synthesis does not typically involve fluorinated cycloalkyl building blocks. The PET tracer design was typically based on the introduction of a fluorine-18 label into the corresponding non-fluorinated ligand or a biologically active compound already having the fluorine atom at the required position. Examples include compounds **681–684** – analogs of 5-HT_{1A} serotonine receptor antagonist WAY-100635,[195,196] tyrosine derivative **685** bearing a [^{18}F] 3-fluorocyclobutyl moiety as a metabolically stable prosthetic group,[207] radiolabeled pan-tropomyosin receptor kinase (Trk) inhibitor **686**,[467] and IDH1 inhibitor **687**[468] (an analog of another known IDH1 inhibitor Ivosidenib bearing the 3,3-difluorocyclobutyl moiety, see section 6.1, with ^{18}F label at the pyridine ring was also suggested[469]) (Figure 68).

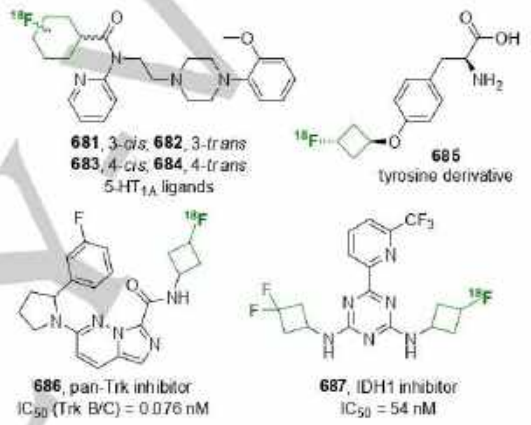


Figure 68. (Potential) PET imaging agents bearing ^{18}F-cycloalkyl moieties

The most successful compound of this series is [^{18}F] Fluciclovine, or [^{18}F] FACBC (somewhat beyond the scope of this review since contains the trisubstituted cyclobutane moiety, Figure 1) – a PET imaging agent described by Goodman and co-workers in 1999.[470] The compound was approved by FDA for prostate cancer imaging in 2016.[471] In this case, the design was somewhat different from that described above – the authors looked for a readily accessible non-natural amino acid that was close enough to the natural counterparts in terms of distribution into tumors and also could be easily ^{18}F-radiolabeled.

7. Conclusions and outlook

Fluorinated cycloalkyl moieties are important structural motifs that recently gained much interest in medicinal chemists, brought a couple of drugs to the market, and much more – into various development stages. Building blocks to introduce these moieties into the molecules of interest are typically prepared via nucleophilic fluorination of cyclic alcohols, carbonyl compounds, epoxides, aziridines, other halides, or sulfonates, as well as by the addition of fluorine and another heteroatom to double bonds. One more classical method that received much attention in recent years is (di)fluorocyclopropanation. Some novel synthetic

methods in this area include selective fluorination at the non-activated or remotely activated C–H bonds, decarboxylative and deborylative fluorinations, *cis*-selective fluorine-retaining hydrogenation, and stereoselective variations of the classical methods mentioned above (see sections 2–4).

The published data shows that all *gem*-difluorinated cycloalkyl building blocks have become readily accessible to medicinal chemists (Figure 4). Their monofluorinated counterparts, although being well-represented in the literature (Figure 2), are covered unevenly, with many "white spots" present. More importantly, efficient diastereoselective approaches to monofluorinated cycloalkyl building blocks are quite rare; even novel methodologies often do not solve this issue, especially for γ- and δ-fluorinated derivatives. Vicinally fluorinated and polyfluorinated building blocks are also presented in a fragmentary manner (Figure 6), and there is much to do for synthetic chemists in this direction.

The impact of the fluorinated cycloalkyl moieties on the key in vitro properties of the compounds (such as acidity/basicity, lipophilicity, conformational behavior, etc.) is not well-understood to date. With several important exceptions published recently (section 5), almost no systematic studies have been done in this area so far, and this might be another direction for the researchers to put their efforts into.

Despite the above obstacles, examples of using fluorinated cycloalkyl building blocks to design medicinally relevant molecules are numerous (section 6). Most often, the fluorinated cycloalkyl groups are used to replace benzene and non-fluorinated cycloalkane moieties. There are some examples where the cyclic CF_2 moiety is used as an isostere of O, C=O, and SO_2 groups.

Nearly 70% of the optimized biologically active compounds described in this review contained *gem*-difluorocycloalkyl moiety, and more than 60% of those were 4,4-difluorocyclohexyl derivatives (Figure 69). This is obviously related to the synthetic and commercial accessibility of the corresponding building blocks, and the situation should change in the future when they become more available from chemical vendors. Most of the compounds were GPCR (31%) or kinase (21%) ligands (Figure 70), which is in accordance with general trends in drug discovery.[472,473]

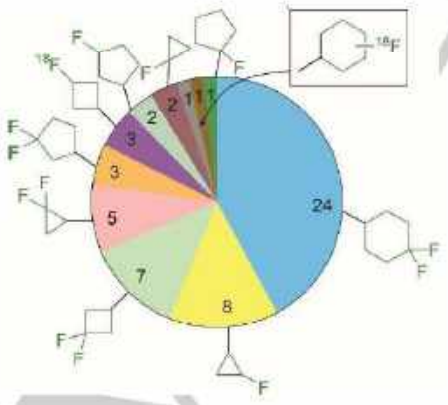


Figure 69. Occurrence of various fluorinated cycloalkyl substituents in the structures of optimized biologically active compounds described in section 6 of this review

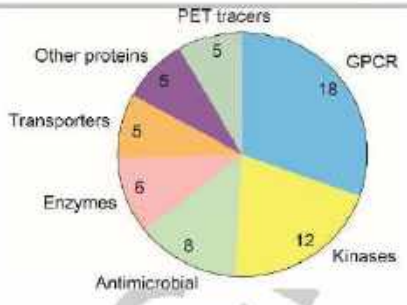


Figure 70. Optimized biologically active fluorinated cycloalkane derivatives described in section 6 of this review by biological target or function

In a vast majority of the examples provided, *gem*-difluorocycloalkyl substituents were introduced to improve the compound's pharmacokinetic properties, in particular, metabolic stability. *gem*-Difluorinated moieties were especially efficient for that purpose. Nevertheless, such modification often also increased compound potency through additional binding to the biological target. We believe that medicinal chemists should pay more attention to the manifold possibilities provided by the fluorinated cycloalkanes in drug design and exploit them efficiently in the future.

Acknowledgements

The work was funded by Enamine Ltd. O.O.G. and M.K.P. received additional funding from Ministry of Education and Sciences of Ukraine, Grants No. 0121U100387 (21BF037-01M) and 0122U001962 (22BF037-02). The authors thank Prof. Andrey A. Tolmachev for his encouragement and support and all the brave people of Ukraine for making this review possible.

Keywords: cycloalkanes • fluorine • building blocks • medicinal chemistry • saturated compounds

References

[1] D. O'Hagan, *J. Fluor. Chem.* **2010**, *131*, 1071–1081.

[2] J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506.

[3] D. Cahard, J.-A. Ma, Eds. , *Emerging Fluorinated Motifs: Synthesis, Properties and Applications*, Wiley-VCH, **2020**.

[4] H. Mei, J. Han, S. Fustero, M. Medio-Simon, D. M. Sedgwick, C. Santi, R. Ruzziconi, V. A. Soloshonok, *Chem. Eur. J.* **2019**, *25*, 11797–11819.

[5] E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315–8359.

[6] H. Mei, J. Han, S. Fustero, M. Medio-Simon, D. M. Sedgwick, C. Santi, R. Ruzziconi, V. A. Soloshonok, *Chem. Eur. J.* **2019**, *25*, 11797–11819.

[7] Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422–518.

[8] N. A. Meanwell, *J. Med. Chem.* **2018**, *61*, 5822–5880.

[9] D. E. Yerien, S. Bonesi, A. Postigo, *Org. Biomol. Chem.* **2016**, *14*, 8398–8427.

[10] K. Müller, in *Fluorine in Life Sciences: Pharmaceuticals, Medicinal Diagnostics, and Agrochemicals*, Elsevier, **2019**, pp. 91–139.
[11] S. Meyer, J. Häfliger, R. Gilmour, *Chem. Sci.* **2021**, *12*, 10686–10695.
[12] P. Shah, A. D. Westwell, *J. Enzyme Inhib. Med. Chem.* **2007**, *22*, 527–540.
[13] K. Müller, in *Fluorine in Life Sciences: Pharmaceuticals, Medicinal Diagnostics, and Agrochemicals Progress in Fluorine Science Series*, Academic Press, **2019**, pp. 91–139.
[14] B. Jeffries, Z. Wang, H. R. Felstead, J. Y. Le Questel, J. S. Scott, E. Chiarparin, J. Graton, B. Linclau, *J. Med. Chem.* **2020**, *63*, 1002–1031.
[15] L. Xing, C. Keefer, M. F. Brown, *J. Fluor. Chem.* **2017**, *198*, 47–53.
[16] C. Dalvit, C. Invernizzi, A. Vulpetti, *Chem. Eur. J.* **2014**, *20*, 11058–11068.
[17] Y. Zafrani, D. Yeffet, G. Sod-Moriah, A. Berliner, D. Amir, D. Marciano, E. Gershonov, S. Saphier, *J. Med. Chem.* **2017**, *60*, 797–804.
[18] J. Pollock, D. Borkin, G. Lund, T. Purohit, E. Dyguda-Kazimierowicz, J. Grembecka, T. Cierpicki, *J. Med. Chem.* **2015**, *58*, 7465–7474.
[19] P. Panini, D. Chopra, in *Hydrogen Bonded Supramolecular Structures*, Springer, Berlin Heidelberg, **2015**, pp. 37–67.
[20] R. Mondal, M. Agbaria, Z. Nairoukh, *Chem. Eur. J.* **2021**, *27*, 7193–7213.
[21] M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633–10640.
[22] O. O. Grygorenko, D. M. Volochnyuk, B. V. Vashchenko, *Eur. J. Org. Chem.* **2021**, 6478–6510.
[23] D. M. Volochnyuk, O. O. Grygorenko, in *Emerging Fluorinated Motifs: Synthesis, Properties and Applications* (Eds.: D. Cahard, J. Ma), Wiley, **2020**, pp. 135–194.
[24] Takeo Taguchi, Midori Okada, *J. Fluor. Chem.* **2000**, *105*, 279–283.
[25] O. O. Grygorenko, O. S. Artamonov, I. V. Komarov, P. K. Mykhailiuk, *Tetrahedron* **2011**, *67*, 803–823.
[26] W. R. Dolbier, M. A. Battiste, *Chem. Rev.* **2003**, *103*, 1071–1098.
[27] E. David, G. Milanole, P. Ivashkin, S. Couve-Bonnaire, P. Jubault, X. Pannecoucke, *Chem. Eur. J.* **2012**, *18*, 14904–14917.
[28] A. D. Dilman, V. V. Levin, *Acc. Chem. Res.* **2018**, *51*, 1272–1280.
[29] T. Itoh, in *Fluorine in Medicinal Chemistry and Chemical Biology*, John Wiley & Sons, Ltd, **2009**, pp. 313–334.
[30] K. S. Adekenova, P. B. Wyatt, S. M. Adekenov, *Beilstein J. Org. Chem.* **2021**, *17*, 245–272.
[31] D. S. Wishart, Y. D. Feunang, A. C. Guo, E. J. Lo, A. Marcu, J. R. Grant, T. Sajed, D. Johnson, C. Li, Z. Sayeeda, N. Assempour, I. Iynkkaran, Y. Liu, A. Maciejewski, N. Gale, A. Wilson, L. Chin, R. Cummings, Di. Le, A. Pon, C. Knox, M. Wilson, *Nucleic Acids Res.* **2018**, *46*, D1074–D1082.
[32] M. Kinhara, T. Takuwa, T. Kambayashi, T. Momose, Y. Takeuchi, *J. Chem. Res. Synopses* **1998**, 652–653.
[33] T. Nishikata, S. Ishida, R. Fujimoto, *Angew. Chem. Int. Ed.* **2016**, *55*, 10008–10012.
[34] S. Mizuta, K. Kitamura, A. Kitagawa, T. Yamaguchi, T. Ishikawa, *Chem. Eur. J.* **2021**, *27*, 5930–5935.
[35] T. A. McTeague, T. F. Jamison, *Angew. Chem. Int. Ed.* **2016**, *55*, 15072–15075.
[36] G. Pan, S. Chen, Chin. Pat. CN110818552, **2020**.
[37] G. Stork, W. S. Worrell, J. J. Pappas, *J. Am. Chem. Soc.* **1960**, *82*, 4315–4323.
[38] N. Mongelli, F. Animati, R. D'Alessio, L. Zuliani, C. Gandolfi, *Synthesis* **1988**, 310–313.
[39] A. I. Ayi, M. Remli, R. Guedj, *J. Fluor. Chem.* **1980**, *16*, 540–541.
[40] A. I. Ayi, W. Remli, R. Guedj, *Tetrahedron Lett.* **1981**, *22*, 1505–1508.
[41] A. I. Ayi, R. Guedj, *J. Fluor. Chem.* **1984**, *24*, 137–151.
[42] M. Remli, A. I. Ayi, R. Guedj, *J. Fluor. Chem.* **1982**, *20*, 677–682.
[43] A. Ourari, R. Condom, R. Guedj, *Can. J. Chem.* **1982**, *60*, 2707–2710.
[44] A. O. Amanetoullah, M. M. Chaabouni, A. Baklouti, *Synth. Commun.* **2006**, *26*, 1155–1161.
[45] I. Chehidi, M. M. Chaabouni, A. Baklouti, *Synth. Commun.* **2006**, *26*, 237–241.
[46] L. D. Hall, D. L. Jones, *Can. J. Chem.* **1973**, *51*, 2902–2913.
[47] D. F. Shellhamer, M. J. Horney, B. J. Pettus, T. L. Pettus, J. M. Stringer, V. L. Heasley, R. G. Syvret, J. M. Dobrolsky, *J. Org. Chem.* **1999**, *64*, 1094–1098.
[48] M. Moens, M. D'Hooghe, N. De Kimpe, *Tetrahedron Lett.* **2013**, *54*, 6110–6113.
[49] R. Gurbanov, A. Sokolov, S. Golovach, K. Melnykov, A. V. Dobrydnev, O. O. Grygorenko, *Synthesis* **2020**, *53*, 1771–1784.
[50] H. Jiang, A. Studer, *Angew. Chem. Int. Ed.* **2018**, *57*, 10707–10711.
[51] C. Wuttke, R. Ford, M. Lilley, U. Grabowska, D. Wiltelius, R. F. W. Jackson, *Synlett* **2012**, 243–246.
[52] A. B. Pinkerton, P. M. Hershberger, S. Peddibhotla, M. P. Maloney, Patrick R. Hedrick, PCT Int. Pat. WO2015200534, **2015**.
[53] H. P. Beck, S. K. Booker, H. Bregman, V. J. Cee, N. Chakka, T. D. Cushing, O. Epstein, B. M. Fox, S. Geuns-Meyer, X. Hao, K. Hibya, J. Hirata, Z. Hua, J. Human, S. Kakuda, P. Lopez, R. Nakajima, K. Okada, S. H. Olson, H. Ono, L. D. Pennington, K. Sasaki, K. Shimada, Y. Shin, R. D. White, R. P. Wurz, S. Yi, X. M. Zheng, PCT Int. Pat. WO2015129926, **2015**.
[54] S. Rozen, A. Hagooly, R. Harduf, *J. Org. Chem.* **2001**, *66*, 7464–7468.
[55] H. Fujisawa, Y. Takeuchi, *J. Fluor. Chem.* **2002**, *117*, 173–176.
[56] F. R. Alexandre, G. Brandt, C. Caillet, D. Chaves, T. Convard, M. Derock, D. Gloux, Y. Griffon, L. Lallos, F. Leroy, M. Liuzzi, A. G. Loi, L. Moulat, C. Musiu, C. Parsy, H. Rahali, V. Roques, M. Seifer, D. Standring, D. Surleraux, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3984–3991.
[57] S. Stavber, M. Jereb, M. Zupan, *Synthesis* **2002**, 2609–2615.
[58] F. G. Zhang, X. Q. Wang, Y. Zhou, H. S. Shi, Z. Feng, J. A. Ma, I. Marek, *Chem. Eur. J.* **2020**, *26*, 15378–15396.
[59] S. Rozen, C. Gal, *J. Fluor. Chem.* **1985**, *27*, 143–148.
[60] S. Rozen, C. Gal, *J. Org. Chem.* **1987**, *52*, 2769–2779.
[61] S. P. Morcillo, E. M. Dauncey, J. Kim, J. J. Douglas, N. S. Sheikh, D. Leonori, S. PMorcillo, E. M. Dauncey, D. Leonori, D. JDouglas, N. S. Sheikh, *Angew. Chem. Int. Ed.* **2018**, *57*, 12945–12949.
[62] A. N. Herron, D. Liu, G. Xia, J. Q. Yu, *J. Am. Chem. Soc.* **2020**, *142*, 2766–2770.
[63] H. Guan, S. Sun, Y. Mao, L. Chen, R. Lu, J. Huang, L. Liu, *Angew. Chem. Int. Ed.* **2018**, *57*, 11413–11417.
[64] D. Bafaluy, Z. Georgieva, K. Muñiz, *Angew. Chem. Int. Ed.* **2020**, *59*, 14241–14245.
[65] G. Alvernhe, E. Koslowska-Gramsz, S. Lacombe-Bar, A. Laurent, *Tetrahedron Lett.* **1978**, *19*, 5203–5206.
[66] S. Hara, S. Q. Chen, T. Hatakeyama, T. Fukuhara, M. Sekiguchi, N. Yoneda, *Tetrahedron Lett.* **1995**, *36*, 6511–6514.
[67] E. D. Bergmann, S. Szinai, *J. Chem. Soc.* **1956**, 1521–1524.
[68] L. Fijer, *Synthesis* **1977**, 189–191.
[69] H. Møllendal, A. Leonov, A. De Meijere, *J. Mol. Struct.* **2004**, 695–

696, 163–169.

[70] A. A. Shah, M. J. Kelly, J. J. Perkins, *Org. Lett.* **2020**, *22*, 2196–2200.

[71] A. Yoneda, T. Fukuhara, S. Hara, *Chem. Commun.* **2005**, 3589–3590.

[72] M. Suwada, T. Fukuhara, S. Hara, *J. Fluor. Chem.* **2007**, *128*, 1121–1125.

[73] T. Umemoto, R. P. Singh, Y. Xu, N. Saito, *J. Am. Chem. Soc.* **2010**, *132*, 18199–18205.

[74] T. Nomoto, T. Fukuhara, S. Hara, *Synlett* **2006**, 1744–1746.

[75] H. S. Chong, X. Sun, Y. Chen, M. Wang, *Tetrahedron Lett.* **2015**, *56*, 946–948.

[76] M. Winkler, N. Klempier, H. Weber, K. R. Grünwald, M. Flock, A. Dransfeld, *Magn. Reson. Chem.* **2008**, *46*, 865–871.

[77] G. Pupo, A. C. Vicini, D. M. H. Ascough, F. Ibba, K. E. Christensen, A. L. Thompson, J. M. Brown, R. S. Paton, V. Gouverneur, *J. Am. Chem. Soc.* **2019**, *141*, 2878–2883.

[78] A. C. Vicini, D. M. Alozie, P. Courtes, G. Roagna, C. Aubert, V. Certal, Y. El-Ahmad, S. Roy, V. Gouverneur, *Org. Process Res. Dev.* **2021**, *25*, 2730–2737.

[79] J. V. Kababinos, J. J. Hazdba, *J. Org. Chem.* **1962**, *27*, 3308–3309.

[80] K. Wiechert, P. Mohr, *Zeitschrift für Chemie* **1965**, *5*, 380–381.

[81] G. A. Olah, D. Meidar, *Isr. J. Chem.* **1978**, *17*, 148–149.

[82] D. Landini, M. Penso, *Tetrahedron Lett.* **1990**, *31*, 7209–7212.

[83] D. F. Shellhamer, A. A. Briggs, B. M. Miller, J. M. Prince, D. H. Scott, V. L. Heasley, *J. Chem. Soc. Perkin Trans. 2* **1996**, *5*, 973–977.

[84] M. Tamura, M. Shibakami, T. Arimura, S. Kurosawa, A. Sekiya, *J. Fluor. Chem.* **1995**, *70*, 1–3.

[85] Y. Akiyama, T. Fukuhara, S. Hara, *Synlett* **2003**, 1530–1532.

[86] D. Wölker, G. Haufe, *J. Org. Chem.* **2002**, *67*, 3015–3021.

[87] T. Inagaki, T. Fukuhara, S. Hara, *Synthesis* **2003**, 1157–1159.

[88] H. Yoshino, K. Matsumoto, R. Hagiwara, Y. Ito, K. Oshima, S. Matsubara, *J. Fluor. Chem.* **2006**, *127*, 29–35.

[89] O. O. Kolodiazhna, D. V Prysiazhnuk, A. O. Kolodiazhna, O. I. Kolodiazhnyi, *Arkivoc* **2022**, 14–26.

[90] E. A. Basso, C. Kaiser, R. Rittner, J. B. Lambert, *J. Org. Chem.* **2002**, *58*, 7865–7869.

[91] O. O. Kolodiazhna, A. O. Kolodiazhna, O. I. Kolodiazhnyi, *Tetrahedron: Asymmetry* **2013**, *24*, 37–42.

[92] J. Graton, G. Compain, F. Besseau, E. Bogdan, J. M. Watts, L. Mtashobya, Z. Wang, A. Weymouth-Wilson, N. Galland, J. Y. Le Questel, B. Lindau, *Chem. Eur. J.* **2017**, *23*, 2811–2819.

[93] C. Toulgui, M. M. Chaabouni, A. Baklouti, *J. Fluor. Chem.* **1990**, *46*, 385–391.

[94] A. Baklouti, A. Hedhli, *J. Fluor. Chem.* **1984**, *25*, 151–156.

[95] I. Pastor, M. Yus, *Curr. Org. Chem.* **2005**, *9*, 1–29.

[96] G. Haufe, S. Bruns, M. Runge, *J. Fluor. Chem.* **2001**, *112*, 55–61.

[97] G. Haufe, S. Bruns, *Adv. Synth. Catal.* **2002**, *344*, 165–171.

[98] J. A. Kalow, A. G. Doyle, *J. Am. Chem. Soc.* **2010**, *132*, 3268–3269.

[99] E. Revunov, F. Zhuravlev, *J. Fluor. Chem.* **2013**, *156*, 130–135.

[100] T. N. Wade, *J. Org. Chem.* **2002**, *45*, 5328–5333.

[101] G. M. Alvernhe, C. M. Ennakoua, S. M. Lacombe, A. J. Laurent, *J. Org. Chem.* **1981**, *46*, 4938–4948.

[102] J. A. Kalow, D. E. Schmitt, A. G. Doyle, *J. Org. Chem.* **2012**, *77*, 4177–4183.

[103] C. H. Ding, L. X. Dai, X. L. Hou, *Synlett* **2004**, *2004*, 2218–2220.

[104] N. Hsueh, G. J. Clarkson, M. Shipman, *Org. Lett.* **2015**, *17*, 3632–3635.

[105] J. A. Kalow, A. G. Doyle, *Tetrahedron* **2013**, *69*, 5702–5709.

[106] R. H. Fan, Y. G. Zhou, W. X. Zhang, X. L. Hou, L. X. Dai, *J. Org. Chem.* **2004**, *69*, 335–338.

[107] S. Noritake, N. Shibata, H. Kawai, M. K. Pandy, S. Nakamura, T. Toru, *Heterocycl. Commun.* **2009**, *15*, 105–113.

[108] W. X. Zhang, L. Su, W. G. Hu, J. Zhou, *Synlett* **2012**, *23*, 2413–2415.

[109] M. Norn, L. Kiss, M. Haukka, S. Fustero, F. Fülop, *Org. Lett.* **2015**, *17*, 1074–1077.

[110] O. E. Okoromoba, Z. Li, N. Robertson, M. S. Mashuta, U. R. Couto, C. F. Tormena, B. Xu, G. B. Hammond, *Chem. Commun.* **2016**, *52*, 13353–13356.

[111] A. Bowers, L. C. Ibáñez, E. Denot, R. Becerra, *J. Am. Chem. Soc.* **1960**, *82*, 4001–4007.

[112] G. Alvernhe, A. Laurent, G. Haufe, *Synthesis* **1987**, 562–564.

[113] M. Hudlicky, *J. Fluor. Chem.* **1986**, *32*, 441–452.

[114] S. Rozen, M. Brand, *Tetrahedron Lett.* **1980**, *21*, 4543–4546.

[115] S. Rozen, M. Brand, *J. Org. Chem.* **1985**, *50*, 3342–3348.

[116] R. D. Evans, J. H. Schauble, *Synthesis* **1987**, 551–554.

[117] F. Camps, E. Chamorro, V. Gasol, A. Guerrero, *J. Org. Chem.* **1989**, *54*, 4294–4298.

[118] M. Kuroboshi, T. Hiyama, *Tetrahedron Lett.* **1991**, *32*, 1215–1218.

[119] U. Yukitaka, U. Masayuki, S. Hideharu, Y. Hirosuke, *Chem. Lett.* **2006**, *22*, 673–676.

[120] G. A. Olah, X.-Y. Li, Q. Wang, G. K. S. Prakash, *Synthesis* **1993**, 693–699.

[121] KuroboshiManabu, HiyamaTamejiro, *Bull. Chem. Soc. Jpn.* **2006**, *68*, 1799–1805.

[122] M. Tamura, M. Shibakami, A. Sekiya, *Synthesis* **1995**, 515–517.

[123] D. F. Shellhamer, B. C. Jones, B. J. Pettus, T. L. Pettus, J. M. Stringer, V. L. Heasley, *J. Fluor. Chem.* **1998**, *88*, 37–39.

[124] S. Kobayashi, M. Sawaguchi, S. Ayuba, T. Fukuhara, S. Hara, *Synlett* **2001**, 1938–1940.

[125] I. Bucsi, B. Török, A. I. Marco, G. Rasul, G. K. S. Prakash, G. A. Olah, *J. Am. Chem. Soc.* **2002**, *124*, 7728–7736.

[126] R. Sasson, S. Rozen, *J. Fluor. Chem.* **2006**, *127*, 962–965.

[127] L. T. C. Crespo, R. D. S. Ribeiro, M. C. S. De Mattos, P. M. Esteves, *Synthesis* **2010**, 2379–2382.

[128] J. Walkowiak, B. Marciniak, H. Koroniak, *J. Fluor. Chem.* **2012**, *143*, 287–291.

[129] S. Yano, S. Hara, *Synthesis* **2015**, *47*, 2839–2843.

[130] N. O. Ilchenko, M. A. Cortes, K. J. Szabó, *ACS Catal.* **2016**, *6*, 447–450.

[131] T. Kitamura, R. Komoto, J. Oyamada, M. Higashi, Y. Kishikawa, *J. Org. Chem.* **2021**, *86*, 18300–18303.

[132] C. Zhang, Z. Li, L. Zhu, L. Yu, Z. Wang, C. Li, *J. Am. Chem. Soc.* **2013**, *135*, 14082–14085.

[133] D. M. Sedgwick, I. López, R. Román, N. Kobayashi, O. E. Okoromoba, B. Xu, G. B. Hammond, P. Barrio, S. Fustero, *Org. Lett.* **2018**, *20*, 2338–2341.

[134] A. S. Kende, *Tetrahedron Lett.* **1959**, *1*, 13–16.

[135] S. Nakanishi, K. I. Morita, E. V. Jensen, *J. Am. Chem. Soc.* **1959**, *81*, 5259–5260.

[136] H. G. Ferguson, P. De Mayo, F. L. M. Pattison, T. Tabata, *Can. J. Chem.* **1963**, *41*, 2099–2100.

[137] J. Bensoam, F. Mathey, *Tetrahedron Lett.* **1977**, *18*, 2797–2800.

[138] B. Zajc, M. Zupan, *J. Chem. Soc. Chem. Commun.* **1980**, 759–760.

[139] B. Zajc, M. Zupan, *J. Org. Chem.* **1982**, *47*, 573–575.

[140] W. J. Middleton, E. M. Bingham, *J. Am. Chem. Soc.* **1980**, *102*, 4845–4846.

[141] S. Stavber, M. Zupan, *J. Chem. Soc. Chem. Commun.* **1981**, 795–796.

[142] S. Stavber, B. Šket, B. Zajc, M. Zupan, *Tetrahedron* **1989**, *45*, 6003–6010.

[143] S. T. Purrington, W. A. Jones, *J. Fluor. Chem.* **1984**, *26*, 43–46.

[144] G. L. Cantrell, R. Filler, *J. Fluor. Chem.* **1985**, *27*, 35–45.

[145] R. E. Banks, R. A. Du Boisson, E. Tsiliopoulos, *J. Fluor. Chem.* **1986**, *32*, 461–466.

[146] R. E. Banks, R. A. Du Boisson, W. D. Morton, E. Tsiliopoulos, *J. Chem. Soc. Perkin Trans. 1* **1988**, 2805–2811.

[147] S. T. Purrington, N. V. Lazaridis, C. L. Bumgardner, *Tetrahedron Lett.* **1986**, *27*, 2715–2716.

[148] T. Umemoto, K. Tomita, *J. Fluor. Chem.* **1987**, *35*, 14.

[149] T. Umemoto, S. Fukami, G. Tomizawa, K. Harasawa, K. Kawada, K. Tomita1, *J. Am. Chem. Soc.* **1990**, *112*, 8563–8575.

[150] A. J. Poss, M. Van Der Puy, D. Nalewajek, G. A. Shia, W. J. Wagner, R. L. Frenette, *J. Org. Chem.* **1991**, *56*, 5962–5964.

[151] R. E. Banks, S. N. Mohialdin-Khaffaf, G. S. Lal, I. Sharif, R. G. Syvret, *J. Chem. Soc. Chem. Commun.* **1992**, 595–596.

[152] F. A. Davis, W. Han, C. K. Murphy, *J. Org. Chem.* **1995**, *60*, 4730–4737.

[153] S. Stavber, M. Zupan, *Tetrahedron Lett.* **1996**, *37*, 3591–3594.

[154] D. Enders, M. R. M. Hüttl, *Synlett* **2005**, 991–993.

[155] R. Kazem Shiroodi, A. S. Dudnik, V. Gevorgyan, *J. Am. Chem. Soc.* **2012**, *134*, 6928–6931.

[156] A. S. Reddy, K. K. Laali, *Tetrahedron Lett.* **2015**, *56*, 5495–5499.

[157] X. Chen, B. Pierce, W. Naing, M. L. Grapperhaus, D. P. Phillion, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3107–3111.

[158] P. Kwiatkowski, T. D. Beeson, J. C. Conrad, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 1738–1741.

[159] Y. S. Xu, Y. Tang, H. J. Feng, J. T. Liu, R. P. Hsung, *Org. Lett.* **2015**, *17*, 572–575.

[160] R. M. Malamakal, W. R. Hess, T. A. Davis, *Org. Lett.* **2010**, *12*, 2186–2189.

[161] A. Toyota, Y. Ono, C. Kaneko, I. Hayakawa, *Tetrahedron Lett.* **1996**, *37*, 8507–8510.

[162] Y. J. Mao, S. J. Lou, H. Y. Hao, D. Q. Xu, *Angew. Chem. Int. Ed.* **2018**, *57*, 14085–14089.

[163] E. N. Pinter, J. E. Bingham, D. I. Abusalim, S. P. Cook, *Chem. Sci.* **2020**, *11*, 1102–1106.

[164] Z. Deng, Z. Zhao, G. He, G. Chen, *Org. Lett.* **2021**, *23*, 3631–3635.

[165] F. Yin, Z. Wang, Z. Li, C. Li, *J. Am. Chem. Soc.* **2012**, *134*, 10401–10404.

[166] L. Huawen, Chin. Pat. CN112279759, **2021**.

[167] S. Ventre, F. R. Petronijevic, D. W. C. Macmillan, *J. Am. Chem. Soc.* **2015**, *137*, 5654–5657.

[168] X. Wu, C. Meng, X. Yuan, X. Jia, X. Qian, J. Ye, *Chem. Commun.* **2015**, *51*, 11864–11867.

[169] J. He, H. Jiang, R. Takise, R. Y. Zhu, G. Chen, H. X. Dai, T. G. M. Dhar, J. Shi, H. Zhang, P. T. W. Cheng, J. Q. Yu, *Angew. Chem. Int. Ed.* **2016**, *55*, 785–789.

[170] J. He, Q. Shao, Q. Wu, J. Q. Yu, *J. Am. Chem. Soc.* **2017**, *139*, 3344–3347.

[171] Z. X. Giustra, X. Yang, M. Chen, H. F. Bettinger, S. Y. Liu, *Angew. Chem. Int. Ed.* **2019**, *58*, 18918–18922.

[172] S. Ren, C. Feng, T. P. Loh, *Org. Biomol. Chem.* **2015**, *13*, 5105–5109.

[173] H. Zhao, X. Fan, J. Yu, C. Zhu, *J. Am. Chem. Soc.* **2015**, *137*, 3490–3493.

[174] K. R. Gassen, B. Baasner, *J. Fluor. Chem.* **1990**, *49*, 127–139.

[175] A. Imura, M. Itoh, A. Miyadera, *Tetrahedron: Asymmetry* **1998**, *9*, 3047–3052.

[176] J. I. Matsuo, Y. I. Tani, Y. I. Hayakawa, *Chem. Lett.* **2004**, *33*, 464–465.

[177] O. Tamura, M. Hashimoto, Y. Kobayashi, T. Katoh, K. Nakatani, M. Kamada, I. Hayakawa, T. Akiba, S. Terashima, *Tetrahedron* **1994**, *50*, 3889–3904.

[178] O. Tamura, M. Hashimoto, Y. Kobayashi, T. Katoh, K. Nakatani, M. Kamada, I. Hayakawa, T. Akiba, S. Terashima, *Tetrahedron Lett.* **1992**, *33*, 3483–3486.

[179] T. Akiba, O. Tamura, M. Hashimoto, Y. Kobayashi, T. Katoh, K. Nakatani, M. Kamada, I. Hayakawa, S. Terashima, *Tetrahedron* **1994**, *50*, 3905–3914.

[180] O. Tamura, M. Hashimoto, Y. Kobayashi, T. Katoh, K. Nakatani, M. Kamada, I. Hayakawa, T. Akiba, S. Terashima, *Tetrahedron Lett.* **1992**, *33*, 3487–3490.

[181] R. Meingale, A. Sperga, K. K. Baldridge, J. Veliks, *Org. Lett.* **2019**, *21*, 7174–7178.

[182] A. Sperga, R. Meingale, A. Kazia, S. Belyakov, J. Veliks, *J. Org. Chem.* **2021**, *86*, 3196–3212.

[183] W. R. Dolbier, O. Phanstiel IV, *Tetrahedron Lett.* **1988**, *29*, 53–56.

[184] G. Haufe, T. C. Rosen, O. G. J. Meyer, R. Fröhlich, K. Rissanen, *J. Fluor. Chem.* **2002**, *114*, 189–198.

[185] T. Shibue, Y. Fukuda, *J. Org. Chem.* **2014**, *79*, 7226–7231.

[186] F. Chen, X. H. Xu, F. L. Qing, *Org. Lett.* **2021**, *23*, 2364–2369.

[187] E. L. Lucas, T. M. McGinnis, A. J. Castro, E. R. Jarvo, *Synlett* **2021**, *32*, 1525–1530.

[188] M. L. Schulte, C. W. Lindsley, *Org. Lett.* **2011**, *13*, 5684–5687.

[189] W. Huang, Y. Yao, Y. J. Xu, C. D. Lu, *J. Org. Chem.* **2018**, *83*, 14777–14785.

[190] N. C. Craig, S. S. Borick, M. A. Fisher, T. R. Tucker, Y. Z. Xiao, *J. Fluor. Chem.* **1992**, *59*, 215–224.

[191] D. S. Ashton, J. M. Tedder, *J. Chem. Soc. B:Phys. Org.* **1971**, 1723–1726.

[192] M. P. Wiesenfeldt, Z. Nairoukh, W. Li, F. Glorius, *Science* **2017**, *357*, 908–912.

[193] G. Bellavance, P. Dubé, B. Nguyen, *Synlett* **2012**, 569–572.

[194] J. C. Leung, T. T. Nguyen, M. Krawiec, D. A. Gao, J. T. Reeves, *Org. Process Res. Dev.* **2021**, *25*, 632–641.

[195] L. Lang, E. Jagoda, B. Schmall, B. K. Vuong, H. R. Adams, D. L. Nelson, R. E. Carson, W. C. Eckelman, *J. Med. Chem.* **1999**, *42*, 1576–1586.

[196] L. Lang, E. Jagoda, Y. Ma, M. B. Sassaman, W. C. Eckelman, *Bioorg. Med. Chem.* **2006**, *14*, 3737–3748.

[197] M. González-Esguevillas, J. Miró, J. L. Jeffrey, D. W. C. MacMillan, *Tetrahedron* **2019**, *75*, 4222–4227.

[198] J. Popovici-Muller, J. O. Saunders, F. G. Salituro, Z. Cai, S. Yan, D. Zhou, PCT Int. Pat. WO2013107405, **2013**.

[199] W. Dai, N. Xi, M. Li, T. Zhang, X. Li, H. Hu, W. Chen, T. Wang, J. Liu, PCT Int. Pat. WO2017048675, **2017**.

[200] K. Graham, H. Schmitt-Willich, D. Franck, PCT Int. Pat. WO2011006621, **2011**.

[201] P. Galatsis, J. L. Henderson, B. L. Kormos, R. G. Kurumbail, M. R. Reese, A. F. Stepan, P. R. Verhoest, T. T. Wager, M. Y. Pettersson, M. R. Gamsey, U.S. Pat. 2017073343, **2017**.

[202] J. Bao, T. J. Henderson, M. M.-C. Lo, J. Mazzola, M. T. Rudd, D. M. Tellers, L. Tong, C. Li, M. Na, PCT Int. Pat. WO2019000238.

[203] S. D. Kuduk, M. R. Wood, PCT Int. Pat. WO2006132837, **2006**.

[204] A. Flohr, R. Jakob-Roetne, R. D. Norcross, C. Riemer, R. D. Norcross, U.S. Pat. 2003149036, **2003**.

[205] K. Nakai, F. Takahashi, K. Fujita, Y. Kozuki, K. Mukoyoshi, M. Inami, N. Asai, PCT Int. Pat. WO2007013673, **2007**.

[206] B. Van Wagenen, R. Ukkiramapandian, J. Clayton, I. Egle, J. Empfield, M. Isaac, F. Ma, A. Slassi, G. Steelman, R. Urbanek, S. Walsh, PCT Int. Pat. WO2007021309, **2007**.

[207] D. Franck, T. Kniess, J. Steinbach, S. Zitzmann-Kolbe, M. Friebe, L. M. Dinkelborg, K. Graham, *Bioorg. Med. Chem.* **2013**, *21*, 643–652.

[208] R. J. M. Goss, S. E. Lanceron, N. J. Wise, S. J. Moss, *Org. Biomol. Chem.* **2006**, *4*, 4071–4073.

[209] G. H. Lovett, S. Chen, X. S. Xue, K. N. Houk, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2019**, *141*, 20031–20036.

[210] W. Liu, X. Huang, M. J. Cheng, R. J. Nielsen, W. A. Goddard, J. T. Groves, *Science* **2012**, *337*, 1322–1325.

[211] W. Liu, X. Huang, M. S. Placzek, S. W. Krska, P. McQuade, J. M. Hooker, J. T. Groves, *Chem. Sci.* **2018**, *9*, 1168–1172.

[212] S. D. Halperin, H. Fan, S. Chang, R. E. Martin, R. Britton, *Angew. Chem. Int. Ed.* **2014**, *53*, 4690–4693.

[213] J. B. Xia, C. Zhu, C. Chen, *Chem. Commun.* **2014**, *50*, 11701–11704.

[214] Y. Q. Chen, S. Singh, Y. Wu, Z. Wang, W. Hao, P. Verma, J. X. Qiao, R. B. Sunoj, J. Q. Yu, *J. Am. Chem. Soc.* **2020**, *142*, 9966–9974.

[215] R. Gianatassio, J. M. Lopchuk, J. Wang, C. M. Pan, L. R. Malins, L. Prieto, T. A. Brandt, M. R. Collins, G. M. Gallego, N. W. Sach, J. E. Spangler, H. Zhu, J. Zhu, P. S. Baran, *Science* **2016**, *351*, 241–246.

[216] Y. Xie, P. W. Sun, Y. Li, S. Wang, M. Ye, Z. Li, *Angew. Chem. Int. Ed.* **2019**, *58*, 7097–7101.

[217] J. Barluenga, J. M. González, P. J. Campos, G. Asensio, *Angew. Chem. Int. Ed.* **1988**, *27*, 1546–1547.

[218] S. Bloom, D. D. Bume, C. R. Pitts, T. Lectka, *Chem. Eur. J.* **2015**, *21*, 8060–8063.

[219] W. R. Dolbier, T. A. Gray, J. J. Keaffaber, L. Celewicz, H. Koroniak, *J. Am. Chem. Soc.* **2002**, *112*, 363–367.

[220] S. Kacem, M. Emondts, A. Bordet, W. Leitner, *Catal. Sci. Technol.* **2020**, *10*, 8120–8126.

[221] D. Seyferth, H. Dertouzos, R. Suzuki, J. Y. P. Mui, *J. Org. Chem.* **1967**, *32*, 2980–2984.

[222] W. R. Dolbier, F. Tian, J. X. Duan, A. R. Li, S. Ait-Mohand, O. Bautista, S. Buathong, J. M. Baker, J. Crawford, P. Anselme, X. H. Cai, A. Modzelewska, H. Koroniak, M. A. Battiste, Q. Y. Chen, *J. Fluor. Chem.* **2004**, *125*, 459–469.

[223] W. P. Gu, J. H. Lin, J. C. Xiao, *Chinese Chem. Lett.* **2014**, *25*, 24–28.

[224] S. Easterwiemann, H. Martinez, W. R. Dolbier, *J. Org. Chem.* **2012**, *77*, 5461–5464.

[225] F. Wang, T. Luo, J. Hu, Y. Wang, H. S. Krishnan, P. V. Jog, S. K. Ganesh, G. K. S. Prakash, G. A. Olah, *Angew. Chem. Int. Ed.* **2011**, *50*, 7153–7157.

[226] P. S. Nosik, A. O. Gerasov, R. O. Boiko, E. Rusanov, S. V. Ryabukhin, O. O. Grygorenko, D. M. Volochnyuk, *Adv. Synth. Catal.* **2017**, *359*, 3126–3136.

[227] R. M. Bychek, V. V. Levterov, I. V. Sadkova, A. A. Tolmachev, P. K. Mykhailiuk, *Chem. Eur. J.* **2018**, *24*, 12291–12297.

[228] P. S. Nosik, S. V. Ryabukhin, O. O. Grygorenko, D. M. Volochnyuk, *Adv. Synth. Catal.* **2018**, *360*, 4104–4114.

[229] O. V. Hryshchuk, A. O. Varenyk, Y. Yurov, Y. O. Kuchkovska, A. V. Tymtsunik, O. O. Grygorenko, *Eur. J. Org. Chem.* **2020**, 2217–2224.

[230] P. S. Nosik, S. V. Ryabukhin, M. O. Pashko, G. P. Grabchuk, O. O. Grygorenko, D. M. Volochnyuk, *J. Fluor. Chem.* **2019**, *217*, 80–89.

[231] A. García-Domínguez, T. H. West, J. J. Primozic, K. M. Grant, C. P. Johnston, G. G. Cumming, A. G. Leach, G. C. Lloyd-Jones, *J. Am. Chem. Soc.* **2020**, *142*, 14649–14663.

[232] R. Gianatassio, S. Kawamura, C. L. Eprile, K. Foo, J. Ge, A. C. Burns, M. R. Collins, P. S. Baran, *Angew. Chem. Int. Ed.* **2014**, *53*, 9851–9855.

[233] L. Li, F. Wang, C. Ni, J. Hu, *Angew. Chem. Int. Ed.* **2013**, *52*, 12390–12394.

[234] A. E. Goetz, H. Becirovic, F. Blasberg, B. Chen, H. J. Clarke, M. Colombo, P. Daddario, D. B. Damon, C. Depretz, Y. R. Dumond, M. D. Grilli, L. Han, T. L. Houck, A. M. Johnson, K. N. Jones, J. Jung, M. Leeman, F. Liu, C. V. Lu, E. J. Mangual, J. D. Nelson, A. L. A. Puchlopek-Demeno, S. G. Ruggeri, P. A. Simonds, B. Sitter, D. E. Virtue, S. Wang, L. Yu, T. Yu, *Org. Process Res. Dev.* **2022**, *26*, 683–697.

[235] X. C. Hang, W. P. Gu, Q. Y. Chen, J. C. Xiao, *Tetrahedron* **2009**, *65*, 6320–6324.

[236] D. Elend, D. Fengas, M. J. Fray, *Synth. Commun.* **2006**, *35*, 657–662.

[237] K. P. Melnykov, D. S. Granat, D. M. Volochnyuk, S. V. Ryabukhin, O. O. Grygorenko, *Synthesis* **2018**, *50*, 4949–4957.

[238] T. Mase, I. N. Houpis, A. Akao, I. Dorziotis, K. Emerson, T. Hoang, T. Iida, T. Itoh, K. Kamei, S. Kato, Y. Kato, M. Kawasaki, F. Lang, J. Lee, J. Lynch, P. Maligres, A. Molina, T. Nemoto, S. Okada, R. Reamer, J. Z. Song, D. Tschaen, T. Wada, D. Zewge, R. P. Volante, P. J. Reider, K. Tomimoto, *J. Org. Chem.* **2001**, *66*, 6775–6786.

[239] K. P. Melnykov, P. S. Nosik, B. B. Kurpil, D. A. Sibgatulin, D. M. Volochnyuk, S. V. Ryabukhin, O. O. Grygorenko, *J. Fluor. Chem.* **2017**, *199*, 60–66.

[240] S. D. Kuduk, R. K. Chang, R. M. DiPardo, C. N. Di Marco, K. L. Murphy, R. W. Ransom, D. R. Reiss, C. Tang, T. Prueksaritanont, D. J. Pettibone, M. G. Bock, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5107–5110.

[241] M. Herasymchuk, K. P. Melnykov, D. V. Yarmoliuk, D. Serhiichuk, V. Rotar, T. Pukhovoi, Y. O. Kuchkovska, S. Holovach, D. M. Volochnyuk, S. V. Ryabukhin, O. O. Grygorenko, *Eur. J. Org. Chem.* **2021**, 6561–6569.

[242] D. A. Price, S. Gayton, M. D. Selby, J. Ahman, S. Haycock-Lewandowski, B. L. Stammen, A. Warren, *Tetrahedron Lett.* **2005**, *46*, 5005–5007.

[243] P. K. Mykhailiuk, V. Starova, V. Iurchenko, S. V. Shishkina, O. V. Shishkin, O. Khilchevskyi, O. Zaporozhets, *Tetrahedron* **2013**, *69*, 4066–4075.

[244] S. J. Haycock-Lewandowski, A. Wilder, J. Ahman, *Org. Process Res. Dev.* **2008**, *12*, 1094–1103.

[245] I. Saidalimu, S. Suzuki, E. Tokunaga, N. Shibata, *Chem. Sci.* **2016**, *7*, 2106–2110.

[246] S. Ishii, Y. Niwa, S. Watanabe, *J. Fluor. Chem.* **2016**, *182*, 41–46.

[247] A. V. Chernykh, K. P. Melnykov, N. A. Tolmacheva, I. S. Kondratov, D. S. Radchenko, C. G. Daniliuc, D. M. Volochnyuk, S. V. Ryabukhin, Y. O. Kuchkovska, O. O. Grygorenko, *J. Org. Chem.* **2019**, *84*, 8487–8496.

[248] S. A. Trofymchuk, D. V. Kliukovskyi, S. V. Semenov, A. R. Khairulin, V. O. Shevchenko, M. Y. Bugera, K. V. Tarasenko, D. M. Volochnyuk, S. V. Ryabukhin, *Synlett* **2020**, *31*, 565–574.

[249] O. Cohen, S. Rozen, *Tetrahedron* **2008**, *64*, 5362–5364.

[250] P. P. Chandrachud, L. Wojtas, J. M. Lopchuk, *J. Am. Chem. Soc.*

2020, *142*, 21743–21750.
[251] C. C. Tseng, H. Noordali, M. Sani, M. Madhani, D. M. Grant, M. P. Frenneaux, M. Zanda, I. R. Greig, *J. Med. Chem.* **2017**, *60*, 2780–2789.
[252] O. Irie, F. Yokokawa, T. Ehara, A. Iwasaki, Y. Iwaki, Y. Hitomi, K. Konishi, M. Kishida, A. Toyao, K. Masuya, H. Gunji, J. Sakaki, G. Iwasaki, H. Hirao, T. Kanazawa, K. Tanabe, T. Kosaka, T. W. Hart, A. Hallett, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4642–4646.
[253] S. S. Stokes, M. Gowravaram, H. Huynh, M. Lu, G. B. Mullen, B. Chen, R. Albert, T. J. O'Shea, M. T. Rooney, H. Hu, J. V. Newman, S. D. Mills, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 85–89.
[254] B. T. Xin, E. M. Huber, G. De Bruin, W. Heinemeyer, E. Maurits, C. Espinal, Y. Du, M. Janssens, E. S. Weyburne, A. F. Kisselev, B. I. Florea, C. Driessen, G. A. Van Der Marel, M. Groll, H. S. Overkleeft, *J. Med. Chem.* **2019**, *62*, 1626–1642.
[255] Q. Zhang, X. Li, W. Zhang, S. Ni, Y. Wang, Y. Pan, *Angew. Chem. Int. Ed.* **2020**, *59*, 21875–21879.
[256] C. Li, J. Wang, L. M. Barton, S. Yu, M. Tian, D. S. Peters, M. Kumar, A. W. Yu, K. A. Johnson, A. K. Chatterjee, M. Yan, P. S. Baran, *Science* **2017**, *356*, eaam7355.
[257] J. J. Dai, X. X. Teng, W. Fang, J. Xu, H. J. Xu, *Chinese Chem. Lett.* **2022**, *33*, 1555–1558.
[258] D. Wei, T. M. Liu, B. Zhou, B. Han, *Org. Lett.* **2020**, *22*, 234–238.
[259] J. Wang, M. Shang, H. Lundberg, K. S. Feu, S. J. Hecker, T. Qin, D. G. Blackmond, P. S. Baran, *ACS Catal.* **2018**, *8*, 9537–9542.
[260] D. Hu, L. Wang, P. Li, *Org. Lett.* **2017**, *19*, 2770–2773.
[261] A. Fawcett, J. Pradeilles, Y. Wang, T. Mutsuga, E. L. Myers, V. K. Aggarwal, *Science* **2017**, *357*, 283–286.
[262] S. Hara, S. Q. Chen, T. Hoshio, T. Fukuhara, N. Yoneda, *Tetrahedron Lett.* **1996**, *37*, 8511–8514.
[263] Y. Kageshima, C. Suzuki, K. Oshiro, H. Amii, *Synlett* **2015**, *26*, 63–66.
[264] P. P. Lin, L. L. Huang, S. X. Feng, S. Yang, H. Wang, Z. S. Huang, Q. Li, *Org. Lett.* **2021**, *23*, 3088–3093.
[265] J. Cantacuzène, J. Leroy, *Tetrahedron Lett.* **1970**, *11*, 3277–3280.
[266] T. B. Patrick, J. J. Scheibel, G. L. Cantrell, *J. Org. Chem.* **1981**, *46*, 3917–3918.
[267] R. E. Lack, C. Canter, J. D. Roberts, *J. Am. Chem. Soc.* **1968**, *90*, 7001–7007.
[268] S. L. Manatt, Ph.D. Thesis, California Institute of Technology, **1959**.
[269] J. B. Lambert, J. D. Roberts, *J. Am. Chem. Soc.* **1965**, *87*, 3884–3890.
[270] W. R. Dolbier, D. M. Al-feki, *J. Org. Chem.* **1987**, *52*, 1872–1874.
[271] S. Ni, A. F. Garrido-Castro, R. R. Merchant, J. N. de Gruyter, D. C. Schmitt, J. J. Mousseau, G. M. Gallego, S. Yang, M. R. Collins, J. X. Qiao, K. S. Yeung, D. R. Langley, M. A. Poss, P. M. Scola, T. Qin, P. S. Baran, *Angew. Chem. Int. Ed.* **2018**, *57*, 14560–14565.
[272] A. Shatskiy, A. Axelsson, E. V. Stepanova, J. Q. Liu, A. Z. Temerdashev, B. P. Kore, B. Blomkvist, J. M. Gardner, P. Dinér, M. D. Karkas, *Chem. Sci.* **2021**, *12*, 5430–5437.
[273] W. Qian, C. Yang, Z. Li, J. Li, J. Li, S. Chen, Eur. Pat. Appl. EP3572413A1, **2018**.
[274] T. Bykova, N. Al-Maharik, A. M. Z. Slawin, M. Bühl, T. Lebl, D. O'Hagan, *Chem. Eur. J.* **2018**, *24*, 13290–13296.
[275] B. W. Anh, F. Takeshita, K. C. Oh, U.S. Pat. 20160326434, **2016**.
[276] L. G. Anello, A. K. Price, R. F. Sweeney, *J. Org. Chem.* **1968**, *33*, 2692–2696.
[277] P. L. Coe, J. H. Sleigh, J. C. Tatlow, *J. Fluor. Chem.* **1980**, *15*, 339–343.
[278] J. Schaab, M. Schwab, D. Kratzert, J. Schwabedissen, H. G. Stammler, N. W. Mitzel, I. Krossing, *Chem. Commun.* **2018**, *54*, 9294–9297.
[279] P. Duhamel, B. Leblond, J. M. Poirier, *J. Chem. Soc. Chem. Commun.* **1993**, 476–477.
[280] P. Duhamel, B. Leblond, L. Bidois-Séry, J. M. Poirier, *J. Chem. Soc. Perkin Trans. 1* **1994**, 2265–2271.
[281] R. D. Simpson, W. Zhao, *Tetrahedron: Asymmetry* **2009**, *20*, 1515–1520.
[282] H. Tsuchiya, M. Iwamoto, H. Miyamoto, C. Sakumoto, T. Tamamizu, Y. Inoshita, Y. Koyama, Y. Sato, T. Kumamoto, *Org. Process Res. Dev.* **2020**, *24*, 1294–1303.
[283] A. J. Durie, T. Fujiwara, R. Cormanich, M. Bühl, A. M. Z. Slawin, D. O'Hagan, *Chem. Eur. J.* **2014**, *20*, 6259–6263.
[284] A. J. Durie, T. Fujiwara, N. Al-Maharik, A. M. Z. Slawin, D. O'Hagan, *J. Org. Chem.* **2014**, *79*, 8228–8233.
[285] N. Al-Maharik, P. Kirsch, A. M. Z. Slawin, D. B. Cordes, D. O'Hagan, *Org. Biomol. Chem.* **2016**, *14*, 9974–9980.
[286] M. S. Ayoup, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan, *Org. Biomol. Chem.* **2015**, *13*, 5621–5624.
[287] T. Bykova, N. Al-Maharik, A. M. Z. Slawin, D. O'Hagan, *Beilstein J. Org. Chem.* **2017**, *13*, 728–733.
[288] N. S. Keddie, A. M. Z. Slawin, T. Lebl, D. Philp, D. O'Hagan, *Nat. Chem.* **2015**, *7*, 483–488.
[289] A. J. Durie, A. M. Z. Slawin, T. Lebl, D. O'Hagan, *Angew. Chem. Int. Ed.* **2012**, *51*, 10086–10088.
[290] A. J. Durie, A. M. Z. Slawin, T. Lebl, P. Kirsch, D. O'Hagan, *Chem. Commun.* **2011**, *47*, 8265–8267.
[291] M. Zupan, B. Sket, *J. Org. Chem.* **1978**, *43*, 696–700.
[292] M. A. Tius, J. K. Kawakami, *Tetrahedron* **1995**, *51*, 3997–4010.
[293] S. Hara, J. Nakahigashi, K. Ishi-i, M. Sawaguchi, H. Sakai, T. Fukuhara, N. Yoneda, *Synlett* **1998**, 495–496.
[294] S. M. Banik, J. W. Medley, E. N. Jacobsen, *J. Am. Chem. Soc.* **2016**, *138*, 5000–5003.
[295] Q. Zhu, D. Ji, T. Liang, X. Wang, Y. Xu, *Org. Lett.* **2015**, *17*, 3798–3801.
[296] E. A. Kauck, A. R. Diesslin, *Ind. Eng. Chem.* **1951**, *43*, 2332–2334.
[297] A. R. Diesslin, E. A. Kauck, J. H. Simons, U.S. Pat. 2567011, **1951**.
[298] T. Abe, M. Tamura, A. Sekiya, *J. Fluor. Chem.* **2005**, *126*, 325–332.
[299] G. S. Phull, R. G. Plevey, R. W. Rendell, J. C. Tatlow, *J. Chem. Soc. Perkin Trans. 1* **1980**, 1507–1511.
[300] T. J. Brice, J. H. Simons, *J. Am. Chem. Soc.* **1951**, *73*, 4016–4017.
[301] R. A. Mitsch, *J. Heterocycl. Chem.* **1964**, *1*, 271–274.
[302] P. B. Sargeant, *J. Org. Chem.* **1970**, *35*, 678–682.
[303] D. C. England, L. Solomon, C. G. Krespan, *J. Fluor. Chem.* **1973**, *3*, 63–89.
[304] Z. Y. Yang, *J. Org. Chem.* **2003**, *68*, 4410–4416.
[305] B. E. Smart, P. J. Krusic, D. C. Roe, Z. Y. Yang, *J. Fluor. Chem.* **2002**, *117*, 199–205.
[306] C. C. Lee, S. T. Lin, S. Y. Ke, *Tetrahedron* **2007**, *63*, 120–125.
[307] C. J. Thomson, Q. Zhang, N. Al-Maharik, M. Bühl, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan, *Chem. Commun.* **2018**, *54*, 8415–8418.
[308] Z. Fang, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan, *Chem. Commun.* **2019**, *55*, 10539–10542.
[309] B. E. Smart, *J. Am. Chem. Soc.* **1974**, *96*, 927–928.
[310] W. R. Dolbier, S. F. Sellers, B. H. Al-Sader, B. E. Smart, *J. Am. Chem. Soc.* **1980**, *102*, 5398–5399.
[311] D. D. Coffman, P. L. Barrick, R. D. Cramer, M. S. Raasch, *J. Am. Chem. Soc.* **1949**, *71*, 490–496.

[312] J. D. Park, H. V. Holler, J. R. Lacher, *J. Org. Chem.* **1960**, *25*, 990–993.

[313] D. R. Baer, *J. Org. Chem.* **1958**, *23*, 1560–1561.

[314] G. Buhr, *Chem. Ber.* **1973**, *106*, 3544–3558.

[315] A. V. Kuchin, O. G. Homutov, V. I. Filyakova, K. I. Paschkevich, *J. Fluor. Chem.* **1991**, *54*, 219.

[316] Y. A. Kotikyan, B. L. Dyatkin, Y. S. Konstantinov, *Bull. Acad. Sci. USSR* **1971**, *20*, 292–295.

[317] R. E. Putnam, J. L. Anderson, W. H. Sharkey, *J. Am. Chem. Soc.* **1961**, *83*, 386–389.

[318] D. C. England, *J. Am. Chem. Soc.* **1961**, *83*, 2205–2206.

[319] A. F. Baxter, J. Schaab, K. O. Christe, R. Haiges, *Angew. Chem. Int. Ed.* **2018**, *57*, 8174–8177.

[320] M. Cavero-Tomas, M. Gowravaram, H. Huynh, H. Ni, S. Stokes, PCT Int. Pat. WO2006040558, **2006**.

[321] J. L. Clark, R. M. Neyyappadath, C. Yu, A. M. Z. Slawin, D. B. Cordes, D. O'Hagan, *Chem. Eur. J.* **2021**, *27*, 16000–16005.

[322] R. D. Chambers, W. K. R. Musgrave, J. Savory, *J. Chem. Soc.* **1961**, 3779–3786.

[323] H. Muramatsu, S. Mokiguchi, K. Inukai, *J. Org. Chem.* **1966**, *31*, 1306–1309.

[324] R. D. Chambers, N. Kelly, J. W. Emsley, W. G. M. Jones, *J. Fluor. Chem.* **1979**, *13*, 49–62.

[325] R. D. Chambers, B. Grievson, N. M. Kelly, *J. Chem. Soc. Perkin Trans. 1* **1985**, 2209–2213.

[326] X. Wu, E. Boz, A. M. Sirkis, A. Y. Chang, T. J. Williams, *J. Fluor. Chem.* **2012**, *135*, 292–302.

[327] J. D. Park, C. D. Bertino, B. T. Nakata, *J. Org. Chem.* **1969**, *34*, 1490–1492.

[328] T. Mill, J. O. Rodin, R. M. Silverstein, C. Woolf, *J. Org. Chem.* **1963**, *28*, 836–839.

[329] R. T. Jacobs, P. R. Bernstein, L. A. Cronk, E. P. Vacek, L. F. Newcomb, D. Aharony, C. K. Buckner, E. J. Kusner, *J. Med. Chem.* **1994**, *37*, 1282–1297.

[330] P. L. Coe, A. W. Mott, J. C. Tatlow, *J. Fluor. Chem.* **1990**, *49*, 21–31.

[331] M. Morgenthaler, E. Schweizer, A. Hoffmann-Röder, F. Benini, R. E. Martin, G. Jaeschke, B. Wagner, H. Fischer, S. Bendels, D. Zimmerli, J. Schneider, F. Diederich, M. Kansy, K. Müller, *ChemMedChem* **2007**, *2*, 1100–1115.

[332] R. Vorberg, N. Trapp, D. Zimmerli, B. Wagner, H. Fischer, N. A. Kratochwil, M. Kansy, E. M. Carreira, K. Müller, *ChemMedChem* **2016**, *11*, 2216–2239.

[333] B. E. Smart, *J. Fluor. Chem.* **2001**, *109*, 3–11.

[334] Q. A. Huchet, B. Kuhn, B. Wagner, H. Fischer, M. Kansy, D. Zimmerli, E. M. Carreira, K. Müller, *J. Fluor. Chem.* **2013**, *152*, 119–128.

[335] K. Müller, *Chim. Int. J. Chem.* **2014**, *68*, 356–362.

[336] Q. A. Huchet, N. Trapp, B. Kuhn, B. Wagner, H. Fischer, N. A. Kratochwil, E. M. Carreira, K. Müller, *J. Fluor. Chem.* **2017**, *198*, 34–46.

[337] D. O'Hagan, Y. Wang, M. Skibinski, A. M. Z. Slawin, *Pure Appl. Chem.* **2012**, *84*, 1587–1595.

[338] Q. A. Huchet, B. Kuhn, B. Wagner, N. A. Kratochwil, H. Fischer, M. Kansy, D. Zimmerli, E. M. Carreira, K. Müller, *J. Med. Chem.* **2015**, *58*, 9041–9060.

[339] N. Erdeljac, G. Kehr, M. Ahlqvist, L. Knerr, R. Gilmour, *Chem. Commun.* **2018**, *54*, 12002–12005.

[340] P. Bentler, N. Erdeljac, K. Bussmann, M. Ahlqvist, L. Knerr, K. Bergander, C. G. Daniliuc, R. Gilmour, *Org. Lett.* **2019**, *21*, 7741–7745.

[341] R. J. Abraham, P. Leonard, C. F. Tormena, *Magn. Reson. Chem.* **2011**, *49*, 23–29.

[342] C. A. Stortz, A. M. Sarotti, *RSC Adv.* **2019**, *9*, 24134–24145.

[343] A. J. Weldon, T. L. Vickrey, G. S. Tschumper, *J. Phys. Chem. A* **2005**, *109*, 11073–11079.

[344] F. Yoshinaga, C. F. Tormena, M. P. Freitas, R. Rittner, R. J. Abraham, *J. Chem. Soc. Perkin Trans. 2* **2002**, 1494–1498.

[345] R. J. Abraham, T. A. D. Smith, W. A. Thomas, *J. Chem. Soc. Perkin Trans. 2* **1996**, *9*, 1949–1955.

[346] E. A. Basso, L. A. Abiko, G. F. Gauze, R. M. Pontes, *J. Org. Chem.* **2011**, *76*, 145–153.

[347] C. B. Francisco, C. S. Fernandes, U. Z. de Melo, R. Rittner, G. F. Gauze, E. A. Basso, *Beilstein J. Org. Chem.* **2019**, *15*, 818–829.

[348] E. Juaristi, R. Notario, *J. Org. Chem.* **2016**, *81*, 1192–1197.

[349] A. J. Durie, A. M. Z. Slawin, T. Lebl, P. Kirsch, D. O'hagan, *Chem. Commun.* **2012**, *48*, 9643–9645.

[350] J. L. Clark, A. Taylor, A. Geddis, R. M. Neyyappadath, B. A. Piscelli, C. Yu, D. B. Cordes, A. M. Z. Slawin, R. A. Cormanich, S. Guldin, D. O'Hagan, *Chem. Sci.* **2021**, *12*, 9712–9719.

[351] B. A. Piscelli, W. Sanders, C. Yu, N. Al Maharik, T. Lebl, R. A. Cormanich, D. O'Hagan, *Chem. Eur. J.* **2020**, *26*, 11989–11994.

[352] S. Holovach, K. P. Melnykov, A. Skreminskiy, M. Herasymchuk, O. Tavtul, D. Aloshyn, P. Borysko, A. B. Rozhenko, S. V. Ryabukhin, D. M. Volochnyuk, O. O. Grygorenko, *Chem. Eur. J.* **2022**, *28*, e202200331.

[353] B. Jeffries, Z. Wang, R. I. Troup, A. Goupille, J. Y. Le Questel, C. Fallan, J. S. Scott, E. Chiarparin, J. Graton, B. Linclau, *Beilstein J. Org. Chem.* **2020**, *16*, 2141–2150.

[354] A. Rodil, S. Bosisio, M. S. Ayoup, L. Quinn, D. B. Cordes, A. M. Z. Slawin, C. D. Murphy, J. Michel, D. O'Hagan, *Chem. Sci.* **2018**, *9*, 3023–3028.

[355] Z. Fang, N. Al-Maharik, A. M. Z. Slawin, M. Bühl, D. O'Hagan, *Chem. Commun.* **2016**, *52*, 5116–5119.

[356] D. O'Hagan, *Chem. Eur. J.* **2020**, *26*, 7981–7997.

[357] P. Zhou, J. Zou, F. Tian, Z. Shang, *J. Chem. Inf. Model.* **2009**, *49*, 2344–2355.

[358] P. Metrangolo, J. S. Murray, T. Pilati, P. Politzer, G. Resnati, G. Terraneo, *CrystEngComm* **2011**, *13*, 6593–6596.

[359] J. C. Cole, R. Taylor, *Cryst. Growth Des.* **2022**, *22*, 1352–1364.

[360] R. E. Rosenberg, *J. Phys. Chem. A* **2018**, *122*, 4521–4529.

[361] S. M. Pratik, A. Nijamudheen, A. Datta, *ChemPhysChem* **2016**, *17*, 2373–2381.

[362] J. Popovici-Muller, R. M. Lemieux, E. Artin, J. O. Saunders, F. G. Salituro, J. Travins, G. Cianchetta, Z. Cai, D. Zhou, D. Cui, P. Chen, K. Straley, E. Tobin, F. Wang, M. D. David, V. Penard-Lacronique, C. Quivoron, V. Saada, S. De Botton, S. Gross, L. Dang, H. Yang, L. Utley, Y. Chen, H. Kim, S. Jin, Z. Gu, G. Yao, Z. Luo, X. Lv, C. Fang, L. Yan, A. Olaharski, L. Silverman, S. Biller, S. S. M. Su, K. Yen, *ACS Med. Chem. Lett.* **2018**, *9*, 300–305.

[363] J. Popovici-Muller, J. O. Saunders, F. G. Salituro, J. M. Travins, S. Yan, F. Zhao, S. Gross, L. Dang, K. E. Yen, H. Yang, K. S. Straley, S. Jin, K. Kunii, V. R. Fantin, S. Zhang, Q. Pan, D. Shi, S. A. Biller, S. M. Su, *ACS Med. Chem. Lett.* **2012**, *3*, 850–855.

[364] Q. Zheng, S. Tang, X. Fu, Z. Chen, Y. Ye, X. Lan, L. Jiang, Y. Huang, J. Ding, M. Geng, M. Huang, H. Wan, *Bioorg. Med. Chem. Lett.* **2017**, *27*, 5262–5268.

[365] M. J. Soth, K. Le, M. E. Di Francesco, M. M. Hamilton, G. Liu, J. P. Burke, C. L. Carroll, J. J. Kovacs, J. P. Bardenhagen, C. A. Bristow,

M. Cardozo, B. Czako, E. De Stanchina, N. Feng, J. R. Garvey, J. P. Gay, M. K. G. Do, J. Greer, M. Han, A. Harms, Z. Herrera, S. Huang, V. Giuliani, Y. Jiang, S. B. Johnson, T. A. Johnson, Z. Kang, P. G. Leonard, Z. Liu, T. McAfoos, M. Miller, P. Morlacchi, R. A. Mullinax, W. S. Palmer, J. Pang, N. Rogers, C. M. Rudin, H. E. Shepard, N. D. Spencer, J. Theroff, Q. Wu, A. Xu, J. A. Yau, G. Draetta, C. Toniatti, T. P. Heffernan, P. Jones, *J. Med. Chem.* **2020**, *63*, 12957–12977.

[366] R. W. Newcomb, U.S. Pat. 6451828, **2002**.

[367] O. Irie, T. Kosaka, T. Ehara, F. Yokokawa, T. Kanazawa, H. Hirao, A. Iwasaki, J. Sakaki, N. Teno, Y. Hitomi, G. Iwasaki, H. Fukaya, K. Nonomura, K. Tanabe, S. Koizumi, N. Uchiyama, S. J. Bevan, M. Malcangio, C. Gentry, A. J. Fox, M. Yaqoob, A. J. Culshaw, A. Hallett, *J. Med. Chem.* **2008**, *51*, 5502–5505.

[368] G. Papeo, H. Posteri, D. Borghi, A. A. Busel, F. Caprera, E. Casale, M. Ciomei, A. Corti, E. Corti, M. D'Anello, M. Fasolini, B. Forte, A. Galvani, A. Isacchi, A. Khvat, M. Y. Krasavin, R. Lupi, P. Orsini, R. Perego, E. Pesenti, D. Pezzetta, S. Raindldi, F. Riccardi-Sirton, A. Scolaro, F. Sola, F. Zuccotto, E. R. Felder, D. Donati, A. Montagnoli, *J. Med. Chem.* **2015**, *58*, 6875–6898.

[369] R. Wang, Y. Cong, M. Li, J. Bao, Y. Qi, J. Z. H. Zhang, *Front. Mol. Biosci.* **2020**, *7*, 50.

[370] E. Blum, J. Zhang, J. Zaluski, D. E. Einstein, E. E. Korshin, A. Kubas, A. Gruzman, G. P. Tochtrop, P. D. Kiser, K. Palczewski, *J. Med. Chem.* **2021**, *64*, 8287–8302.

[371] A. Wood, D. Armour, in *Progress in Medicinal Chemistry*, Elsevier, **2005**, pp. 239–271.

[372] N. Ray, *Drug Des. Devel. Ther.* **2008**, *2*, 151–161.

[373] W. M. Kazmierski, K. S. Gudmundsson, S. C. Piscitelli, in *Annual Reports in Medicinal Chemistry*, Academic Press, **2007**, pp. 301–320.

[374] Q. Tan, Y. Zhu, J. Li, Z. Chen, G. W. Han, I. Kufareva, T. Li, L. Ma, G. Fenalti, J. Li, W. Zhang, X. Xie, H. Yang, H. Jiang, V. Cherezov, H. Liu, R. C. Stevens, Q. Zhao, B. Wu, *Science* **2013**, *341*, 1387–1390.

[375] R. C. Lemoine, A. C. Petersen, L. Setti, T. Baldinger, J. Wanner, A. Jekle, G. Heilek, A. deRosier, C. Ji, D. M. Rotstein, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1674–1676.

[376] W. Chen, P. Zhan, E. De Clercq, X. Liu, *Curr. Pharm. Des.* **2012**, *18*, 100–112.

[377] C. G. Barber, D. C. Blakemore, J. Y. Chiva, R. L. Eastwood, D. S. Middleton, K. A. Paradowski, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1499–1503.

[378] D. M. Rotstein, C. R. Melville, F. Padilla, D. Cournoyer, E. K. Lee, R. Lemoine, A. C. Petersen, L. Q. Setti, J. Wanner, L. Chen, L. Filonova, D. G. Loughhead, J. Manka, X. F. Lin, S. Gleason, S. Sankuratri, C. Ji, A. deRosier, M. Dioszegi, G. Heilek, A. Jekle, P. Berry, C. I. Mau, P. Weller, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3116–3119.

[379] R. C. Lemoine, A. C. Petersen, L. Setti, J. Wanner, A. Jekle, G. Heilek, A. DeRosier, C. Ji, P. Berry, D. Rotstein, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 704–708.

[380] C. K. Arnatt, B. A. Falls, Y. Yuan, T. J. Raborg, R. R. Masvekar, N. El-Hage, D. E. Selley, A. V. Nicola, P. E. Knapp, K. F. Hauser, Y. Zhang, *Bioorg. Med. Chem.* **2016**, *24*, 5969–5987.

[381] C. Schwehm, B. Kellam, A. E. Garces, S. J. Hill, N. D. Kindon, T. D. Bradshaw, J. Li, S. J. F. Macdonald, J. E. Rowedder, L. A. Stoddart, M. J. Stocks, *J. Med. Chem.* **2017**, *60*, 1534–1554.

[382] P. Peng, H. Chen, Y. Zhu, Z. Wang, J. Li, R. H. Luo, J. Wang, L. Chen, L. M. Yang, H. Jiang, X. Xie, B. Wu, Y. T. Zheng, H. Liu, *J. Med. Chem.* **2018**, *61*, 9621–9636.

[383] M. Packiarajan, C. G. M. Ferreira, S. P. Hong, A. D. White, G. Chandrasena, X. Pu, R. M. Brodbeck, A. J. Robichaud, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6469–6474.

[384] M. Packiarajan, M. Grenon, S. Zorn, A. T. Hopper, A. D. White, G. Chandrasena, X. Pu, R. M. Brodbeck, A. J. Robichaud, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4037–4043.

[385] A. P. Degnan, D. Maxwell, A. Balakrishnan, J. M. Brown, A. Easton, M. Gulianello, U. Hanumegowda, M. Hill-Drzewi, R. Miller, K. S. Santone, A. Senapati, E. E. Shields, D. V. Sivarao, R. Westphal, V. J. Whiterock, X. Zhuo, J. J. Bronson, J. E. Macor, *Bioorg. Med. Chem. Lett.* **2016**, *26*, 5871–5876.

[386] M. E. Layton, M. J. Kelly, T. J. Harlingh, PCT Int. Pat. WO2011109277, **2011**.

[387] S. Célanire, G. Duvey, S. Poli, J. P. Rocher, in *Annual Reports in Medicinal Chemistry*, Academic Press, **2012**, pp. 71–88.

[388] D. W. Engers, C. M. Niswender, C. D. Weaver, S. Jadhav, U. N. Menon, R. Zamorano, P. J. Conn, C. W. Lindsley, C. R. Hopkins, *J. Med. Chem.* **2009**, *52*, 4115–4118.

[389] S. R. Bollinger, D. W. Engers, J. D. Panarese, M. West, J. L. Engers, M. T. Loch, A. L. Rodriguez, A. L. Blobaum, C. K. Jones, A. Thompson Gray, P. J. Conn, C. W. Lindsley, C. M. Niswender, C. R. Hopkins, *J. Med. Chem.* **2019**, *62*, 342–358.

[390] M. Mitsuya, K. Kobayashi, K. Kawakami, A. Satoh, Y. Ogino, T. Kakikawa, N. Ohtake, T. Kimura, H. Hirose, A. Sato, T. Numazawa, T. Hasegawa, K. Noguchi, T. Mase, *J. Med. Chem.* **2000**, *43*, 5017–5029.

[391] Y. Ogino, N. Ohtake, K. Kobayashi, T. Kimura, T. Fujikawa, T. Hasegawa, K. Noguchi, T. Mase, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2167–2172.

[392] S. Gupta, S. Malhotra, S. Sinha, S. K. Singh, R. K. Singh, S. Krishna, P. Chhabra, T. Chaira, J. Kannayiram, P. Sharma, S. Aeron, J. Kaur, N. Kumar, J. Sattigeri, R. K. Shirumalla, J. Paliwal, S. G. Dastidar, I. A. Cliffe, A. Ray, P. Bhalnagar, *Eur. J. Pharmacol.* **2011**, *656*, 219–228.

[393] J. W. Schubert, S. T. Harrison, J. Mulhearn, R. Gomez, R. Tyrebor, K. Jones, J. Bunda, B. Hanney, J. M. C. Wai, C. Cox, J. A. McCauley, J. M. Sanders, B. Magliaro, J. O'Brien, N. Pajkovic, S. L. Huszar Agrapides, A. Taylor, A. Gotter, S. M. Smith, J. Ustaner, S. Browne, S. Risso, M. Egbertson, *ChemMedChem* **2019**, *14*, 943–951.

[394] T. M. Largent-Milnes, T. W. Vanderah, *Expert Opin. Ther. Pat.* **2010**, *20*, 291–305.

[395] K. Kobayashi, M. Uchiyama, H. Ito, H. Takahashi, T. Yoshizumi, H. Sakoh, Y. Nagatomi, M. Asai, H. Miyazoe, T. Tsujita, M. Hirayama, S. Ozaki, T. Tani, Y. Ishii, H. Ohta, O. Okamoto, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3627–3631.

[396] K. Kobayashi, T. Tsujita, H. Ito, S. Ozaki, T. Tani, Y. Ishii, S. Okuda, K. Tadano, T. Fukuroda, H. Ohta, O. Okamoto, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4729–4732.

[397] Y. Sugimoto, K. Kobayashi, M. Asai, A. Ohno, K. Yamada, S. Ozaki, H. Ohta, O. Okamoto, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4611–4616.

[398] Z. Li, W. Chen, J. J. Hale, C. L. Lynch, S. G. Mills, R. Hajdu, C. A. Keohane, M. J. Rosenbach, J. A. Milligan, G. J. Shei, G. Chrebet, S. A. Parent, J. Bergstrom, D. Card, M. Forrest, E. J. Quackenbush, L. A. Wickham, H. Vargas, R. M. Evans, H. Rosen, S. Mandala, *J. Med. Chem.* **2005**, *48*, 6169–6173.

[399] L. Yan, R. Budhu, P. Huo, C. L. Lynch, J. J. Hale, S. G. Mills, R.

Hajdu, C. A. Keohane, M. J. Rosenbach, J. A. Milligan, G. J. Shei, G. Chrebet, J. Bergstrom, D. Card, S. M. Mandala, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3564–3568.

[400] V. J. Colandrea, I. E. Legiec, P. Huo, L. Yan, J. J. Hale, S. G. Mills, J. Bergstrom, D. Card, G. Chebret, R. Hajdu, C. A. Keohane, J. A. Milligan, M. J. Rosenbach, G. J. Shei, S. M. Mandala, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2905–2908.

[401] S. D. Kuduk, C. Ng, D. M. Feng, J. M. C. Wai, R. S. L. Chang, C. M. Harrell, K. L. Murphy, R. W. Ransom, D. Reiss, M. Ivarsson, G. Mason, S. Boyce, C. Tang, T. Prueksaritanont, R. M. Freidinger, D. J. Pettibone, M. G. Bock, *J. Med. Chem.* **2004**, *47*, 6439–6442.

[402] M. R. Wood, K. M. Schimpa, J. J. Kim, B. L. Wan, K. L. Murphy, R. W. Ransom, R. S. L. Chang, C. Tang, T. Prueksaritanont, T. J. Detwiler, L. A. Hettrick, E. R. Landis, Y. M. Leonard, J. A. Krueger, S. D. Lewis, D. J. Pettibone, R. M. Freidinger, M. G. Bock, *J. Med. Chem.* **2006**, *49*, 1231–1234.

[403] M. R. Wood, K. M. Schimpa, J. J. Kim, S. D. Kuduk, R. K. Chang, C. N. Di Marco, R. M. DiPardo, B. L. Wan, K. L. Murphy, R. W. Ransom, R. S. L. Chang, M. A. Holahan, J. J. Cook, W. Lemaire, S. D. Mosser, R. A. Bednar, C. Tang, T. Prueksaritanont, A. A. Wallace, Q. Mei, J. Yu, D. L. Bohn, F. C. Clayton, E. D. Adarayn, G. R. Sitko, Y. M. Leonard, R. M. Freidinger, D. J. Pettibone, M. G. Bock, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 716–720.

[404] K. Schnatbaum, M. Schaudt, R. Stragies, J. R. Pfeifer, C. Gibson, E. Locardi, D. Scharn, U. Richter, H. Kalkhof, K. Dinkel, G. Zischinsky, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1233–1236.

[405] J. Boström, K. Berggren, T. Elebring, P. J. Greasley, M. Wilstermann, *Bioorg. Med. Chem.* **2007**, *15*, 4077–4084.

[406] J. Boström, R. I. Olsson, J. Tholander, P. J. Greasley, E. Ryberg, H. Nordberg, S. Hjorth, L. Cheng, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 479–482.

[407] P. F. Cirillo, D. S. Thomson, D. Reither, A. Berry, L. Wu, E. R. Hickey, PCT Int. Pat. WO2008064054, **2008**.

[408] S. Ahmad, W. N. Washburn, A. S. Hernandez, S. Bisaha, K. Ngu, W. Wang, M. A. Pelleymounter, D. Longhi, N. Flynn, A. V. Azzara, K. Rohrbach, J. Devenny, S. Rooney, M. Thomas, S. Glick, H. Godonis, S. Harvey, H. Zhang, B. Gemzik, E. B. Janovitz, C. Huang, L. Zhang, J. A. Robl, B. J. Murphy, *J. Med. Chem.* **2016**, *59*, 8848–8858.

[409] D. R. Witty, J. H. Bateson, G. J. Hervieu, P. Jeffrey, C. N. Johnson, A. I. Muir, P. J. O'Hanlon, G. Stemp, A. J. Stevens, K. M. Thewlis, S. Wilson, K. Y. Winborn, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4865–4871.

[410] D. L. Hertzog, K. A. Al-Barazanji, E. C. Bigham, M. J. Bishop, C. S. Britt, D. L. Carlton, J. P. Cooper, A. J. Daniels, D. M. Garrido, A. S. Goetz, M. K. Grizzle, Y. C. Guo, A. L. Handlon, D. M. Ignar, R. O. Morgan, A. J. Peat, F. X. Tavares, H. Zhou, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4723–4727.

[411] W. N. Washburn, M. Manfredi, P. Devasthale, G. Zhao, S. Ahmad, A. Hernandez, J. A. Robl, W. Wang, J. Mignone, Z. Wang, K. Ngu, M. A. Pelleymounter, D. Longhi, R. Zhao, B. Wang, N. Huang, N. Flynn, A. V. Azzara, J. C. Barrish, K. Rohrbach, J. J. Devenny, S. Rooney, M. Thomas, S. Glick, H. E. Godonis, S. J. Harvey, M. J. Cullen, H. Zhang, C. Caporuscio, P. Stetsko, M. Grubb, B. D. Maxwell, H. Yang, A. Apedo, B. Gemzik, E. B. Janovitz, C. Huang, L. Zhang, C. Freeden, B. J. Murphy, *J. Med. Chem.* **2014**, *57*, 7509–7522.

[412] A. B. Pinkerton, S. Peddibhotla, F. Yamamoto, L. M. Slosky, Y. Bai, P. Maloney, P. Hershberger, M. P. Hedrick, B. Falter, R. J. Ardecky, L. H. Smith, T. D. Y. Chung, M. R. Jackson, M. G. Caron, L. S. Barak, *J. Med. Chem.* **2019**, *62*, 8357–8363.

[413] S. Peddibhotla, M. P. Hedrick, P. Hershberger, P. R. Maloney, Y. Li, M. Milewski, P. Gosalia, W. Gray, A. Mehta, E. Sugarman, B. Hood, E. Suyama, K. Nguyen, S. Heynen-Genel, S. Vasile, S. Salaniwal, D. Stonich, Y. Su, A. Mangravita-Novo, M. Vicchiarelli, G. P. Roth, L. H. Smith, T. D. Y. Chung, G. R. Hanson, J. B. Thomas, M. G. Caron, L. S. Barak, A. B. Pinkerton, *ACS Med. Chem. Lett.* **2013**, *4*, 846–851.

[414] M. Méndez, H. Matter, E. Defossa, M. Kurz, S. Lebreton, Z. Li, M. Lohmann, M. Löhn, H. Mors, M. Podeschwa, N. Rackelmann, J. Riedel, P. Safar, D. S. Thorpe, M. Schäfer, D. Weitz, K. Breitschopf, *J. Med. Chem.* **2020**, *63*, 2292–2307.

[415] K. J. Moriarty, H. Takahashi, S. S. Pullen, H. H. Khine, R. H. Sallati, E. L. Raymond, J. R. Woska, D. D. Jeanfavre, G. P. Roth, M. P. Winters, L. Qiao, D. Ryan, R. DesJarlais, D. Robinson, M. Wilson, M. Bobko, B. N. Cook, H. Y. Lo, P. A. Nemoto, M. A. Kashem, J. P. Wolak, A. White, R. L. Magolda, B. Tomczuk, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5545–5549.

[416] J. Wityak, K. F. McGee, M. P. Conlon, R. H. Song, B. C. Duffy, B. Clayton, M. Lynch, G. Wang, E. Freeman, J. Haber, D. B. Kitchen, D. D. Manning, J. Ismail, Y. Khmelnitsky, P. Michels, J. Webster, M. Ingoyen, M. Luche, M. Hultman, M. Bai, I. D. Kuck, R. Newell, M. Lamers, P. Leonard, D. Yates, K. Matthews, L. Ongeri, S. Clifton, T. Mead, S. Deupree, P. Wheelan, K. Lyons, C. Wilson, A. Kiselyov, L. Toledo-Sherman, M. Beconi, I. Muñoz-Sanjuan, J. Bard, C. Dominguez, *J. Med. Chem.* **2015**, *58*, 2967–2987.

[417] G. Xu, Y. Zhang, H. Wang, Z. Guo, X. Wang, X. Li, S. Chang, T. Sun, Z. Yu, T. Xu, L. Zhao, Y. Wang, W. Yu, *Eur. J. Med. Chem.* **2020**, *196*, 112354.

[418] J. Liang, A. Van Abbema, M. Balazs, K. Barrett, L. Berezhkovsky, W. Blair, C. Chang, D. Delarosa, J. Devoss, J. Driscoll, C. Eigenbrot, N. Ghilardi, P. Gibbons, J. Halladay, A. Johnson, P. B. Kohli, Y. Lai, Y. Liu, J. Lyssikatos, P. Mantik, K. Menghrajani, J. Murray, I. Peng, A. Sambrone, S. Shia, Y. Shin, J. Smith, S. Sohn, V. Tsui, M. Ultsch, L. C. Wu, Y. Xiao, W. Yang, J. Young, B. Zhang, B. Y. Zhu, S. Magnuson, *J. Med. Chem.* **2013**, *56*, 4521–4536.

[419] J. Liang, V. Tsui, A. Van Abbema, L. Bao, K. Barrett, M. Beresini, L. Berezhkovsky, W. S. Blair, C. Chang, J. Driscoll, C. Eigenbrot, N. Ghilardi, P. Gibbons, J. Halladay, A. Johnson, P. Bir Kohli, Y. Lai, M. Limatta, P. Mantik, K. Menghrajani, J. Murray, A. Sambrone, Y. Xiao, S. Shia, Y. Shin, J. Smith, S. Sohn, M. Stanley, M. Ultsch, B. Zhang, L. C. Wu, S. Magnuson, *Eur. J. Med. Chem.* **2013**, *67*, 175–187.

[420] C. Liu, J. Lin, R. Moslin, J. S. Tokarski, J. Muckelbauer, C. Y. Chang, J. Tredup, D. Xie, H. Park, P. Li, D. R. Wu, J. Strnad, A. Zupa-Fernandez, L. Cheng, C. Chaudhry, J. Chen, C. Chen, H. Sun, P. Elzinga, C. D'Arienzo, K. Gillooly, T. L. Taylor, K. W. McIntyre, L. Salter-Cid, L. J. Lombardo, P. H. Carter, N. Aranibar, J. R. Burke, D. S. Weinstein, *ACS Med. Chem. Lett.* **2019**, *10*, 383–388.

[421] R. Moslin, D. Gardner, J. Santella, Y. Zhang, J. V. Duncia, C. Liu, J. Lin, J. S. Tokarski, J. Strnad, D. Pedicord, J. Chen, Y. Blat, A. Zupa-Fernandez, L. Cheng, H. Sun, C. Chaudhry, C. Huang, C. D'Arienzo, J. S. Sack, J. K. Muckelbauer, C. Chang, J. Tredup, D. Xie, N. Aranibar, J. R. Burke, P. H. Carter, D. S. Weinstein, *Medchemcomm* **2017**, *8*, 700–712.

[422] J. J. Crawford, W. Lee, A. R. Johnson, K. J. Delatorre, J. Chen, C. Eigenbrot, J. Heidmann, S. Kakiuchi-Kiyota, A. Katewa, J. R. Kiefer, L. Liu, J. W. Lubach, D. Misner, H. Purkey, K. Reif, J. Vogt, H. Wong, C. Yu, W. B. Young, *ACS Med. Chem. Lett.* **2020**, *11*, 1588–1597.

[423] S. H. Kwon, S. Kim, A. Y. Park, S. Lee, C. G. Gadhe, B. A. Seo, J. S. Park, S. Jo, Y. Oh, S. H. Kweon, S. X. Ma, W. R. Kim, M. Kim, H. Kim, J. E. Kim, S. Lee, J. Lee, H. S. Ko, *J. Med. Chem.* **2021**, *64*, 15091–15110.

[424] T. Chen, V. Sorna, S. Choi, L. Call, J. Bearss, K. Carpenter, S. L. Warner, S. Sharma, D. J. Bearss, H. Vankayalapati, *Bioorg. Med. Chem. Lett.* **2017**, *27*, 5473–5480.

[425] A. Fensome, C. M. Ambler, E. Arnold, M. E. Banker, M. F. Brown, J. Chrencik, J. D. Clark, M. E. Dowty, I. V. Efremov, A. Flick, B. S. Gerstenberger, A. Gopalsamy, M. M. Hayward, M. Hegen, B. D. Hollingshead, J. Jussif, J. D. Knafels, D. C. Limburg, D. Lin, T. H. Lin, B. S. Pierce, E. Salah, R. Sharma, P. T. Symanowicz, J. B. Telliez, J. I. Trujillo, F. F. Vajdos, F. Vincent, Z. K. Wan, L. Xing, X. Yang, X. Yang, L. Zhang, *J. Med. Chem.* **2018**, *61*, 8597–8612.

[426] H. Sakai, H. Inoue, K. Murata, T. Toba, Y. Shimmyo, N. Nara, S. ya Ueno, Y. Igawa, N. Takemoto, *Bioorg. Med. Chem.* **2020**, *28*, 115562.

[427] M. H. Keylor, A. Gulati, S. D. Kattar, R. E. Johnson, R. W. Chau, K. A. Margrey, M. J. Ardolino, C. Zarate, K. E. Poremba, V. Simov, G. J. Morriello, J. J. Acton, B. Pio, X. Yan, R. L. Palte, S. E. McMinn, L. Nogle, C. A. Lesburg, D. Adpressa, S. Lin, S. Neelamkavil, P. Liu, J. Su, L. G. Hegde, J. D. Woodhouse, R. Faltus, T. Xiong, P. J. Ciaccio, J. Piesvaux, K. M. Otte, H. B. Wood, M. E. Kennedy, D. J. Bennett, E. F. Dimauro, M. J. Fell, P. H. Fuller, *J. Med. Chem.* **2022**, *65*, 838–856.

[428] J. P. Strachan, D. C. Kombo, A. Mazurov, R. Heemstra, B. S. Bhatti, R. Akireddy, S. Murthy, L. Miao, J. E. Jett, J. Speake, M. Bencherif, *Eur. J. Med. Chem.* **2014**, *86*, 60–74.

[429] Y. Xiao, S. Karra, A. Goutopoulos, N. T. Morse, S. Zhang, M. Dhanabal, H. Tian, J. Seenisamy, J. Jayadevan, R. Caldwell, J. Potnick, M. Bleich, E. Chekler, B. Sherer, V. Sriraman, *Bioorg. Med. Chem. Lett.* **2019**, *29*, 1660–1664.

[430] M. M. Miller, Y. Liu, J. Jiang, J. A. Johnson, M. Kamau, D. S. Nirschl, Y. Wang, L. Harikrishnan, D. S. Taylor, A. Y. A. Chen, X. Yin, R. Seethala, T. L. Peterson, T. Zvyaga, J. Zhang, C. S. Huang, R. R. Wexler, M. A. Poss, R. Michael Lawrence, L. P. Adam, M. E. Salvati, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6503–6508.

[431] B. A. Patel, B. Abel, A. M. Barbuti, U. K. Velagapudi, Z. S. Chen, S. V. Ambudkar, T. T. Talele, *J. Med. Chem.* **2018**, *61*, 834–864.

[432] E. H. Demont, C. W. Chung, R. C. Furze, P. Grandi, A. M. Michon, C. Wellaway, N. Barrett, A. M. Bridges, P. D. Craggs, H. Diallo, D. P. Dixon, C. Douault, A. J. Emmons, E. J. Jones, B. V. Karamshi, K. Locke, D. J. Mitchell, B. H. Mouzon, R. K. Prinjha, A. D. Roberts, R. J. Sheppard, R. J. Watson, P. Bamborough, *J. Med. Chem.* **2015**, *58*, 5649–5673.

[433] P. Bamborough, C. W. Chung, R. C. Furze, P. Grandi, A. M. Michon, R. J. Sheppard, H. Barnett, H. Diallo, D. P. Dixon, C. Douault, E. J. Jones, B. Karamshi, D. J. Mitchell, R. K. Prinjha, C. Rau, R. J. Watson, T. Werner, E. H. Demont, *J. Med. Chem.* **2015**, *58*, 6151–6178.

[434] P. Bamborough, C. wa Chung, E. H. Demont, R. C. Furze, A. J. Bannister, K. H. Che, H. Diallo, C. Douault, P. Grandi, T. Kouzarides, A. M. Michon, D. J. Mitchell, R. K. Prinjha, C. Rau, S. Robson, R. J. Sheppard, R. Upton, R. J. Watson, *Angew. Chem. Int. Ed.* **2016**, *55*, 11382–11386.

[435] P. Bamborough, C. W. Chung, R. C. Furze, P. Grandi, A. M. Michon, R. J. Watson, D. J. Mitchell, H. Barnett, R. K. Prinjha, C. Rau, R. J. Sheppard, T. Werner, E. H. Demont, *J. Med. Chem.* **2018**, *61*, 8321–8336.

[436] A. Dolbois, L. Batiste, L. Wiedmer, J. Dong, M. Brütsch, D. Huang, N. M. Deerain, D. Spiliotopoulos, I. Cheng-Sánchez, E. Laul, C. Nevado, P. Śledź, A. Caflisch, *ACS Med. Chem. Lett.* **2020**, *11*, 1573–1580.

[437] K. Hashimoto, B. Saito, N. Miyamoto, Y. Oguro, D. Tomita, Z. Shiokawa, M. Asano, H. Kakei, N. Taya, M. Kawasaki, H. Sumi, M. Yabuki, K. Iwai, S. Yoshida, M. Yoshimatsu, K. Aoyama, Y. Kosugi, T. Kojima, N. Morishita, D. R. Dougan, G. P. Snell, S. Imamura, T. Ishikawa, *J. Med. Chem.* **2013**, *56*, 1228–1246.

[438] Z. Shiokawa, K. Hashimoto, B. Saito, Y. Oguro, H. Sumi, M. Yabuki, M. Yoshimatsu, Y. Kosugi, Y. Debori, N. Morishita, D. R. Dougan, G. P. Snell, S. Yoshida, T. Ishikawa, *Bioorg. Med. Chem.* **2013**, *21*, 7938–7954.

[439] J. K. Holden, J. J. Crawford, C. L. Noland, S. Schmidt, J. R. Zbieg, J. A. Lacap, R. Zang, G. M. Miller, Y. Zhang, P. Beroza, R. Reja, W. Lee, J. Y. K. Tom, R. Fong, M. Steffek, S. Clausen, T. J. Hagenbeek, T. Hu, Z. Zhou, H. C. Shen, C. N. Cunningham, *Cell Rep.* **2020**, *31*, 107809.

[440] M. Békés, D. R. Langley, C. M. Crews, *Nat. Rev. Drug Discov.* **2022**, *21*, 181–200.

[441] P. Soares, M. S. Gadd, J. Frost, C. Galdeano, L. Ellis, O. Epemolu, S. Rocha, K. D. Read, A. Ciulli, *J. Med. Chem.* **2018**, *61*, 599–618.

[442] M. Girardini, C. Maniaci, S. J. Hughes, A. Testa, A. Ciulli, *Bioorg. Med. Chem.* **2019**, *27*, 2466–2479.

[443] X. Han, C. Wang, C. Qin, W. Xiang, E. Fernandez-Salas, C. Y. Yang, M. Wang, L. Zhao, T. Xu, K. Chinnaswamy, J. Delproposto, J. Stuckey, S. Wang, *J. Med. Chem.* **2019**, *62*, 941–964.

[444] L. Chen, L. Han, S. Mao, P. Xu, X. Xu, R. Zhao, Z. Wu, K. Zhong, G. Yu, X. Wang, *Eur. J. Med. Chem.* **2021**, *216*, 113307.

[445] V. Zoppi, S. J. Hughes, C. Maniaci, A. Testa, T. Gmaschitz, C. Wieshofer, M. Koegl, K. M. Riching, D. L. Daniels, A. Spallarossa, A. Ciulli, *J. Med. Chem.* **2019**, *62*, 699–726.

[446] J. S. Disch, J. M. Duffy, E. C. Y. Lee, D. Gikunju, B. Chan, B. Levin, M. I. Monteiro, S. A. Talcott, A. C. Lau, F. Zhou, A. Kozhushnyan, N. E. Westlund, P. B. Mullins, Y. Yu, M. Von Rechenberg, J. Zhang, Y. A. Arnautova, Y. Liu, Y. Zhang, A. J. McRiner, A. D. Keefe, A. Kohlmann, M. A. Clark, J. W. Cuozzo, C. Huguet, S. Arora, *J. Med. Chem.* **2021**, *64*, 5049–5066.

[447] A. Bricelj, C. Steinebach, R. Kuchta, M. Gütschow, I. Sosič, *Front. Chem.* **2021**, *9*, 463.

[448] K. J. Aldred, R. J. Kerns, N. Osheroff, *Biochemistry* **2014**, *53*, 1565–1574.

[449] S. Atarashi, M. Imamura, Y. Kimura, A. Yoshida, I. Hayakawa, *J. Med. Chem.* **1993**, *36*, 3444–3448.

[450] Y. Kimura, S. Atarashi, K. Kawakami, K. Sato, I. Hayakawa, *J. Med. Chem.* **1994**, *37*, 3344–3352.

[451] S. Hegde, M. Schmidt, in *Annual Reports in Medicinal Chemistry* (Ed.: J.E. Macor), Elsevier/AP, **2009**, p. 712.

[452] S. J. Teague, *Drug Discov. Today* **2011**, *16*, 398–411.

[453] T. Odagiri, H. Inagaki, M. Nagamochi, T. Kitamura, S. Komoriya, H. Takahashi, *J. Med. Chem.* **2018**, *61*, 7234–7244.

[454] S. Komoriya, T. Odagiri, H. Inagaki, M. Nagamochi, R. Miyauchi, K. I. Yoshida, T. Kitamura, H. Takahashi, *Chem. Pharm. Bull.* **2019**, *67*, 47–58.

[455] D. Murugesan, P. C. Ray, T. Bayliss, G. A. Prosser, J. R. Harrison, K. Green, C. Soares De Melo, T. S. Feng, L. J. Street, K. Chibale, D. F. Warner, V. Mizrahi, O. Epemolu, P. Scullion, L. Ellis, J. Riley, Y. Shishikura, L. Ferguson, M. Osuna-Cabello, K. D. Read, S. R. Green, D. A. Lamprecht, A. J. C. Steyn, T. R. Ioerger, J. Sacchettini,

K. Y. Rhee, K. Arora, C. E. Barry, P. G. Wyatt, H. I. M. Boshoff, *ACS Infect. Dis.* **2018**, *4*, 954–969.

[456] M. B. Harbut, B. Yang, R. Liu, T. Yano, C. Vilchèze, B. Cheng, J. Lockner, H. Guo, C. Yu, S. G. Franzblau, H. M. Petrassi, W. R. Jacobs, H. Rubin, A. K. Chatterjee, F. Wang, *Angew. Chem. Int. Ed.* **2018**, *57*, 3478–3482.

[457] A. T. Nchinda, C. Le Manach, T. Paquet, D. González Cabrera, K. J. Wicht, C. Brunschwig, M. Njoroge, E. Abay, D. Taylor, N. Lawrence, S. Wittlin, M. B. Jiménez-Díaz, M. Santos Martínez, S. Ferrer, I. Angulo-Barturen, M. J. Lafuente-Monasterio, J. Duffy, J. Burrows, L. J. Street, K. Chibale, *J. Med. Chem.* **2018**, *61*, 4213–4227.

[458] P. C. Ting, R. Kuang, H. Wu, R. G. Aslanian, J. Cao, D. W. Kim, J. F. Lee, J. Schwerdt, G. Zhou, S. Wainhaus, T. A. Black, A. Cacciapuoti, P. M. McNicholas, Y. Xu, S. S. Walker, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1819–1822.

[459] S. S. Walker, Y. Xu, I. Triantafyllou, M. F. Waldman, C. Mendrick, N. Brown, P. Mann, A. Chau, R. Patel, N. Bauman, C. Norris, B. Antonacci, M. Gumani, A. Cacciapuoti, P. M. McNicholas, S. Wainhaus, R. J. Herr, R. Kuang, R. G. Aslanian, P. C. Ting, T. A. Black, *Antimicrob. Agents Chemother.* **2011**, *55*, 5099–5106.

[460] M. Côté, J. Misasi, T. Ren, A. Bruchez, K. Lee, C. M. Filone, L. Hensley, Q. Li, D. Ory, K. Chandran, J. Cunningham, *Nature* **2011**, *477*, 344–348.

[461] H. Liu, Y. Tian, K. Lee, P. Krishnan, M. K. M. Wang, S. Whelan, E. Mevers, V. Soloveva, B. Dedic, X. Liu, J. M. Cunningham, *J. Med. Chem.* **2018**, *61*, 6293–6307.

[462] Y. Kim, S. Lovell, K.-C. Tiew, S. R. Mandadapu, K. R. Alliston, K. P. Battaile, W. C. Groutas, K.-O. Chang, *J. Virol.* **2012**, *86*, 11754–11762.

[463] A. D. Rathnayake, J. Zheng, Y. Kim, K. D. Perera, S. Mackin, D. K. Meyerholz, M. M. Kashipathy, K. P. Battaile, S. Lovell, S. Perlman, W. C. Groutas, K. O. Chang, *Sci. Transl. Med.* **2020**, *12*, 5332.

[464] C. S. Dampalla, A. D. Rathnayake, K. D. Perera, A. R. M. Jesri, H. N. Nguyen, M. J. Miller, H. A. Thurman, J. Zheng, M. M. Kashipathy, K. P. Battaile, S. Lovell, S. Perlman, Y. Kim, W. C. Groutas, K. O. Chang, *J. Med. Chem.* **2021**, *64*, 17846–17865.

[465] M. M. Alauddin, *Am. J. Nucl. Med. Mol. Imaging* **2012**, *2*, 55.

[466] J. McConathy, R. J. Voll, W. Yu, R. J. Crowe, M. M. Goodman, *Appl. Radiat. Isot.* **2003**, *58*, 657–666.

[467] V. Bernard-Gauthier, J. J. Bailey, A. Aliaga, A. Kostikov, P. Rosa-Neto, M. Wuest, G. M. Brodeur, B. J. Bedell, F. Wuest, R. Schirrmacher, *Medchemcomm* **2015**, *6*, 2184–2193.

[468] S. K. Chitneni, H. Yan, M. R. Zalutsky, *ACS Med. Chem. Lett.* **2018**, *9*, 606–611.

[469] T. Wang, Q. Lin, Y. Zhang, Z. Xu, D. Shi, Y. Cheng, Z. Fu, H. Tan, D. Cheng, H. Shi, *Bioorg. Med. Chem.* **2022**, *53*, 116525.

[470] T. M. Shoup, J. Olson, J. M. Hoffman, J. Votaw, D. Eshima, L. Eshima, V. M. Camp, M. Stabin, D. Votaw, M. M. Goodman, *J. Nucl. Med.* **1999**, *40*, 331–338.

[471] M. Gusman, J. A. Aminshanfi, J. G. Peacock, S. B. Anderson, M. N. Clemenshaw, K. P. Banks, *Radiographics* **2019**, *39*, 822–841.

[472] R. Santos, O. Ursu, A. Gaulton, A. P. Bento, R. S. Donadi, C. G. Bologa, A. Karlsson, B. Al-Lazikani, A. Hersey, T. I. Oprea, J. P. Overington, *Nat. Rev. Drug Discov.* **2017**, *16*, 34.

[473] B. Zdrazil, L. Richter, N. Brown, R. Guha, *Sci. Rep.* **2020**, *10*, 1–15.

WILEY-VCH



Future Medicinal Chemistry

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ifmc20

Fluorinated building blocks in drug design: new pathways and targets

Oleksandr O Grygorenko & Kostiantyn P Melnykov

To cite this article: Oleksandr O Grygorenko & Kostiantyn P Melnykov (2024) Fluorinated building blocks in drug design: new pathways and targets, Future Medicinal Chemistry, 16:14, 1375-1378, DOI: 10.1080/17568919.2024.2379229

To link to this article: https://doi.org/10.1080/17568919.2024.2379229

View supplementary material

Published online: 29 Jul 2024.

Submit your article to this journal

Article views: 471

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=ifmc20

FUTURE MEDICINAL CHEMISTRY
2024, VOL. 16, NO. 14, 1375–1378
https://doi.org/10.1080/17568919.2024.2379229

Taylor & Francis
Taylor & Francis Group

EDITORIAL

Check for updates

Fluorinated building blocks in drug design: new pathways and targets

Oleksandr O Grygorenko[*,a,b] and Kostiantyn P Melnykov[a,b]

[a]Enamine Ltd. (www.enamine.net), Winston Churchill Street 78, Kyiv, 02094, Ukraine; [b]Taras Shevchenko National University of Kyiv, Volodymyrska Street 60, Kyiv, 01601, Ukraine

ARTICLE HISTORY Received 18 April 2024; Accepted 3 July 2024
KEYWORDS building blocks; drug discovery; fluorine; fluoroalkyl; novel chemotypes; organofluorine compounds

The outstanding role of fluorine in drug discovery has been mentioned too many times previously so its detailed discussion in one more article on the subject is abundant. In the last decade, there were years when up to 50% of US FDA approved drugs were organofluorine compounds [1], and 12 of them were brought to the market in 2023 [2]. While a vast majority of recently approved fluorinated drugs still contain F or CF_3 groups attached to benzene or other aromatic ring, there is a clear trend toward the wider representation of other fluorinated chemotypes, especially at various discovery and development phases. These include fluoro-, *gem*-difluoro-, vicinal and 'skipped' di/polyfluoro-, fluoroalkyl- (especially CF_3- and CHF_2-) substituted aliphatic compounds, in particular, carbo- and heterocycles [3,4]; compounds with fluoroalkoxy (mostly OCF_3), *N*-fluoroalkyl (mostly NCF_3), fluorinated sulfoximine, CF_2Cl/OCF_2Cl, SF_5 groups, etc. (Supplementary Figure S1 in the Supplementary Material) [5].

While introducing these moieties at the late stages is a very important trend in current organic chemistry, the synthetic strategy based on the use of fluorinated building blocks remains the dominating approach in drug discovery [6]. However, there is a significant gap between novel synthetic pathways toward fluorine-containing group introduction and those methods commonly used to obtain new fluorinated building block targets. Apart from the slow adaptation of novel synthetic methodologies in medicinal chemistry in general, several other reasons might be behind that. A good approach to the fluorinated building blocks synthesis must be compatible with chemotypes considered 'attractive' in early drug discovery; (protected) functional groups commonly used in medicinal chemistry (alternatively, such groups can be introduced along with fluorine-containing moiety); multigram scale. In many cases, none or not all of the above criteria are met or at least demonstrated to be met.

There are several relatively new strategies for introducing fluorine-containing groups that can be promising for the synthesis of fluorinated building blocks. One of them relies on direct radical or transition metal-catalyzed C–H fluorination, fluoroalkylation, fluoroalkoxylation, etc. (Supplementary Scheme S1A) [7–9]. Typically, (hetero)aromatic substrates are compatible with the above methods, and they either require the presence of directing groups or can potentially suffer from regioselectivity issues. Another notable limitation of the strategy in its current state is related to compatibility with functional groups required in target building blocks, which is often difficult to predict from the reaction scope demonstrated. In general, the approach is often outlined as very promising for late-stage modification.

The decarboxylative strategy is another relatively new methodology that can be used to introduce fluorine-containing substituents into the molecules of interest (Supplementary Scheme S1B) [10]. Due to the high accessibility of various functionalized carboxylic acids, this strategy can be relatively easily implemented into the building block synthesis. The applicability of the method to sp^3-enriched, saturated ring systems is also notable. Due to the radical nature of the process, low stereoselectivity can be an important drawback of the methodology. For example, we have recently used fluorodecarboxylation for the preparation of 2-fluorocyclobutanecarboxylic acid as a mixture of diastereomers that were separated through derivatization. A related very promising approach is based on the deborylative strategy [11] that had limited applications for the building block preparation so far.

Electrophilic addition of fluorine-containing group and (masked) functional group to C=C (or C≡C) bonds is a classical approach to organofluorine compounds; recently, however, a number of its radical and transition metal-catalyzed versions were proposed [12] (Supplementary Scheme S1C). An

CONTACT Oleksandr O. Grygorenko gregor@univ.kiev.ua
Supplemental data for this article can be accessed at https://doi.org/10.1080/17568919.2024.2379229
© 2024 Informa UK Limited, trading as Taylor & Francis Group

important illustration of this strategy is double bond fluoro- or fluoroalkylborylation [13]. While the full potential of these newer methods for the synthesis of fluorinated building blocks is yet to be revealed, their compatibility with low-molecular-weight sp^3-rich cyclic systems and typically observed stereoselectivity can be advantageous. However, it is apparent that this approach can only produce vicinally substituted derivatives. As an interesting extension, asymmetric intramolecular Pd^{II}-catalyzed aminofluorination of non-activated alkenes providing chiral 3-fluoropiperidines (including spirocyclic) can be mentioned [14].

Other notable methods that have received attention recently include transformations of *gem*-difluorinated alkenes [15] (Supplementary Scheme S1D), fluorohomologation [16] (*E*), strain-release reactions with fluorine-containing agents [17] (*F*), and reactions of silicon-based difluorocarbene reagents ($TMSCF_2X$), in particular, *gem*-difluorocyclopropanation [18] (G). An important version of the latter approach involves the use of CF_3SiMe_3-based systems (Ruppert-Prakash reagent). The original protocol for this transformation was developed by Prakash, Hu and co-workers; we have used this method extensively for the building block synthesis (see [19] and references cited therein). An important aspect of the discussed research area is the preparation of chiral fluorine-containing building blocks. Among the methods introduced recently for that purpose, chemoenzymatic synthesis of organofluorine compounds [20] or nucleophilic addition to chiral fluoroalkyl-substituted sulfinimides [21] can be mentioned.

While the significance of the above-referenced strategies is beyond being questioned, with a few exceptions like those cited above, most recent works on the synthesis of novel fluorinated building blocks rely on the classical transformations of organofluorine chemistry. Thus, a majority of mono- and *gem*-difluorinated, as well as fluoroalkyl-substituted saturated carbo- and heterocyclic compounds were prepared using nucleophilic fluorination of alcohols or their activated derivatives, or carbonyl compounds (typical reagents: KF, DAST, Morph-DAST, XtalFluor-E, etc.) [3,4] (Supplementary Figure S2A). While the same approach was involved in the synthesis of alicyclic and saturated heterocyclic building blocks with vicinal and 'skipped' [22] fluorination patterns (including renowned O'Hagan's facially polarized 'Janus' cycloalkanes [23]), other methods included nucleophilic epoxide ring opening (e.g., with $Et_3N{\cdot}3HF$) or electrophilic fluorination (e.g., with NFSI or SelectFluor) (Supplementary Figure S2B). Notably, many efforts were put into evaluating physicochemical, conformational and metabolic properties of the aforementioned chemotypes (in particular, acidity/basicity and lipophilicity) and the corresponding fluorine-containing substituent effects [3].

Due to the unusual nature of the corresponding chemotypes, special synthetic methodologies were required for the preparation of $OCHF_2$-/OCF_3-, NCF_3-, SF_5-substituted, and other related building blocks (Supplementary Figure S2C). For example, recently reported multikilogram-scale synthesis of di- and trifluoromethoxy-substituted proline derivatives relied on the transition metal-catalyzed di- or trifluoromethylation of 4-hydroxyproline [24,25]. For the synthesis of *N*-trifluoromethyl heterocyclic building blocks, base-mediated alkylation with CF_2Br_2 followed by reaction with $AgBF_4$, as well as electrophilic *N*-trifluoromethylation using Togni reagents, was typically applied [26]. Chlorination in the presence of KF (giving SF_4Cl-substituted derivatives) followed by nucleophilic substitution with AgF or $AgBF_4$ is the most straightforward method to obtain aromatic SF_5-substitued building blocks [27].

The presented editorial on the chemistry of fluorinated building blocks for drug design is by no means comprehensive; in fact, it was focused on the pathways and targets used extensively in the last 5 years. Still, we hope that it provides a general understanding of the field. It should be mentioned though that the use of fluorinated molecules in medicinal chemistry should be reasonable since overloading the potential drug molecule much fluorine may be harmful. We believe that the proposed discussion will stimulate closing of the gap between development of novel synthetic pathways and their implementation toward desirable building blocks, wider application of the highlighted building block classes in early drug discovery programs, and (re)discovery of novel fluorine-containing chemotypes. In other words, we anticipate extended applications of fluorinative C–H modifications, fluorodecarboxylation, electrophilic addition of the fluorine-containing groups to the double/triple bonds, and other methods mentioned in the first part of this review to the synthesis of fluorine-containing building blocks, along with the classical methods like nucleophilic or electrophilic fluorination. On the other hand, the so-called 'neglected' or 'overlooked' fluorinated chemotypes like $OCHF_2$-/OCF_3-, NCF_3-, SF_5-substituted compounds, derivatives of saturated rings with vicinal and 'skipped' fluorination patterns (and likely other chemotypes that were not though of at the moment) will progress further through the drug discovery process.

Acknowledgments

The authors thank AO Tolmachov for his encouragement and support and all the brave people of Ukraine for making this work possible.

Author contributions

Conceptualization, investigation, data curation, supervision, writing (OO Grygorenko); investigation, data curation (KP Melnykov).

Financial disclosure

The work was funded by Enamine Ltd. OO Grygorenko received additional funding from Ministry of Education and Science of Ukraine, grant No. 0122U001962 (22BF037-02). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Competing interests disclosure

The authors are employees of Enamine Ltd. offering flurinated building blocks from the company's catalog.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

ORCID

Oleksandr O Grygorenko
https://orcid.org/0000-0002-6036-5859
Kostiantyn P Melnykov
https://orcid.org/0009-0003-6522-681X

References

1. Inoue M, Sumii Y, Shibata N. Contribution of organofluorine compounds to pharmaceuticals. ACS Omega. 2020;5:10633–10640. doi:10.1021/acsomega.0c00830
2. Wang Q, Bian Y, Dhawan G, et al. FDA approved fluorine-containing drugs in 2023. Chinese Chem Lett. 2024;109780. doi:10.1016/j.cclet.2024.109780
3. Grygorenko OO, Melnykov KP, Holovach S, et al. Fluorinated cycloalkyl building blocks for drug discovery. ChemMedChem. 2022;17:e202200365. doi:10.1002/cmdc.202200365
4. Ryabukhin SV, Bondarenko DV, Trofymchuk SA, et al. Azaheterocyclic building blocks with in-ring CF_2-Fragment. Chem Rec. 2024;24:e202300283. doi:10.1002/tcr.202300283
5. Cahard D, Ma J. Emerging fluorinated motifs - synthesis, properties, and applications. Mainheim, Germany: Wiley-VCH Verlag GmbH & Co. KGaA.; 2020.
6. Grygorenko OO, Volochnyuk DM, Vashchenko BV. Emerging building blocks for medicinal chemistry: recent synthetic advances. Eur J Org Chem. 2021;6478–6510. doi:10.1002/ejoc.202100857
7. Fernandes AJ, Giri R, Houk KN, et al. Review and theoretical analysis of fluorinated radicals in direct C_{Ar}–H functionalization of (hetero)arenes. Angew Chem Int Ed. 2024;63:e202318377. doi:10.1002/anie.202318377
8. Purushotam N, Bera A, Banerjee D. Recent advances on non-precious metal-catalysed fluorination, difluoromethylation, trifluoromethylation, and perfluoroalkylation of N-heteroarenes. Org Biomol Chem. 2023;21:9298–9315. doi:10.1039/D3OB01132A
9. Szpera R, Moseley DFJ, Smith LB, et al. The fluorination of C–H bonds: developments and perspectives. Angew Chem Int Ed. 2019;58:14824–14848. doi:10.1002/anie.201814457
10. Xiao P, Pannecoucke X, Bouillon JP, et al. Wonderful fusion of organofluorine chemistry and decarboxylation strategy. Chem Soc Rev. 2021;50:6094–6151. doi:10.1039/D1CS00216C
11. Pattison G. Fluorination of organoboron compounds. Org Biomol Chem. 2019;17:5651–5660. doi:10.1039/C9OB00832B
12. Lin D, Coe M, Krishnamurti V, et al. Recent advances in visible light-mediated radical fluoroalkylation, -alkoxylation, -alkylthiolation, -alkylselenolation, and -alkylamination. Chem Rec. 2023;23:e202300104. doi:10.1002/tcr.202300104
13. Ma X, Kuang Z, Song Q. Recent advances in the construction of fluorinated organoboron compounds. JACS Au. 2022;2:261–279. doi:10.1021/jacsau.1c00129
14. Hou C, Chen P, Liu G. Enantioselective palladium(II)-catalyzed oxidative aminofluorination of unactivated alkenes with $Et_4NF{\cdot}3HF$ as a fluoride source. Angew Chem Int Ed. 2020;59:2735–2739. doi:10.1002/anie.201913100
15. Sorrentino JP, Altman RA. Fluorine-retentive strategies for the functionalization of gem-difluoroalkenes. Synthesis. 2021;53:3935–3950. doi:10.1055/A-1547-9270
16. Fasano V, Winter N, Noble A, et al. Divergent, stereospecific mono- and difluoromethylation of boronic esters. Angew Chem Int Ed. 2020;59:8502–8506. doi:10.1002/anie.202002246
17. Kraemer Y, Ghiazza C, Ragan AN, et al. Strain-release pentafluorosulfanylation and tetrafluoro(aryl)sulfanylation of [1.1.1]propellane: reactivity and structural insight. Angew Chem Int Ed. 2022;61:e202211892. doi:10.1002/anie.202211892
18. Xie Q, Hu J. A journey of the development of privileged difluorocarbene reagents $TMSCF_2X$ (X = Br, F, Cl) for organic synthesis. Acc Chem Res. 2024;57:693–713. doi:10.1021/acs.accounts.3c00719
19. Nosik PS, Ryabukhin SV, Grygorenko OO, et al. Transition metal-free gem-difluorocyclopropanation of alkenes with CF_3SiMe_3–NaI system: a recipe for electron-deficient substrates. Adv Synth Catal. 2018;360:4104–4114. doi:10.1002/adsc.201801006
20. Fang J, Halt D, Head-Gordon M, et al. Chemoenzymatic platform for synthesis of chiral organofluorines based on type II aldolases. Angew Chem Int Ed. 2019;58:11841–11845. doi:10.1002/anie.201906805
21. Truong VL, Ménard MS, Dion I. Asymmetric syntheses of 1-Aryl-2,2,2-trifluoroethylamines via diastereoselective 1,2-addition of arylmetals to 2-Methyl-N-(2,2,2-trifluoroethylidene)propane-2-sulfinamide. Org Lett. 2007;9:683–685. doi:10.1021/ol063001q

22. Troup RI, Jeffries B, Saudain REB, et al. Skipped fluorination motifs: synthesis of building blocks and comparison of lipophilicity trends with vicinal and isolated fluorination motifs. J Org Chem. 2021;86:1882–1900. doi:10.1021/acs.joc.0c02810
23. O'Hagan D. The emergence and properties of selectively fluorinated 'Janus' cyclohexanes. Chem Rec. 2023;23:e202300027. doi:10.1002/tcr.202300027
24. Cabrera PJ, Allais C, Arcari JT, et al. Rapid multikilogram scale-up of di- and trifluoromethoxy proline derivatives. Org Process Res Dev. 2024;24:1119–1128. doi:10.1021/acs.oprd.3c00493
25. Hao BY, Han YP, Zhang Y, et al. New synthetic approaches toward OCF_3-containing compounds. Org Biomol Chem. 2023;21:4926–4954. doi:10.1039/D3OB00258F
26. Lei Z, Chang W, Guo H, et al. A brief review on the synthesis of the N-CF_3 motif in heterocycles. Molecules. 2023;28:3012. doi:10.3390/molecules28073012
27. Kordnezhadian R, Li BY, Zogu A, et al. Chemistry of pentafluorosulfanyl derivatives and related analogs: from synthesis to applications. Chem Eur J. 2022;28:e202201491. doi:10.1002/chem.202201491

Last of the *gem*-Difluorocycloalkanes 2: Synthesis of Fluorinated Cycloheptane Building Blocks

Maksym Herasymchuk,[a,b] Dr. Kostiantyn P. Melnykov,[a,b] Dmytro V. Yarmoliuk,[a] Dmytro Serhiichuk,[a], Valeriia Rotar,[a,c] Timur Pukhovoi,[a,c] Yuliya O. Kuchkovska,[a,b] Sergey Golovach,[a,d] Prof. Dr. Dmitriy M. Volochnyuk,[a,b,d] Prof. Dr. Sergey V. Ryabukhin,*[a,b] Dr. Oleksandr O. Grygorenko[a,b]

[a] Enamine Ltd.
Chervonotkatska Street 78, Kyiv 020941, Ukraine
E-mail: s.v.ryabukhin@gmail.com
URL: www.enamine.net
[b] Taras Shevchenko National University of Kyiv
Volodymyrska Street 60, Kyiv 01601, Ukraine
[c] National Technical University of Ukraine 'Igor Sikorsky Kyiv Polytechnic Institute'
Prospect Peremogy 37, Kyiv 03056, Ukraine
[d] Institute of Organic Chemistry, National Academy of Sciences of Ukraine
Chervonotkatska Street 78, Kyiv 02094, Ukraine

Abstract: The *gem*-difluorocycloalkane family was extended by all isomeric monofunctionalized *gem*-difluorocycloheptanes that were synthesized on a multigram scale. The preparation of the corresponding building blocks containing either carboxylic acid, amine or ketone functional group was achieved from readily accessible starting materials either via six-membered ring homologation or deoxofluorination of the appropriate seven-membered cyclic ketones.

Introduction

Fluorinated substituents have found a broad application in medicinal chemistry[1–5] and chemical biology,[6,7] and have become outstanding isosteric replacements for diverse functional groups.[8,9] Introduction of fluorine atoms is commonly used for the modulation of physicochemical and pharmacokinetic properties, potency, and selectivity. A prominent feature of such optimization is the possibility to control the degree of alteration of various properties by rational selection of the fluorinated fragment along with the most suitable position to introduce it.[10–13] Therefore, design and synthesis of new fine-tuned fluorinated motifs has become an advantageous topic with a great potential for application in other research fields.[14]

One promising type of fluorinated substituents which gained an increased attention recently involves mono-, di- and polyfluoro-substituted cycloalkanes. The decreased conformational flexibility of cycloalkane scaffolds can be used to fix spatial orientation of the dipole moments of both fluorinated fragment and additional functional group. For example, O'Hagan and colleagues implemented this approach into the design of facially-polarised 'Janus face' all-*cis* trifluorocyclopropanes **1**,[15] tetrafluorocyclohexanes **2** (and their penta- and hexa-fluorinated analogues),[16–19] as well as tetrafluorocyclohexane derivatives **3**[20] containing two *gem*-difluoromethylene moieties (Figure 1, **A**).

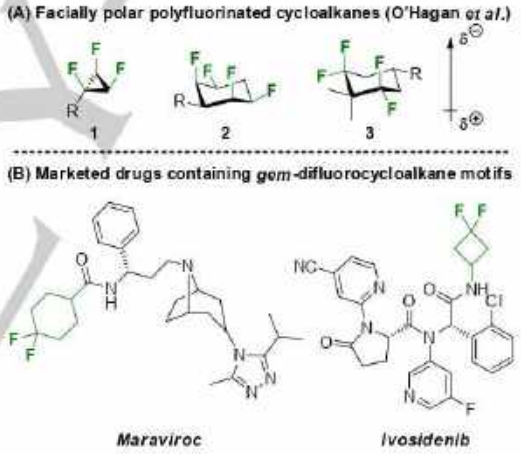


Figure 1. Face-polarized trifluorocyclopropanes and tetrafluorocyclohexanes reported by O'Hagan *et al.* (**A**); marketed drugs containing *gem*-difluorocyclohexane and *gem*-difluorocyclobutane motifs (**B**)

Among the fluorinated cycloalkane substituents that have already found a successful application in medicinal chemistry are *gem*-difluorocyclohexane and *gem*-difluorocyclobutane motifs present in marketed drugs maraviroc[21] and ivosidenib[22] (approved in 2007 and 2018, respectively, Figure 1, **B**).

All the aforementioned works have motivated us to develop convenient synthetic routes to all isomeric *gem*-difluorocycloalkanes which can be used to access multigram quantities of the corresponding building blocks. To date, we have reported a series of works on the preparation of three-to-six-membered fluorinated alicyclic compounds.[23–28] Yet, the Reaxys database search[29] has revealed that the synthesis and application of higher homologues – *gem*-difluorinated cycloheptane derivatives

– remain to be underexplored in both papers[30–32] and patents (Figure 2, **A**). Meanwhile, it should be stressed out that the aforementioned cycloheptane building blocks are not just yet other representatives of the *gem*-difluorocycloalkane homologous series. Recently, we have shown that seven-membered rings provide unique three-dimensional disposition of the functional groups attached that cannot be easily achieved by lower homologues.[33] Therefore, *gem*-difluorinated cycloheptanes can be considered as promising building blocks for drug discovery that substantially extend possible relative orientations of the corresponding functional moieties present in their molecules.

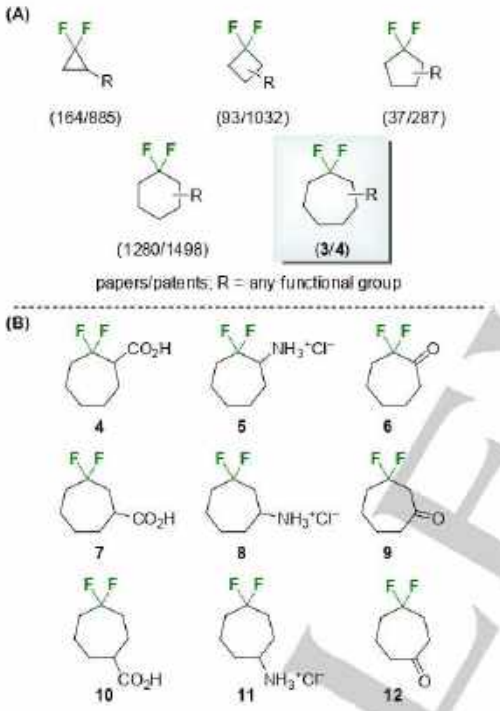
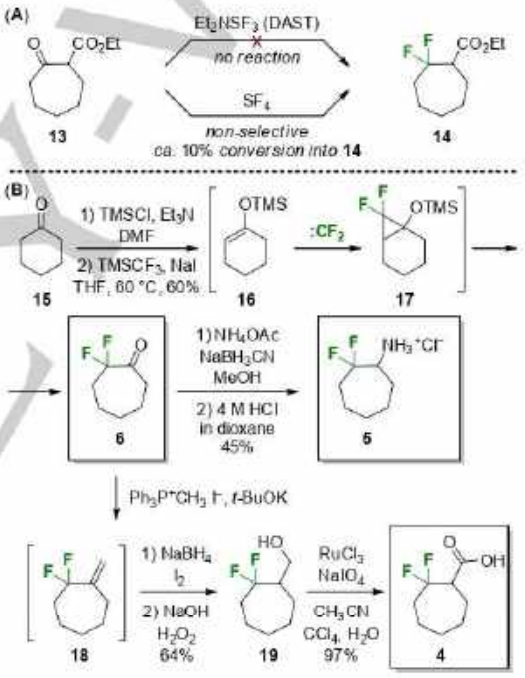


Figure 2. *Reaxys*® database search of papers/patents referencing monosubstituted *gem*-difluorocycloalkanes (**A**); structures of *gem*-difluorocycloheptane building blocks obtained in this work (**B**).

In this work, we describe straightforward and efficient synthesis of all isomeric monofunctionalized *gem*-difluorocycloheptanes on a multigram scale (Figure 2, **B**). In particular, we have aimed at the preparation of the corresponding carboxylic acids **4**, **7**, **10**, amine derivatives **5**, **8**, **11**, and ketones **6**, **9**, **12** due to the versatile utility of these functional groups in medicinal chemistry. Noteworthy (and somewhat unexpectedly), the previous methodologies for the synthesis of the corresponding five- and six-membered counterparts appeared to be not applicable for the preparation of building blocks **4**–**12**; therefore, development of different synthetic pathways was necessary for these compounds.

Results and Discussion

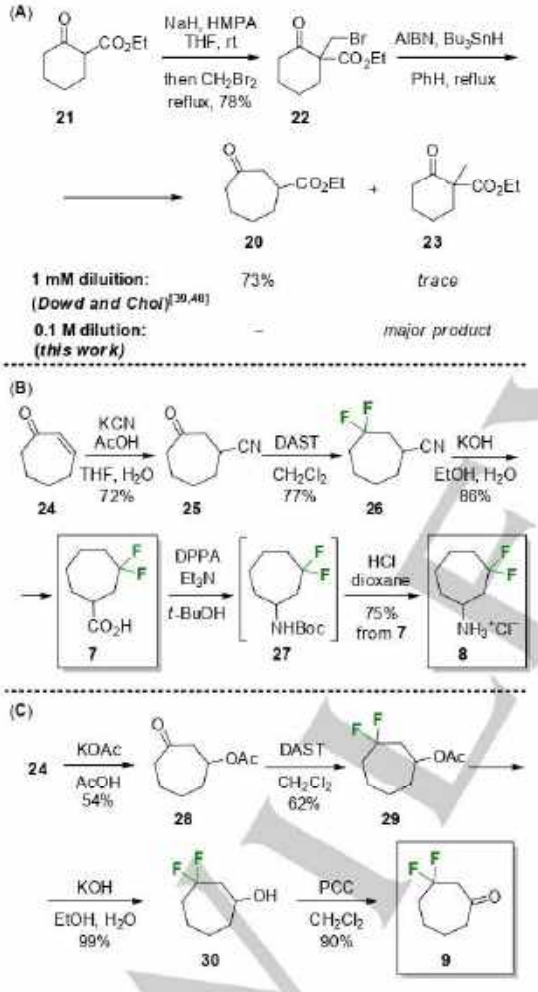
Our initial attempts to access 2,2-difluorocycloheptanecarboxylic acid **4** were based on deoxofluorination of the cycloheptanone moiety of ketoester **13** (Scheme 1, **A**). However, no reaction took place when **13** was treated with Et_2NSF_3 (DAST). In our previous report on the deoxofluorination of β-keto esters, it was also shown that **13** reacted unselectively upon treatment with SF_4 and gave target derivative **14** with low conversion.[34] These results motivated us to examine an alternative approach – homologation of the corresponding six-membered ring derivatives.



Scheme 1. Unsuccessful attempts of deoxofluorination of β-keto ester **13** (**A**), synthesis of *gem*-difluorocycloheptane derivatives **4**–**6** (**B**).

A facile transformation of cyclohexanone (**15**) into 2,2-difluoro-substituted cycloheptanone **6** (Scheme 1, **B**) was previously described by Amii and colleagues.[35] In their work, $BrCF_2CO_2Na$ was used as the difluorocarbene source that was added to silyl enol ether **16** at 150 °C to give siloxydifluorocyclopropane intermediate **17**. In contrast to the Amii's report, herein we suggested application of the $TMSCF_3$–NaI system for the formation of difluorocarbene under milder conditions.[26,27,36–38]

With this system, up to 150 g of **6** could be obtained per one load (60% yield from **15**). The next reductive amination of **6** followed by treatment with 4 M HCl in dioxane allowed to obtain the target amine derivative **5** in 45% yield. Furthermore, 2,2-difluorocycloheptanone (**6**) was also used as a synthetic intermediate for the preparation of carboxylic acid **4**. In this case, Wittig olefination of **6** followed by hydroboration–oxidation of **18** gave alcohol **19** (64% yield from **6**) that was next oxidized into acid **4** with high (97%) yield using $RuCl_3$–$NaIO_4$ system.



Scheme 2. Unsuccessful attempts of preparation of **20** by AIBN-promoted radical rearrangement of **22** (**A**); synthesis of *gem*-difluorocycloheptane derivatives **7**, **8** (**B**), and **9** (**C**).

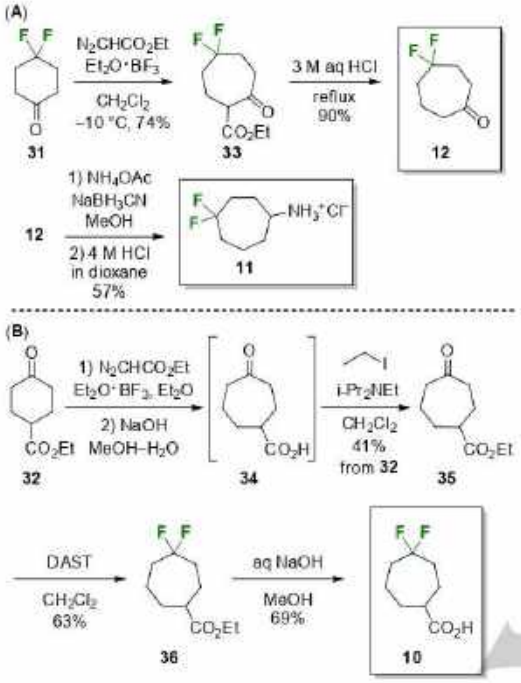
Synthesis of 3,3-difluorocycloheptanecarboxylic acid **7** commenced from testing the possibility of scaling up the procedure that was previously reported by Dowd and Choi (Scheme 2, **A**).[39,40] According to their work, a milligram amount of ester **20** was obtained by alkylation of β-keto ester **21** followed by AIBN-promoted radical rearrangement of **22**. It was shown that this transformation proceeded with formation of **20** (73% yield) in a mixture with a trace amount of **23** under high dilution conditions (1 mM solution of *n*-Bu_3SnH) or upon prolonged addition of *n*-Bu_3SnH using a syringe pump (10 mM solution). However, all our attempts to decrease the degree of dilution and adjust the reported procedure for the synthesis of **20** on the multigram scale were unsuccessful and led to the predominant formation of **23**. Therefore, the six-membered ring homologation strategy was abandoned in the case of fluorinated cycloheptane derivative **7**.

Meanwhile, application of cyclohept-2-enone (**24**) as a starting material for the synthesis of fluorinated cycloheptanes **7**–**9** appeared to be a convenient alternative and allowed us to obtain carboxylic acid **7** in just three steps (Scheme 2, **B**). Hydrocyanation of **24** followed by deoxofluorination of **25** with DAST was used to form *gem*-difluorocycloheptane-derived nitrile **26** (55% yield over two steps). The next alkaline hydrolysis of **26** gave the target compound **7** in 86% yield. Derivative **7** was further converted into amine hydrochloride **8** by Curtius rearrangement – Boc-deprotection of **27** in 75% overall yield.

Analogously, 3,3-difluorocycloheptanone (**9**) was prepared in just four synthetic steps starting from **24** (Scheme 2, **C**). Sequential addition of HOAc to **24** (54% yield) and deoxofluorination of **28** with DAST (62% yield) provided fluorinated intermediate **29**. After alkaline hydrolysis of **29**, the resulting alcohol **30** was subjected to the oxidation reaction using PCC to give target ketone **9** in 89% yield over two steps.

Finally, the remaining *gem*-difluorocycloheptane derivatives **10**–**12** were obtained from either cyclohexanone substrate **31** or **32** by ring homologation using diazoalkane reagent (Scheme 3, **A**). Treatment of 4,4-difluorocyclohexanone (**31**) with ethyl diazoacetate followed by acidic hydrolysis and decarboxylation of **33** was used for the preparation of 4,4-difluorocycloheptanone (**12**) (67% over two steps). The next reductive amination of **12** along with protonation in 4 M HCl solution in 1,4-dioxane provided target product **11** in 57% yield.

Alternatively, ring homologation of ethyl 4-oxocyclohexane-carboxylate (**32**) followed by diester hydrolysis and decarboxylation under basic conditions was carried out for the preparation of seven-membered δ-keto carboxylic acid **34** (Scheme 3, **B**). Compound **34** was further converted into ester **35** (41% yield from **32**) and next subjected to deoxofluorination step using DAST (63% yield). Alkaline hydrolysis of the obtained intermediate **36** allowed to obtain carboxylic acid **10** in 69% yield.



Scheme 3. Synthesis of *gem*-difluorocycloheptane derivatives **12**, **11** (**A**), and **10** (**B**).

Conclusions

A previously synthesized library of three-to-six membered cycloalkanes bearing a *gem*-difluoromethylene moiety was complemented with nine functionalized *gem*-difluorocycloheptane derivatives. The target building blocks were obtained in two to six synthetic steps from commercially available starting materials. Three strategies were used to access the target compounds with variable position of additional group: cyclohexanone homologation with difluorocarbene for the preparation of 1-functionalized 2,2-difluoro-substituted cycloheptanes (27–60% overall yield), cyclohept-2-enone functionalization/deoxofluorination – for 3,3-difluoro-substituted cycloheptanes (30–48% yield), and homologation of either fluorinated or non-fluorinated cylohexanones using diazoalkane reagent – for 4,4-difluoro-substituted cycloheptanes (18–67% yield). The described synthetic approaches allowed us to obtain target products on multigram scale (up to 133 g). The accessed fluorinated motifs present a great interest to medicinal chemistry and can be potentially used in drug optimization programs.

Experimental Section

General methods. The solvents were purified according to the standard procedures.[41] Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded at 500 MHz or 400 MHz, 470 or 376 MHz, and 126 MHz or 101 MHz, respectively. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LC/MSD SL instrument (chemical ionization (APCI), electrospray ionization (ESI)) and Agilent 5890 Series II 5972 GC/MS instrument (electron impact ionization (EI)).

2,2-Difluorocycloheptanone (6). Compound **15** (161 g, 1.64 mol) and triethylamine (180 mL, 2.46 mol) were dissolved in DMF (2.5 L), and Me_3SiCl (184 mL, 1.97 mol) was added in one portion. The mixture was stirred at 80 °C for 12 h. The mixture was cooled to rt, poured into ice-cold water (2.5 L) and then washed with hexane (5×800 mL). The combined organic phases were washed with ice-cold water (3×500 mL) and brine (2×400 mL), dried over Na_2SO_4, filtered, and concentrated to obtain compound **16** (250 g) as orange liquid.

Crude product **16** (250 g) and NaI (44.0 g, 0.294 mol) were dissolved in THF (3 L) in a conical flat-bottomed flask, and CF_3SiMe_3 (402 mL, 2.94 mol) was added (CAUTION! The reaction may proceed too vigorously at the higher scale, so that further scale-up should be avoided). The reaction mixture was heated carefully to 61 °C in an oil bath upon stirring. When the reaction started, the stirring was stopped; shortly after, a vigorous reaction occurred that caused boiling of the solution. After that, the external heating was continued for additional 18 h. Then the mixture was cooled to rt and evaporated. The residue was dissolved in *t*-BuOMe (1400 mL) and stirred for 15 min. The precipitate was filtered off, and the solution was concentrated to give **17** (283 g) that was used further without purification.

Crude product **17** (283 g) was dissolved in MeOH (4 L), and Na_2CO_3 (136 g, 1.28 mol) was added. The mixture was stirred at rt for 30 min, the inorganic sludge was filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in *t*-BuOMe (1.5 L) and washed with water (3×400 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was subjected to column chromatography (gradient hexane to hexane – *t*-BuOMe (85:15) as eluent) to produce compound **6**. Yield 133 g (55% over 3 steps). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (t, *J* = 6.7 Hz, 2H), 2.07 (tt, *J* = 15.2, 6.1 Hz, 2H), 1.87 – 1.78 (m, 2H), 1.75 – 1.67 (m, 2H), 1.65 – 1.58 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.4 (t, *J* = 27.3 Hz), 118.7 (t, *J* = 250.9 Hz), 39.0, 33.9 (t, *J* = 23.9 Hz), 27.7, 23.7, 23.0 (t, *J* = 5.8 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –105.5 ppm. MS (EI): *m/z* = 148 [M]$^+$. Anal. Calcd. for $C_7H_{10}F_2O$: C 56.75; H 6.80. Found: C 56.35; H 6.78.

2,2-Difluorocycloheptanaminium chloride (5). Compound **6** (94.7 g, 0.640 mol) was dissolved in MeOH (3.5 L), and ammonium acetate (493 g, 6.40 mol) was added. The reaction mixture was stirred at rt for 1 h, then $NaBH_3CN$ (121 g, 1.93 mol) was added in five nearly equal portions, and the mixture was stirred for 18 h. The mixture was concentrated, diluted with water (1.2 L), and 10% aq NaOH was added to pH = 12. The aqueous phase was extracted with CH_2Cl_2 (3×500 mL), the combined organic phases were dried over Na_2SO_4 and filtered. 4 M HCl in dioxane (750 mL) was added to the CH_2Cl_2 solution, and the precipitate formed was filtered to give **5**. Yield 53.6 g (45%). White solid, mp 144–146 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 3H), 3.66 (dt, *J* = 19.5, 8.6 Hz, 1H), 2.26 – 2.04 (m, 2H), 1.99 – 1.87 (m, 1H), 1.82 – 1.72 (m, 1H), 1.71 – 1.36 (m, 6H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ 124.0 (dd, *J* = 247.1, 242.8 Hz), 55.3 (dd, *J* = 25.8, 21.9 Hz), 33.9 (t, *J* = 23.7 Hz), 26.1, 26.0, 23.0, 18.9 (t, *J* = 6.4 Hz) ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ –88.8 (d,

J = 240.6 Hz), –106.2 (d, J = 240.6 Hz) ppm. MS (APCI): m/z = 150 [M – Cl]$^+$. Anal. Calcd. for $C_7H_{12}ClF_2N$: C 45.29; H 7.60; N 7.55; Cl 19.10. Found: C 45.34; H 7.93; N 7.37; Cl 19.44.

(2,2-Difluorocycloheptyl)methanol (19). To a suspension of triphenylphosphonium iodide (15.0 g, 37.1 mmol) in THF (100 mL), *t*-BuOK (4.00 g, 35.6 mmol) was added at 0–5 °C, and the mixture was stirred for 30 min. A solution of ketone **6** (5.00 g, 33.8 mmol) in THF (50 mL) was added dropwise at the same temperature. The reaction mixture was stirred at 0–5 °C for 15 min and at rt for 4 h (monitored by ^{19}F NMR spectra). After the starting material disappeared, the reaction mixture was filtered, and the filtrate containing **18** was used in the next step. A solution of I_2 (10.3 g, 40.5 mmol) in THF (100 mL) was added to a suspension of powdered $NaBH_4$ (3.20 g, 84.4 mmol) in THF (70 mL) dropwise at rt. The reaction mixture was stirred for 30 min, which was accompanied by discoloring. Then, the solution of alkene **18** in THF was added dropwise over 10 min, and the resulting mixture was stirred for 90 min (monitored by ^{19}F NMR spectra). 3 M aq NaOH (45 mL) was added dropwise over 30 min (CAUTION! Exothermic reaction). Then, 30% aq H_2O_2 (16 mL) was added dropwise over the next 30 min. The resulting mixture was stirred at rt for 1 h, diluted with brine (200 mL), and extracted with EtOAc (3×100 mL). The combined organic layers was evaporated in vacuo, and the residue was redissolved in CH_2Cl_2 (150 mL). The traces of water were separated; the organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by column chromatography to give **19**. Yield 3.55 g (64%). Yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87 (dd, J = 11.3, 5.3 Hz, 1H), 3.63 (t, J = 11.3, 6.2 Hz, 1H), 2.18 – 1.96 (m, 3H), 1.95 – 1.83 (m, 2H), 1.78 – 1.71 (m, 2H), 1.70 – 1.63 (m, 1H), 1.54 – 1.48 (m, 1H), 1.47 – 1.39 (m, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 128.2 (dd, J = 243.3, 241.7 Hz), 62.4 (dd, J = 8.7, 3.2 Hz), 49.6 (t, J = 22.2 Hz), 37.8 (t, J = 26.0 Hz), 28.7, 27.6, 25.1 (d, J = 8.9 Hz), 20.9 (dd, J = 8.3, 4.9 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –86.5 (d, J = 242.6 Hz), –102.1 (d, J = 242.6 Hz) ppm. MS (EI): m/z = 144 [M – HF]$^+$, 114 [M – HF – CH_2O]$^+$. Anal. Calcd. for $C_8H_{14}F_2O$: C 58.52; H 8.59. Found: C 58.36; H 8.36.

2,2-Difluorocycloheptanecarboxylic Acid (4). To a mixture of alcohol **19** (3.80 g, 23.1 mmol) and $NaIO_4$ (19.8 g, 92.6 mmol) in CCl_4 (40 mL), CH_3CN (40 mL), H_2O (60 mL), and $RuCl_3 \cdot xH_2O$ (0.260 g, 1.16 mmol) were added, the mixture was stirred at rt for 2 h and neutralized with saturated aq. $NaHCO_3$ (30 mL). The precipitate was filtered and washed with H_2O (20 mL). The combined filtrates were extracted with $CHCl_3$ (2×25 mL), the aqueous phase was separated, acidified with 10% aq $NaHSO_4$ to pH = 3, and extracted with EtOAc (3×40 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give **4**. Yield 4.00 g (97%). Colorless solid, mp 51–53 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.60 (s, 1H), 3.09 (ddd, J = 17.2, 9.6, 3.6 Hz, 1H), 2.36 – 2.07 (m, 2H), 2.04 – 1.78 (m, 3H), 1.77 – 1.64 (m, 2H), 1.61 – 1.45 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.0 (d, J = 6.8 Hz), 124.5 (dd, J = 246.6, 243.0 Hz), 52.8 (dd, J = 26.8, 23.9 Hz), 36.8 (t, J = 25.1 Hz), 27.4, 25.8, 25.2 (t, J = 4.5 Hz), 20.7 (dd, J = 8.2, 4.8 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –85.8 (d, J = 249.0 Hz), –93.1 (d, J = 249.0 Hz) ppm. MS (APCI): m/z = 177 [M – H]$^-$. Anal. Calcd. for $C_8H_{12}F_2O_2$: C 53.93; H 6.79. Found: C 53.76; H 6.85.

3-Oxocycloheptanecarbonitrile (25).[42] A mixture of cyclohept-2-enone (100 g, 91% purity, 0.908 mol) and AcOH (55 mL, 0.960 mol) in THF (1.8 L) was added to a solution of KCN (117 g, 1.80 mol) in H_2O (300 mL). The reaction mixture was stirred at 80 °C overnight, cooled to rt and diluted with H_2O (1.8 L). The resulting solution was extracted with CH_2Cl_2 (3×1 L). The combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated under vacuo. The obtained residue was dissolved in *t*-BuOMe (1 L) and filtered through a plug of silica gel (800 g) that was washed with additional *t*-BuOMe (1 L). The resulting solution was concentrated *in vacuo* to give the crude product with 90% purity (110 g). Purification of the title compound was performed by vacuo distillation (120 °C / 0.5 mbar). Yield 90.8 g (72%). Yellow oil, bp = 120 °C/0.5 mbar. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.05 – 2.93 (m, 1H), 2.86 – 2.71 (m, 2H), 2.68 – 2.57 (m, 1H), 2.55 – 2.46 (m, 1H), 2.03 – 1.89 (m, 3H), 1.81 – 1.67 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.1, 120.8, 45.5, 43.7, 33.4, 27.4, 26.7, 23.5 ppm. MS (EI): m/z = 137 [M]$^+$. Anal. Calcd. for $C_8H_{11}NO$: C 70.04; H 8.08; N 10.21. Found: C 69.78; H 7.74; N 10.07.

3,3-Difluorocycloheptanecarbonitrile (26). To a solution of ketone **25** (25.0 g, 182 mmol) in CH_2Cl_2 (1 L), Et_2NSF_3 (DAST, 146.8 g, 911 mmol) was added dropwise at rt. The reaction mixture was stirred at 40 °C for 48 h and then poured into sat aq $NaHCO_3$ (1 L). After stirring for 30 min, the layers were separated and aqueous phase was extracted with CH_2Cl_2 (2×400 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated under vacuo to give 27.5 g of the crude product. Purification of the title compound was performed by column chromatography (hexanes – EtOAc (40:1) as eluent, R_f = 0.30). Yield 22.3 g (77%). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.89 (t, J = 9.2 Hz, 1H), 2.57 – 2.27 (m, 2H), 2.19 – 2.03 (m, 3H), 1.96 – 1.76 (m, 2H), 1.72 – 1.58 (m, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 124.4 (t, J = 241.0 Hz), 121.4, 40.2 (t, J = 29.3 Hz), 37.3 (t, J = 26.0 Hz), 32.3, 26.1, 24.7 (dd, J = 10.2, 5.4 Hz), 20.7 (dd, J = 7.8, 4.8 Hz) ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ –85.0 (ddq, J = 249.5, 22.1, 11.0 Hz), –90.3 (dtt, J = 249.5, 23.5, 13.0 Hz) ppm. MS (EI): m/z = 159 [M]$^+$. Anal. Calcd. for $C_8H_{11}F_2N$: C 60.36; H 6.97; N 8.80. Found: C 60.52; H 7.34; N 8.88.

3,3-Difluorocycloheptanecarboxylic acid (7). A solution of KOH (35.2 g, 628 mmol) in H_2O (200 mL) was added to a solution of nitrile **26** (20.0 g, 126 mmol) in EtOH (200 mL), and the solution was heated at 70 °C for 72 h. The resulting solution was allowed to cool to rt and concentrated under reduced pressure. The residue was diluted with H_2O (200 mL) and washed with CH_2Cl_2 (150 mL). The aqueous layer was then separated, acidified with $NaHSO_4$ and extracted with CH_2Cl_2 (3×200 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated under vacuo to give pure product. Yield 19.2 g (86%). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.54 (br s, 1H), 2.65 (t, J = 10.8 Hz, 1H), 2.49 (q, J = 12.9 Hz, 1H), 2.25 – 1.99 (m, 4H), 1.85 – 1.74 (m, 1H), 1.73 – 1.51 (m, 4H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.7, 125.4 (dd, J = 239.3, 239.2 Hz), 39.1 (dd, J = 29.3, 27.5 Hz), 38.7 (d, J = 10.9 Hz), 37.8 (t, J = 26.2 Hz), 31.6, 26.8, 21.1 (t, J = 6.3 Hz) ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –84.3 (d, J = 244.7 Hz), –91.8 (d, J = 244.7 Hz) ppm. MS (APCI): m/z = 177 [M – H]$^-$. Anal. Calcd. for $C_8H_{12}F_2O_2$: C 53.93; H 6.79. Found: C 54.22; H 6.92.

***tert*-Butyl (3,3-difluorocycloheptyl)carbamate (27).** To a solution of carboxylic acid **7** (9.50 g, 53.3 mmol) in *t*-BuOH (100 mL), Et_3N (6.40 g, 63.9 mmol) was added and was followed by the addition of $(PhO)_2P(O)N_3$ (DPPA, 17.6 g, 63.9 mmol). After heating the reaction mixture at 80 °C for 18h, it was allowed to cool to rt and was concentrated under reduced pressure. The residue was dissolved in *t*-BuOMe (200 mL), washed with sat aq Na_2CO_3 (2×100 mL) and with aq $NaHSO_4$ (100 mL), dried over anhydrous Na_2SO_4 and then concentrated under vacuo. The crude product (12.1 g) was used in the next step without additional purification. An analytical sample was obtained after purification by column chromatography (hexanes – EtOAc (4:1) as eluent, R_f = 0.39). Beige solid, mp 77–79 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59 (s, 1H), 3.81 (s, 1H), 2.40 (q, J = 13.1 Hz, 1H), 2.21 – 1.92 (m, 4H), 1.80 – 1.65 (m, 2H), 1.63 – 1.49 (m, 3H), 1.44 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.9, 125.1 (dd, J = 241.6, 238.3 Hz), 79.6, 46.0, 44.2 (t, J = 25.2 Hz), 37.6 (t, J = 25.9 Hz), 35.7, 28.5, 25.1, 21.5 ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –86.1 (d, J = 247.0 Hz), –87.6 (d, J = 247.0 Hz) ppm. MS (EI): m/z = 249 [M$^+$], 193 [M – C(CH_3)$_2$$CH_2$]$^+$, 149 [M – CO_2 – C(CH_3)$_2$$CH_2$]$^+$.

Anal. Calcd. for $C_{12}H_{21}F_2NO_2$: C 57.81; H 8.49; N 5.62. Found: C 57.92; H 8.56; N 5.49.

3,3-Difluorocycloheptanaminium chloride (8). Crude compound **27** (12.1 g) was dissolved in 4 M HCl in dioxane (100 mL) and stirred at rt for 18 h. The resulting solution was concentrated under reduced pressure, and the residue was triturated with *t*-BuOMe. The solid product was filtered and dried under vacuo. Yield 7.50 g (75%) over 2 steps from **7** (9.50 g, 53.3 mmol). White solid, mp 187–189 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (s, 3H), 3.36 – 3.31 (m, 1H), 2.48 – 2.42 (m, 1H), 2.39 – 2.23 (m, 1H), 2.20 – 2.08 (m, 1H), 2.07 – 1.93 (m, 2H), 1.83 – 1.69 (m, 1H), 1.69 – 1.55 (m, 2H), 1.55 – 1.39 (m, 2H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 124.8 (dd, J = 239.4, 239.0 Hz), 45.6 (dd, J = 12.7, 2.4 Hz), 41.2 (t, J = 28.0 Hz), 36.6 (t, J = 25.4 Hz), 32.7, 24.2, 20.2 (t, J = 6.4 Hz) ppm. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –82.0 (d, J = 243.8 Hz), –87.0 (d, J = 243.8 Hz) ppm. MS (APCI): m/z = 150 [M – Cl]$^+$. Anal. Calcd. for $C_7H_{14}ClF_2N$: C 45.29; H 7.60; N 7.55; Cl 19.10. Found: C 45.58; H 7.24; N 7.88; Cl 19.30.

3-Oxocycloheptyl acetate (28). To a solution of cyclohept-2-enone (30.0 g, 91% purity, 273 mmol) in glacial AcOH (75 mL), KOAc (30.0 g, 306 mol) was added. After the maximum conversion of 60% was achieved (7 days), the reaction mixture was neutralized carefully with saturated aq $NaHCO_3$ and extracted with CH_2Cl_2 (3×300 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated under vacuo. The product was purified by column chromatography (hexanes – EtOAc (4:1) as eluent, R_f = 0.48). Cyclohept-2-enone (12.2 g) was also recovered from the reaction mixture (R_f = 0.81). Yield 25.3 g (54%). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 – 5.07 (m, 1H), 2.80 – 2.74 (m, 2H), 2.51 – 2.45 (m, 2H), 2.01 (s, 3H), 1.95 (q, J = 7.1 Hz, 1H), 1.88 – 1.76 (m, 2H), 1.7xt5 – 1.66 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.4, 170.0, 69.3, 48.3, 44.4, 35.2, 24.9, 23.9, 21.2 ppm. MS (EI): m/z = 170 [M]$^+$, 110 [M – CH_3CO_2H]$^+$. Anal. Calcd. for $C_9H_{14}O_3$: C 63.51; H 8.29. Found: C 63.23; H 8.06.

3,3-Difluorocycloheptyl acetate (29). Compound **28** (5.00 g, 29.4 mmol) was dissolved in CH_2Cl_2 (500 mL), and DAST (23.8 g, 148 mmol) was added dropwise at rt. The reaction mixture was stirred at 40 °C for 48 h, then DAST (4.75 g, 29.5 mmol) was added, and the mixture was stirred at the same temperature for additional 18 h. The reaction mixture was poured into saturated aq $NaHCO_3$ (1500 mL). After stirring for 30 min, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×200 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and the solvents were removed in vacuo. The compound was purified by column chromatography (hexanes – EtOAc (20:1) as eluent, R_f = 0.45). Yield 3.51 g (62%). Yellowish oil, bp 33 °C/0.5 mbar. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 – 4.93 (m, 1H), 2.47 – 2.27 (m, 2H), 2.23 – 2.05 (m, 2H), 2.04 (s, 3H), 1.98 – 1.90 (m, 1H), 1.80 – 1.69 (m, 2H), 1.68 – 1.56 (m, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 124.5 (t, J = 239.9 Hz), 68.9 (dd, J = 10.1, 5.4 Hz), 43.1 (t, J = 27.8 Hz), 37.8 (t, J = 26.0 Hz), 34.2, 24.3, 21.5 (t, J = 6.4 Hz), 21.3 ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –84.4 (d, J = 245.2 Hz), –87.7 (d, J = 245.2 Hz) ppm. MS (EI): m/z = 112 [M – CH_3CO_2H – HF]$^+$. Anal. Calcd. for $C_9H_{14}F_2O_2$: C 56.24; H 7.34. Found: C 56.41; H 7.21.

3,3-Difluorocycloheptanol (30). Compound **29** (0.300 g, 1.56 mmol) was dissolved in MeOH (5 mL), and a solution of KOH (0.360 g, 6.42 mmol) in water (2 mL) was added. The reaction mixture was stirred at rt for 1 h (monitored by TLC). MeOH was removed in vacuo, the residue was diluted with water (5 mL) and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated in vacuo. Yield 0.231 g (99%). Yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.98 (s, 1H), 2.43 (q, J = 13.9 Hz, 1H), 2.31 – 2.08 (m, 2H), 2.04 – 1.89 (m, 2H), 1.83 – 1.73 (m, 1H), 1.72 – 1.61 (m, 2H), 1.60 – 1.46 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 124.8 (t, J = 239.5 Hz), 66.9 (dd, J = 10.8, 4.1 Hz), 46.4 (t, J = 26.0 Hz), 38.2, 37.9 (t, J = 26.1 Hz), 24.3, 21.5 (t, J = 6.3 Hz) ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –84.1 (d, J = 246.6 Hz), –87.5 (d, J = 246.6 Hz) ppm. MS (EI): m/z = 130 [M – HF]$^+$, 112 [M – HF – H_2O]$^+$. Anal. Calcd. for $C_7H_{12}F_2O$: C 55.99; H 8.05. Found: C 56.38; H 7.98.

3,3-Difluorocycloheptanone (9). Compound **30** (100 mg, 0.667 mmol) was dissolved in CH_2Cl_2 (5 mL), and pyridinium chlorochromate (0.334 g, 1.55 mmol) was added in one portion. The reaction mixture was stirred at rt for 5 h (monitored by TLC), then filtered through a silica gel pad (1 g) that was then washed with CH_2Cl_2 (50 mL). The solvent was removed in vacuo to obtain **9**. Yield 89.8 mg (91%). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.10 (t, J = 14.5 Hz, 2H), 2.58 – 2.53 (m, 2H), 2.19 (t, J = 13.4 Hz, 2H), 1.88 – 1.78 (m, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.5 (t, J = 7.4 Hz), 121.6 (t, J = 241.5 Hz), 52.2 (t, J = 28.0 Hz), 44.0, 38.5 (t, J = 25.5 Hz), 23.4, 23.2 (t, J = 6.4 Hz) ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –91.7 ppm. MS (EI): m/z = 148 [M]$^+$, 128 [M – HF]$^+$. Anal. Calcd. for $C_7H_{10}F_2O$: C 56.75, H 6.80. Found: C 56.48; H 6.69.

Ethyl 5,5-Difluoro-2-oxocycloheptanecarboxylate (33). A three-necked flask was charged with **31** (70.0 g, 522 mmol) and dry CH_2Cl_2 (1.4 L) under nitrogen atmosphere. The mixture was cooled to –10 °C and stirred for 15 min. Then a solution of $Et_2O{\cdot}BF_3$ (85.2 mL, 678 mmol) in CH_2Cl_2 (350 mL) was added dropwise at –10 °C. The resulting mixture was stirred at the same temperature for 10 min, and a solution of ethyl diazoacetate (72.2 mL, 678 mmol) in CH_2Cl_2 (350 mL) was added dropwise. The mixture was stirred for an additional 1 h at the same temperature, then allowed to warm to rt and quenched with 30% aq K_2CO_3 (700 mL). The organic phase was separated and washed with brine (2×500 mL), then dried over Na_2SO_4, filtered, and evaporated in vacuo. Yield 88.6 g (73%). Orangeish amorphous solid. The compound existed as *ca.* 1:2 mixture of ketone and enol tautomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.68 (s, 0.7H), 4.22 (q, J = 6.0 Hz, 2H), 3.58 – 3.49 (m, 0.3H), 2.81 – 2.71 (m, 0.3H), 2.64 – 2.54 (m, 0.3H), 2.51 – 2.41 (m, 2.7H), 2.38 – 2.25 (m, 0.7H), 2.23 – 2.12 (m, 1H), 2.09 – 1.99 (m, 1.7H), 1.98 – 1.85 (m, 1.3H), 1.37 – 1.24 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.1 (ketone $\underline{C}O$), 177.0 (enol $\underline{C}OH$), 172.4 and 169.6 ($\underline{C}O_2Et$), 124.4 (m, $\underline{C}F_2$), 100.8 (enol $\underline{C}(COH)CO_2Et$), 61.7 ($\underline{C}H_2CO_2Et$), 61.0 and 58.6 ($O\underline{C}H_2$), 36.1 (t, J = 24.2 Hz) and 35.4 (t, J = 26.9 Hz, $\underline{C}H_2CF_2$), 35.4 ($\underline{C}H_2CO$), 33.2 (t, J = 26.3 Hz) and 32.5 (t, J = 28.0 Hz, $\underline{C}H_2CF_2$), 28.0 (t, J = 6.8 Hz) and 17.8 (t, J = 6.6 Hz, $\underline{C}H_2CH_2CF_2$), 14.4 and 14.2 (CH_3) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –91.7 (d, J = 246.0 Hz), –96.1 (d, J = 246.0 Hz) ppm. Anal. Calcd. for $C_{10}H_{14}F_2O_3$: C 54.54; H 6.41. Found: C 54.31; H 6.81.

4,4-Difluorocycloheptanone (12). A mixture of **33** (250 g, 1.13 mol) and 3 M aq HCl (600 mL) was heated at reflux overnight, then cooled to rt and evaporated under reduced pressure. The residue was purified by flash chromatography (gradient hexanes to hexanes – *t*-BuOMe (85:15) as eluent). Yield 150 g (90%). Yellowish liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 – 2.51 (m, 4H), 2.23 – 2.03 (m, 4H), 1.92 – 1.81 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.7, 124.0 (t, J = 240.3 Hz), 43.3, 38.1 (t, J = 26.2 Hz), 35.8 (t, J = 6.6 Hz), 32.3 (t, J = 27.8 Hz), 17.7 (t, J = 6.4 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –93.6 ppm. MS (EI): m/z = 148 [M]$^+$, 128 [M – HF]$^+$. Anal. Calcd. for $C_7H_{10}F_2O$: C 56.75; H 6.80. Found: C 56.80; H 6.84.

4,4-Difluorocycloheptanaminium chloride (11). Compound **12** (12.0 g, 81.0 mmol) was dissolved in MeOH (350 mL). Ammonium acetate (62.4 g, 0.810 mol) was added, and the reaction mixture was stirred at rt for 30 min. Then $NaBH_3CN$ (15.3 g, 244 mmol) was added, and the resulting mixture was stirred at rt overnight, and then diluted with water (180 mL). 10% aq Na_2CO_3 was added to pH = 12, and the mixture was extracted

with CH_2Cl_2 (3×100 mL). The organic phase was washed with brine (90 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. 4 M HCl in dioxane (100 mL) was added to the residue, and the resulting mixture was stirred at rt for 3 h. The precipitate was filtered, washed with diethyl ether (100 mL), and dried in vacuo. Yield 8.27 g (55%). Beige solid, mp 186–188 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 3H), 3.31 – 3.17 (m, 1H), 2.31 – 1.87 (m, 6H), 1.82 – 1.36 (m, 4H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 126.6 (t, J = 238.7 Hz), 50.4, 37.3 (t, J = 26.2 Hz), 32.1, 32.0 (t, J = 27.2 Hz), 24.5 (dd, J = 9.1, 4.0 Hz), 17.2 (dd, J = 6.9, 4.9 Hz) ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ –83.8 (d, J = 238.4 Hz), –85.3 (d, J = 238.4 Hz) ppm. Anal. Calcd. for $C_7H_{14}ClF_2N$: C 45.29; H 7.60; N 7.55; Cl 19.10. Found: C 44.91; H 7.45; N 7.79; Cl 19.04.

Ethyl 4-Oxocycloheptanecarboxylate (35).[43] Ethyl 4-oxocyclohexanecarboxylate (**32**) (50.0 g, 294 mmol) was dissolved in Et_2O (750mL) and cooled to 0 °C. Solution of BF_3-Et_2O (55 mL) in Et_2O (150 mL) was added dropwise and then a solution of ethyldiazoacetate (55 mL, 90% solution in CH_2Cl_2) in Et_2O (150 mL) was added slowly to the reaction mixture. The resulting solution was stirred at 0 °C for 2h and then at rt for additional 2h (monitored by ^{1}H NMR). After the full conversion of starting material was achieved, aq $NaHCO_3$ (1 L) was added and the mixture was stirred for 10 min. After the complete neutralization of the solution the organic layer was separated and concentrated in vacuo. The residue was dissolved in MeOH (500 mL), solution of NaOH (50.0 g, 1.25 mol) in H_2O (450 mL) was added and the reaction mixture was stirred for 24h. MeOH was evaporated under vacuum. The remaining aqueous phase was washed with CH_2Cl_2 (2×200 mL), acidified with aq $NaHSO_4$ to pH = 3 and then extracted with t-BuOMe (3×300 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give crude 4-oxocycloheptanecarboxylic acid (**34**) (35.2 g, ca. 80% purity according to ^{1}H NMR) which was used in the next step without additional purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 2.81 – 2.30 (m, 5H), 2.23 – 2.07 (m, 2H), 2.05 – 1.83 (m, 2H), 1.82 – 1.61 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.1, 180.9, 46.2, 43.5, 41.5, 32.4, 26.1, 22.3 ppm. i-Pr_2NEt (38.0 g, 294 mmol) was added to a solution of crude compound **34** (35.2 g, ca. 80% purity) in CH_2Cl_2 (500 mL). Ethyl iodide (68.8 g, 441 mmol) was added dropwise and the solution was stirred at rt for 48 h. The resulting mixture was washed with aq $NaHSO_4$ (500 mL). The organic phase was dried over anhydrous Na_2SO_4 and solvent was removed in vacuo. The residue was purified by column chromatography using hexane:t-BuOMe (2:1) as eluent (R_f = 0.4) to give pure compound **35**. Yield 22.1 g (41% from compound **32**). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (q, J = 7.1 Hz, 2H), 2.60 (ddd, J = 15.9, 7.3, 2.9 Hz, 1H), 2.56 – 2.43 (m, 4H), 2.16 – 2.04 (m, 2H), 2.00 – 1.81 (m, 2H), 1.78 – 1.69 (m, 1H), 1.69 – 1.61 (m, 1H), 1.25 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.7, 175.1, 60.6, 46.6, 43.6, 41.7, 32.7, 26.4, 22.5, 14.3 ppm. MS (EI): m/z = 184 [M]$^+$, 139 [M – OC_2H_5]$^+$. Anal. Calcd. for $C_{10}H_{16}O3$: C 65.19; H 8.75. Found: C 65.33; H 8.63.

Ethyl 4,4-Difluorocycloheptanecarboxylate (36).

Compound **35** (22.0 g, 119 mmol) was dissolved in CH_2Cl_2 (440 mL) and DAST (95.9 g, 595 mmol) was added dropwise at rt. The reaction mixture was stirred for at rt for 72 h and the 85% conversion of the starting material (according to GCMS) was achieved (the further addition of DAST (19.2 g, 119 mmol) did not influence the conversion). The resulting mixture was neutralized with aq $NaHCO_3$ (1000 mL). The organic layer was separated, filtered through a thin layer of silica and concentrated in vacuo. The residue was purified by vacuum distillation (bp 49 °C / 1 mbar) to give compound **4**. Yield 15.5 g (63%). Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.17 – 4.09 (m, 2H), 2.58 – 2.50 (m, 1H), 2.27 – 2.08 (m, 2H), 2.06 – 1.89 (m, 4H), 1.85 – 1.70 (m, 3H), 1.60 – 1.51 (m, 1H), 1.30 – 1.22 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 126.4 (t, J = 239.5 Hz), 44.6, 38.0 (t, J = 26.6 Hz), 35.3 (t, J = 27.2 Hz), 30.8, 23.1 (t, J = 6.8 Hz), 19.7 (t, J = 6.2 Hz), 14.3 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ –86.0 (dq, J = 20.1, 13.9 Hz, 1F), –86.5 (dq, J = 20.1, 13.9 Hz, 1F) ppm. MS (EI). m/z = 206 [M]$^+$, 186 [M – HF]$^+$, 161 [M – OC_2H_5]$^+$. Anal. Calcd. for $C_{10}H_{16}F_2O_2$: C 58.24, H 7.82. Found: C 58.60; H 7.84.

4,4-Difluorocycloheptanecarboxylic Acid (10). A solution of NaOH (2.33 g, 58.2 mmol) in H_2O (4 mL) was added to the solution of ester **4** (10.0 g, 48.5 mmol) in MeOH (200 mL). The reaction mixture was stirred at rt overnight. The solution was concentrated in vacuo, the residue was diluted with water (100 mL) and then acidified with 20% aq HCl to pH = 2. The product was extracted with CH_2Cl_2 (3x75 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to give pure product **5**. Yield 5.96 g (69%). Beige solid, mp 74–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.78 (br s, 1H), 2.61 (tt, J = 9.4, 4.9 Hz, 1H), 2.33 – 2.17 (m, 1H), 2.16 – 1.90 (m, 5H), 1.90 – 1.72 (m, 3H), 1.66 – 1.48 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.2, 126.2 (t, J = 239.7 Hz), 44.2, 38.1 (t, J = 26.6 Hz), 35.1 (t, J = 27.2 Hz), 30.5, 22.8 (t, J = 6.8 Hz), 19.6 (t, J = 6.3 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –86.9, –87.0 ppm. MS (EI). m/z = 158 [M – HF]$^+$. Anal. Calcd. for $C_8H_{12}F_2O_2$: C 53.93; H 6.79. Found: C 53.83; H 6.62.

Acknowledgments

The work was funded by Enamine Ltd. O.O.G. was also funded by Ministry of Education and Science of Ukraine (Grant No. 19BF037-03). The authors thank Prof. Andrey A. Tolmachev for his encouragement and support, and Ms. Mariana Pereblynis for her help with manuscript preparation.

Keywords: fluorine • cycloalkane • cycloheptane • deoxofluorination • building blocks

[1] S. Swallow, in *Prog. Med. Chem.*, Elsevier B.V., **2015**, pp. 65–133.
[2] J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506.
[3] Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422–518.
[4] S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330.
[5] E. A. Ilardi, E. Vitaku, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 2832–2842.
[6] I. Ojima, *J. Org. Chem.* **2013**, *78*, 6358–6383.
[7] I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, John Wiley & Sons, Ltd, Chichester, UK, **2009**.
[8] N. A. Meanwell, *J. Med. Chem.* **2018**, *61*, 5822–5880.
[9] E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315–8359.
[10] K. Muller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886.
[11] K. Müller, in *Fluor. Life Sci. Pharm. Med. Diagnostics, Agrochem.*, Elsevier, **2019**, pp. 91–139.
[12] K. Müller, *Chim. Int. J. Chem.* **2014**, *68*, 356–362.
[13] A. V. Chernykh, O. S. Oliinyk, Y. O. Kuchkovska, D. M. Volochnyuk, V.

S. Yarmolchuk, O. O. Grygorenko, *J. Org. Chem.* **2020**, *85*, 12692–12702.
[14] J. Ma, D. Cahard, Eds. , *Emerging Fluorinated Motifs*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2020**.
[15] Z. Fang, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan, *Chem. Commun.* **2019**, *55*, 10539–10542.
[16] D. O'Hagan, *Chem. Eur. J.* **2020**, *26*, 7881–7997.
[17] A. J. Durie, A. M. Z. Slawin, T. Lebl, P. Kirsch, D. O'Hagan, *Chem. Commun.* **2012**, *48*, 9643.
[18] M. P. Wiesenfeldt, Z. Nairoukh, W. Li, F. Glorius, *Science* **2017**, *357*, 908–912.
[19] Z. Fang, N. Al-Maharik, A. M. Z. Slawin, M. Bühl, D. O'Hagan, *Chem. Commun.* **2016**, *52*, 5116–5119.
[20] M. J. Jones, R. Callejo, A. M. Z. Slawin, M. Bühl, D. O'Hagan, *Beilstein J. Org. Chem.* **2016**, *12*, 2823–2827.
[21] P. Dorr, M. Westby, S. Dobbs, P. Griffin, B. Irvine, M. Macartney, J. Mori, G. Rickett, C. Smith-Burchnell, C. Napier, et al., *Antimicrob. Agents Chemother.* **2005**, *49*, 4721–4732.
[22] J. Popovici-Muller, R. M. Lemieux, E. Artin, J. O. Saunders, F. G. Salituro, J. Travins, G. Cianchetta, Z. Cai, D. Zhou, D. Cui, et al., *ACS Med. Chem. Lett.* **2018**, *9*, 300–305.
[23] A. V. Chernykh, K. P. Melnykov, N. A. Tolmacheva, I. S. Kondratov, D. S. Radchenko, C. G. Daniliuc, D. M. Volochnyuk, S. V. Ryabukhin, Y. O. Kuchkovska, O. O. Grygorenko, *J. Org. Chem.* **2019**, *84*, 8487–8496.
[24] K. Melnykov, D. Granat, D. Volochnyuk, S. Ryabukhin, O. Grygorenko, *Synthesis* **2018**, *50*, 4949–4957.
[25] K. P. Melnykov, P. S. Nosik, B. B. Kurpil, D. A. Sibgatulin, D. M. Volochnyuk, S. V. Ryabukhin, O. O. Grygorenko, *J. Fluor. Chem.* **2017**, *199*, 60–66.
[26] P. S. Nosik, S. V. Ryabukhin, O. O. Grygorenko, D. M. Volochnyuk, *Adv. Synth. Catal.* **2018**, *360*, 4104–4114.
[27] P. S. Nosik, A. O. Gerasov, R. O. Boiko, E. Rusanov, S. V. Ryabukhin, O. O. Grygorenko, D. M. Volochnyuk, *Adv. Synth. Catal.* **2017**, *359*, 3126–3136.
[28] O. V. Hryshchuk, A. O. Varenyk, Y. Yurov, Y. O. Kuchkovska, A. V. Tymtsunik, O. O. Grygorenko, *Eur. J. Org. Chem.* **2020**, 2217–2224.
[29] Reaxys Database. www.reaxys.com (accessed Sep 01, 2020).
[30] S. Hara, S.-Q. Chen, T. Hoshio, T. Fukuhara, N. Yoneda, *Tetrahedron Lett.* **1996**, *37*, 8511–8514.
[31] K. Isogai, J. Sakai, K. Kosugi, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1349–1353.
[32] E. S. Glazer, R. Knorr, C. Ganter, J. D. Roberts, *J. Am. Chem. Soc.* **1972**, *94*, 6026–6032.
[33] O. O. Grygorenko, P. Babenko, D. M. Volochnyuk, O. Ralevskyi, I. V. Komarov, *RSC Adv.* **2016**, *6*, 17595–17605.
[34] S. A. Trofymchuk, D. V. Kliukovskyi, S. V. Semenov, A. R. Khairulin, V. O. Shevchenko, M. Y. Bugera, K. V. Tarasenko, D. M. Volochnyuk, S. V. Ryabukhin, *Synlett* **2020**, *31*, 565–574.
[35] Y. Kageshima, C. Suzuki, K. Oshiro, H. Amii, *Synlett* **2014**, *26*, 63–66.
[36] A. García-Domínguez, T. H. West, J. J. Primozic, K. M. Grant, C. P. Johnston, G. G. Cumming, A. G. Leach, G. C. Lloyd-Jones, *J. Am. Chem. Soc.* **2020**, *142*, 14649–14663.
[37] F. Wang, T. Luo, J. Hu, Y. Wang, H. S. Krishnan, P. V. Jog, S. K. Ganesh, G. K. S. Prakash, G. A. Olah, *Angew. Chemie Int. Ed.* **2011**, *50*, 7153–7157.
[38] R. M. Bychek, V. V. Levterov, I. V. Sadkova, A. A. Tolmachev, P. K. Mykhailiuk, *Chem. Eur. J.* **2018**, *24*, 12291–12297.
[39] P. Dowd, S. C. Choi, *J. Am. Chem. Soc.* **1987**, *109*, 3493–3494.
[40] P. Dowd, S.-C. Choi, *Tetrahedron* **1989**, *45*, 77–90.
[41] W. L. F. Armarego, C. Chai, *Purification of Laboratory Chemicals*, Elsevier: Oxford, **2003**.
[42] H. Newman, T. L. Fields, *Tetrahedron* **1972**, *28*, 4051–4058.
[43] H. Liu, C. Sun, N.-K. Lee, R. F. Henry, D. Lee, *Chem. Eur. J.* **2012**, *18*, 11889–11893.

WILEY-VCH

Fluoroalkyl-containing 1,2-disubstituted cyclobutanes: advanced building blocks for medicinal chemistry

Oleksandr P. Demchuk,[a,b] Oleksandr V. Hryshchuk,[a,c] Bohdan V. Vashchenko,[a,c] Serhii A. Trofymchuk,[a] Dr. Kostiantyn P. Melnykov,[a,c] Artem Skreminskiy,[a] Prof. Dr. Dmitriy M. Volochnyuk,[a,b,c] Dr. Oleksandr O. Grygorenko*[a,c]

[a] O. P. Demchuk, O. V. Hryshchuk, B. V. Vashchenko, S. A. Trofymchuk, Dr. K. P. Melnykov, A. Skreminskiy, Prof. Dr. D. M. Volochnyuk Dr. O. O. Grygorenko
Enamine Ltd. (www.enamine.net),
Chervonotkatska Street 78, Kyiv 02094, Ukraine
[b] O. P. Demchuk, Prof. Dr. D. M. Volochnyuk,
Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanska Street 5, Kyiv 02660, Ukraine
[c] B. V. Vashchenko, Dr. K. P. Melnykov, Prof. Dr. D. M. Volochnyuk, Dr. O. O. Grygorenko
Taras Shevchenko National University of Kyiv
Volodymyrska Street 60, Kyiv 01601, Ukraine
E-mail: gregor@univ.kiev.ua (O. O. G)

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

Abstract: Synthesis of previously unavailable 1,2-disubstituted cyclobutane building blocks bearing mono-, di- and trifluoromethyl groups are disclosed. The key steps included deoxofluorination or TMAF-mediated nucleophilic substitution in the appropriate bifunctional cyclobutanes; for the CF_3-substituted derivatives, alternative methods based on cyano- or azidotrifluoromethylation of cyclobutene using the Togni reagent II were also proposed. All methods provided *trans* diastereomers of the target primary amines and carboxylic acids (6 representatives) and were suitable for their multigram preparation. Furthermore, dissociation constants (pK_a) and lipophilicity ($logP$) values were measured to evaluate the effect of the fluoroalkyl substituents on acidity/basicity and lipophilicity of the building blocks obtained.

Introduction

Fluorinated conformationally restricted motifs are widely recognized as promising chemotypes for modern drug discovery.[1–3] Introducing the fluorinated substituents into saturated ring systems has a complex impact on the physico-chemical properties, which is important to ADMET parameters of the corresponding derivatives including, for example, hERG inhibition or P-glycoprotein efflux.[4–6] A number of recent papers discussed the effect of mono-, di- and poly-fluorinated alkyl groups on total molecular polarity regarding the relative spatial arrangement of the fluorine atoms.[7–13]

Among the known fluorinated ring systems, cyclobutane derivatives are of special interest for modern synthetic and medicinal chemistry, partially due to the unique conformational properties of the cyclobutane ring.[14–20] In turn, several CF_3-, CHF_2- and CH_2F-containing cyclobutanes have found their application to date, including diagnostic agents for PET imaging, i.e. Fluciclovine (FACBC)[21] or its homolog FMACBC (**1**),[22,23] conformationally constrained fluorinated analogs of γ-aminobutyric acid (GABA) (**2**[22]) or serine/threonine (**3**[24,25]), the tools for solid-state ^{19}F NMR peptide studies, as well as reagents for the synthesis of peptidomimetics (Figure 1). CF_3-substitued cyclobutane derivatives were also studied as potent rat cannabinoid-1 receptor inhibitors,[26] as well as fungicides (e.g. **4**, a potent inhibitor of scytalone dehydratase).[27,28] The presence of the CHF_2 substituent in the cyclobutane moiety of compound **5** was found to be advantageous as compared to the non-fluorinated analogues in a series of compounds active against hepatitis C virus.[29]

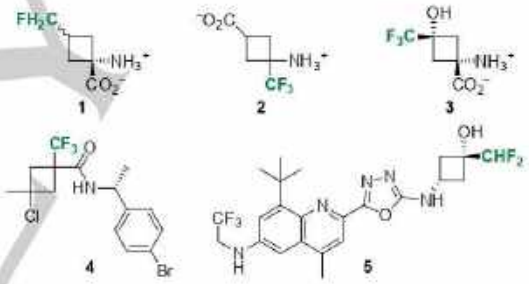


Figure 1. Some useful fluoroalkyl-substituted cyclobutanes

All the compounds shown in Figure 1 demonstrate the 1,3-substitution pattern of the fluorinated cyclobutane fragment; this is partially related to their more or less satisfactory synthetic accessibility. The known approaches to install the fluoroalkyl group onto the cyclobutane ring relied on deoxofluorination[30–33] or decarboxylative trifluoromethylation[34] of carboxylic acids, the addition of the Ruppert–Prakash reagent or its CHF_2-substituted analogue to C=O and C=N bonds,[35,36] fluoride-mediated nucleophilic substitution,[37] metal-catalyzed C(sp^3)–Br[38] and C(sp^3)–H[39] trifluoromethylation, direct side-chain C(sp^3)–H fluorination,[40] rearrangement of fluoroalkyl-substituted cyclopropanes,[41–43] difluoromethylation of cyclobutene with CHF_2I,[44] and other methods. Meanwhile, the corresponding 1,2-disubstituted fluorinated counterparts have been largely underrepresented in the literature to date.[38,41,44] Taking into account this fact, in this work, we have aimed at the preparation of simplest 1,2-disubstituted cyclobutane-derived building blocks **6–11** bearing mono-, di- and trifluoromethyl groups (Figure 2). Moreover, an effect of the fluoroalkyl substituents on the physico-chemical properties (i.e. acidity/basicity and lipophilicity) of the corresponding derivatives was also studied.

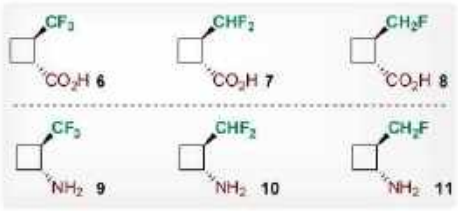
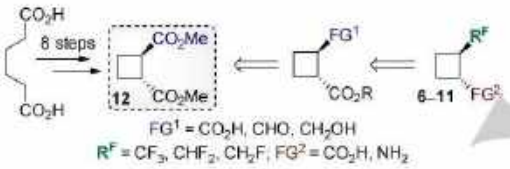


Figure 2. The target compounds of this work

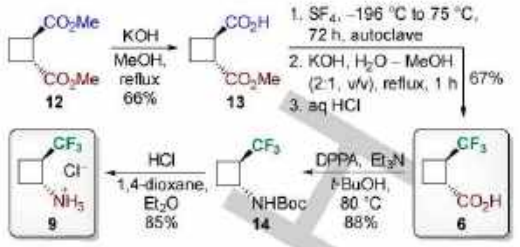
Results and Discussion

It was envisaged that target molecules **6–11** could be obtained from *trans*-cyclobutane-1,2-dicarboxylate **12**, with deoxofluorination or fluoride-mediated nucleophilic substitution as the key steps for the CF_3-/CHF_2- and CH_2F-substituted derivatives, respectively (Scheme 1). Intermediate **12** was prepared in eight steps (albeit many of them were performed in a one-pot manner) according to the literature protocols starting from adipic acid.[45,46]



Scheme 1. Retrosynthetic analysis of building blocks **6–11**

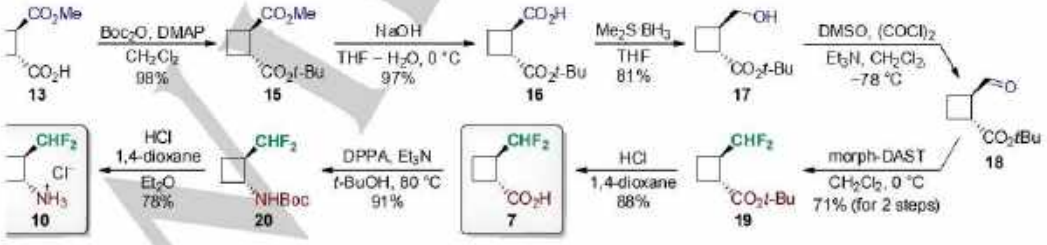
The reaction sequence proposed in this work commenced with the chemoselective hydrolysis of **12** into corresponding monoester **13** (66% yield). The deoxofluorination of **13** with SF_4 in a Hastelloy autoclave, followed by alkaline hydrolysis of the ester group provided the target product **6** in 67% yield (Scheme 2). The DPPA-mediated Curtius rearrangement of **6** in the presence of Et_3N in *t*-BuOH gave *N*-Boc-protected amine **14** (88% yield), that was treated with 4 M HCl – 1,4-dioxane in Et_2O to obtain hydrochloride **9** (85% yield).



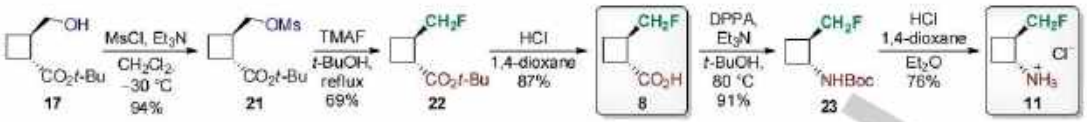
Scheme 2. Synthesis of CF_3-substituted building blocks **6** and **9** (relative configurations are shown)

Since chemoselective reduction of monoester **13** appeared to be unfruitful, it was transformed into *tert*-butyl counterpart **15** by the DMAP-mediated reaction with Boc_2O (98% yield), followed by selective alkaline hydrolysis of orthogonally protected derivative **16** with NaOH in THF – H_2O (97% yield) (Scheme 3). 2-(Hydroxymethyl)cyclobutanecarboxylate **17** thus obtained was oxidized into the corresponding aldehyde **18** using the Swern reagent. Although the product **18** could be isolated and fully characterized, it was advantageous to use derivative **18** directly in the key deoxofluorination step without additional isolation and purification due to its instability upon storage. The reaction with morph-DAST proceeded smoothly in CH_2Cl_2 and resulted in the formation of CHF_2-substituted cyclobutanecarboxylate **19** in 71% yield (over two steps). The subsequent acid-mediated *tert*-butyl group cleavage provided the target carboxylic acid **7** in 88% yield. The modified Curtius rearrangement in the presence of Et_3N in *t*-BuOH gave *N*-Boc-protected amine **20** (91% yield), that was involved in mild protecting group cleavage (4 M HCl – 1,4-dioxane in Et_2O) giving CHF_2-substituted cyclobutanamine hydrochloride **10** (78% yield).

Next, hydroxyester **17** was used for the preparation of CH_2F-substituted building blocks **8** and **11**. Thus, derivative **17** was transformed into corresponding mesylate **21** (94% yield), that was then involved in the TMAF-mediated nucleophilic substitution giving 2-(fluoromethyl)cyclobutanecarboxylate **22** (69% yield, Scheme 4). Ester **22** was smoothly transformed into the target carboxylic acid **8** upon treatment with HCl – 1,4-dioxane (87% yield).



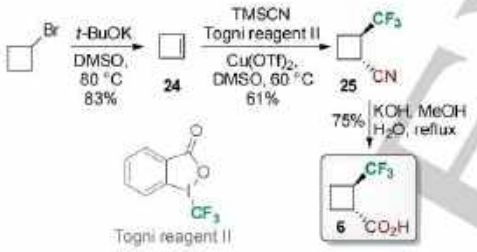
Scheme 3. Preparation of CHF_2-substituted building blocks **7** and **10** (relative configurations are shown)



Scheme 4. Synthesis of CH_2F-substituted building blocks **8** and **11** (relative configurations are shown)

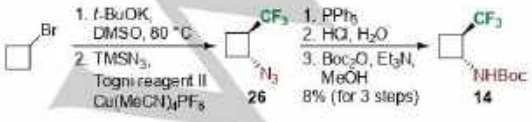
Further reactions included the modified Curtius rearrangement of **8** (91% yield) and Boc group cleavage in derivative **23** thus obtained, which gave hydrochloride **11** in 76% yield.

None of the steps in the aforementioned reaction sequences was accompanied by epimerization of the chiral centers, so that pure *trans* isomers of the target building blocks were obtained. Furthermore, all the steps were efficient and scalable, which allowed obtaining up to 65 g for carboxylic acids **6–8** and up to 30 g for the primary amines **9–11** in a single run. Nevertheless, the overall reaction sequences were rather lengthy, the shortest of them including 11 steps (in the case of **6**). Therefore, we have considered an alternative approach to the synthesis of **6** based on the cyanotrifluoromethylation of cyclobutene (**24**, obtained from bromocyclobutane). In particular, treatment of **24** with the Togni reagent II in the presence of TMSCN and $Cu(OTf)_2$ in DMSO provided *trans*-CF_3-substituted cyclobutanecarbonitrile **25** as a single diastereomer in 61% yield after distillation in *vacuo* (Scheme 5). Subsequent alkaline hydrolysis of nitrile **25** finished the synthesis of target building block **6** (75% yield).



Scheme 5. Alternative synthesis of compound **6** (relative configurations are shown)

Analogously, to shorten the synthetic scheme for the preparation of **9**, the direct azidotrifluoromethylation of *in-situ*-generated cyclobutene with the Togni reagent II and $TMSN_3$ in the presence of $Cu(MeCN)_4PF_6$ was performed. This reaction provided azidocyclobutane **26**, which was immediately involved in the Staudinger reaction followed by *N*-protection reaction with Boc_2O (Scheme 6). However, this approach was much efficient as less efficient as compared to the Curtius rearrangement of



Scheme 6. An alternative approach to **14** via azidotrifluoromethylation (relative configurations are shown)

carboxylic acid **6** – *N*-Boc-protected amine **14** was obtained in only 8% overall yield.

Physicochemical Properties. In order to evaluate an impact of the fluoroalkyl moiety on the carboxylate or amino groups at the cyclobutane core, pK_a values were measured for carboxylic acids **6–8** and amines **9–11** (Figure 3). It was found that the values varied in an expected manner within the studied series. Thus, introducing the fluoromethyl group into the cyclobutanecarboxylic acid, as well as the subsequent addition of the fluorine atoms increased acidity by 0.11 (**8**), 0.12 (**7**), and 0.39 (**6**) pK_a units, respectively. For the corresponding amines, a maximum difference of 1.03 pK_a units was observed for **9** and **10**, and the observed values followed a general rule-of-thumb: introducing the fluorine atoms into the γ-position of aliphatic amine leads to the decrease of pK_a by *ca.* 0.7 units per each γ-F.[4,13]

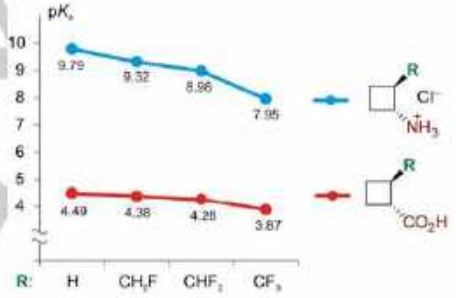
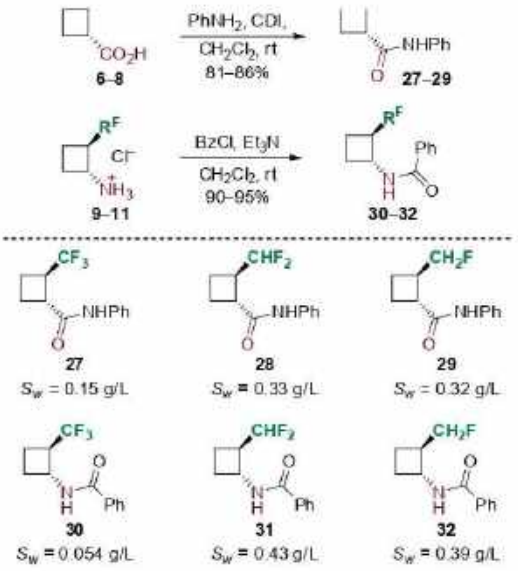


Figure 3. Measured pK_a values (23 °C) for building blocks **6–11**, as well as the parent cyclobutane derivatives (R = H[17])

To evaluate the effect of the fluoroalkyl substituents on the lipophilicity, compounds **6–8** and **9–11** were transformed into the corresponding amides **27–29** and **30–32**, respectively (Scheme 7). In the series of compounds **27–29**, the measured Log*P* values followed the trend reported in the literature for the acyclic fluorinated derivatives bearing the *F*-atoms at the *C*-3 position: $CH_2F \leq CHF_2 << CF_3$,[13] with ΔlogP of 0.11 for **27** and **28**, and 0.66 for **28** and **29** (Figure 4). Interestingly, introducing either CH_2F or CHF_2 group instead of the hydrogen atom slightly diminished the lipophilicity of the compounds in these series, even despite the increased carbon atom count. The isomeric cyclobutanamide-derived amides **30–32** demonstrated similar behavior, with slightly lower log*P* values as compared to **27–29**. Finally, aqueous solubility (S_w) of compounds **27–32** varied symbatically with their lipophilicity, with the CF_3-substituted derivatives being the least soluble.



Scheme 7. Synthesis and measured aqueous solubilities (S_w, 23 °C) of derivatives **27–32** (relative configurations are shown)

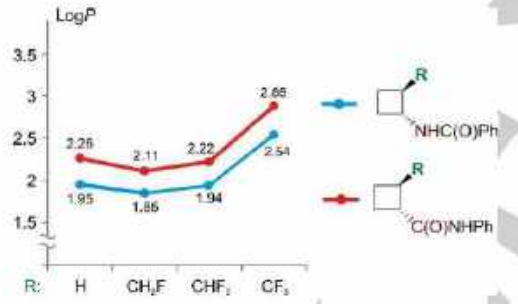


Figure 4. Measured Log*P* values (23 °C) for derivatives **27–32**, as well as the parent cyclobutanes (R = H[47])

Conclusions

Despite growing interest in fluoroalkyl-substituted cycloalkanes, the simplest 1,2-disubstituted cyclobutane derivatives were virtually omitted in the literature previously. In this work, we disclosed several efficient approaches to diastereomerically pure mono-, di- and trifluoromethyl-substituted cyclobutane building blocks, i.e. carboxylic acids and primary amines. A general but multistep approach to the target compounds relied on the deoxofluorination or fluoride-mediated nucleophilic substitution in the appropriate 1,2-difunctionalized cyclobutanes, in turn obtained from dimethyl *trans*-cyclobutane-1,2-dicarboxylate. For the CF_3-substituted cyclobutanes, a shorter reaction sequence was also proposed that involved cyanotrifluoromethylation of cyclobutene as the key step. The proposed methods and provided *trans*-1,2-disubstituted cyclobutane carboxylic acids (on up to 65 g scale in a single run) and the corresponding primary amines (up to 30 g);[50] therefore, these advanced fluorinated building blocks are now readily available for drug discovery programs.

The pK_a values of the target compounds, as well as the parent cyclobutanamine and cyclobutanecarboxylic acid followed the theoretically predicted trend and correlated with the literature data for acyclic analogues, which indicated that acidity/bacisity within the series was affected mainly by the extent of through-bond polarization caused by the fluorine atoms. The lipophilicity varied according to the following pattern: H > CH_2F ≤ CHF_2 << CF_3, which is also in accordance with the literature data for the acyclic counterparts. It is interesting to note that introducing CH_2F or even CHF_2 substituent into the cyclobutane ring instead of the hydrogen atom either did not change or increased hydrophilicity of the compounds, even despite higher carbon atom count.

Experimental Section

The solvents were purified according to the standard procedures.[48] All starting materials were available from Enamine Ltd. or purchased from other commercial sources. Melting points were measured on MPA100 OptiMelt automated melting point system. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^1H, $^{13}C\{^1H\}$ and ^{19}F NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^1H NMR, 126 MHz for $^{13}C\{^1H\}$ NMR and 470 MHz for ^{19}F NMR) and Varian Unity Plus 400 spectrometer (at 400 MHz for ^1H NMR, 101 MHz for $^{13}C\{^1H\}$ NMR and 376 MHz for ^{19}F NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^1H and $^{13}C\{^1H\}$ in $CDCl_3$, 2.50 and 39.52 ppm for ^1H and $^{13}C\{^1H\}$ in DMSO-d_6. Coupling constants (*J*) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)).

(1*R,2*R**)-2-(Methoxycarbonyl)cyclobutanecarboxylic acid (13).**[49] Dimethyl ester **12** (290 g, 1.68 mol) was dissolved in MeOH (2.5 L), and the solution was warmed up to reflux. Then, KOH (99.2 g, 1.77 mol) in MeOH (500 mL) was added dropwise for 90 min. The resulting mixture was refluxed for 30 min, then cooled to rt, and evaporated in *vacuo*. The residue was partitioned between H_2O (2.0 L) and CH_2Cl_2 (1.0 L). The aqueous layer was separated, acidified with 6 M aq HCl to pH = 1 and extracted with CH_2Cl_2 (3×500 mL). Combined layers were washed with brine (500 mL), dried over Na_2SO_4, filtered, and evaporated in *vacuo*. Yield 176 g (66%). Yellowish liquid. Starting material **16** (80.1 g) was also recovered by evaporation of CH_2Cl_2 solution obtained upon partitioning. Yellowish liquid. ^1H NMR (500 MHz, $CDCl_3$) δ 11.19 (s, 1H), 3.65 (s, 3H), 3.48 – 3.33 (m, 2H), 2.22 – 2.05 (m, 4H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 179.2, 173.9, 52.0, 40.1, 39.9, 21.9, 21.8. GC/MS (EI): *m/z* = 127 [M–OMe]$^+$, 140 [M–H_2O]$^+$. Anal. Calcd. for $C_7H_{10}O_4$: C 53.16; H 6.37. Found: C 53.49; H 6.71.

(1*R,2*R**)-2-(Trifluoromethyl)cyclobutanecarboxylic acid (6). Method A (from 13):** Monoester **13** (4.59 g, 29.0 mmol) was placed into a 60-mL Hastelloy autoclave, which was then cooled to –196 °C and evacuated. Next, SF_4 (9.40 g, 87.0 mmol) was condensed into the autoclave, and the reaction mixture was kept at 75 °C. The completion of the reaction was

monitored by ^{19}F NMR spectra (ca. 72 h). Then, the gaseous products were released carefully, and the reaction mixture was poured into a solution of KOH (6.51 g, 116 mmol) in H_2O – MeOH (2:1, v/v, 45 mL). The resulting mixture was refluxed for 1 h, then cooled to rt, and evaporated in *vacuo*. The residue was acidified with 12 M aq HCl (15 mL) and extracted with Et_2O (2×30 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated in *vacuo*. The crude product was purified by distillation in *vacuo*. Yield 3.27 g (67%). **Method B (from 25):** Compound **25** (74.1 g, 0.497 mol) was added to a solution of KOH (111 g, 1.99 mol) in H_2O (1 L), and the resulting mixture was refluxed overnight. Then, it was washed with CH_2Cl_2 (2×500 mL), acidified to pH = 1 with 6 M HCl, and extracted with CH_2Cl_2 (2×500 mL). The combined organic layers were washed with brine (500 mL), dried over Na_2SO_4, filtered, and evaporated. The residue was purified by distillation in *vacuo* (59–60 °C, 2 mbar). Yield 62.6 g (75%). Colorless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 11.57 (s, 1H), 3.41 – 3.09 (m, 2H), 2.29 – 2.08 (m, 4H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 179.2, 125.9 (q, J = 276 Hz), 39.0 (q, J = 31.5 Hz), 37.4 (q, J = 3.5 Hz), 21.5, 17.8 (q, J = 3.3 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –74.5. GC/MS (EI): m/z = 99 [M–CF_3]$^+$, 124 [M–CO_2]$^+$, 168 [M]$^+$. Anal. Calcd. for $C_6H_7F_3O_2$: C 42.87; H 4.20. Found: C 42.73; H 4.07.

***tert*-Butyl ((1*R**,2*R**)-2-(trifluoromethyl)cyclobutyl)carbamate (14).** **Method A (from 6):** Et_3N (16.6 g, 0.164 mol) was added to a solution of **6** (25.0 g, 0.149 mol) in *t*-BuOH (250 mL), and the resulting mixture was warmed up to 75 °C. DPPA (41.0 g, 0.149 mol) was added dropwise at 75 °C, the resulting mixture was stirred at 80 °C overnight, then evaporated in *vacuo* to dryness. The residue was partitioned between saturated aq K_2CO_3 (250 mL) and CH_2Cl_2 (400 mL), the organic layer was separated, the aqueous phase was back-extracted with CH_2Cl_2 (250 mL). Combined organic layers were washed with brine (250 mL), dried over Na_2SO_4, filtered, and evaporated in *vacuo*. Yield 31.3 g (88%). **Method B (from cyclobutene):** Togni reagent II (78.2 g, 0.248 mol) and $Cu(MeCN)_4PF_6$ (1.85 g, 4.96 mmol) were dissolved in MeCN (1 L). Then, cyclobutene[51] (16.1 g, 0.298 mol; see preparation of **25**) and $TMSN_3$ (42.9 g, 372 mmol) were added under argon atmosphere, the mixture was stirred at rt for 12 h, and PPh_3 (102 g, 0.391 mol) was added in portions. When the gas evolution ceased, 4 M aq HCl (200 mL) was added at rt, the resulting mixture was stirred at rt overnight, then evaporated. The residue was partitioned between H_2O (250 mL) and $CHCl_3$ (250 mL), the organic phase was separated, the aqueous phase was washed with $CHCl_3$ (250 mL). Organic layers were combined, and saturated aq $NaHCO_3$ was added to pH = 9. The resulting mixture was diluted with MeOH (250 mL), and Boc_2O (81.1 g, 0.372 mol) was added dropwise at rt. The reaction mixture was stirred at rt overnight, then most of MeOH was evaporated in *vacuo*. The aqueous residue was extracted with CH_2Cl_2 (2×200 mL), the combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and evaporated in *vacuo*. The residue was purified by column chromatography using gradient hexanes – *t*-BuOMe as eluent. Yield 4.73 g (8%). Colorless solid; mp 102–103 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 4.79 (s, 1H), 4.18 (s, 1H), 3.05 – 2.62 (m, 1H), 2.27 (q, J = 8.9 Hz, 1H), 2.02 – 1.86 (m, 2H), 1.80 – 1.74 (m, 1H), 1.44 (s, 9H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 154.5, 125.7 (q, J = 277 Hz), 79.8, 45.5, 28.2, 26.6, 14.8 (q, J = 2.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –72.7. MS (ESI): m/z = 262 [M+Na]$^+$. Anal. Calcd. for $C_{10}H_{16}F_3NO_2$: C 50.21; H 6.74; N 5.85. Found: C 49.96; H 6.34; N 5.57.

(1*R,2*R**)-2-(Trifluoromethyl)cyclobutanaminium chloride (9).** 4 M HCl – 1,4-dioxane (70 mL) was added to a solution of **14** (31.3 g, 0.131 mol) in Et_2O (300 mL), and the resulting mixture was stirred at rt overnight. The precipitate formed was filtered, washed with Et_2O (300 mL), and dried in *vacuo* (0.5 mbar). Yield 19.5 g (85%). Colorless solid; mp 194–197 °C. ^1H NMR (500 MHz, DMSO-d_6) δ 8.61 (s, 3H), 3.84 – 3.74 (m, 1H), 3.56 – 3.46 (m, 1H), 2.22 – 2.03 (m, 3H), 1.89 – 1.79 (m, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 125.5 (q, J = 276.5 Hz), 43.5 (q, J = 3.8 Hz), 40.9 (q, J = 30.6 Hz), 22.8, 15.20 (q, J = 3.5 Hz). ^{19}F NMR (470 MHz, DMSO-d_6) δ –70.6. GC/MS (EI): m/z = 120 [M–HCl–F]$^+$. MS (ESI): m/z = 140 [M+H]$^+$. Anal. Calcd. for $C_5H_9ClF_3N$: C 34.20; H 5.17; N 7.98; Cl 20.19. Found: C 34.08; H 4.78; N 7.60; Cl 19.91.

(1*R,2*R**)-1-*tert*-Butyl 2-methyl cyclobutane-1,2-dicarboxylate (15).** Boc_2O (254 g, 1.16 mol) was added dropwise to a solution of **13** (176 g, 1.11 mol) and DMAP (4.07 g, 33.3 mmol) in CH_2Cl_2 (1.5 L). When the gas evolution ceased, the resulting mixture was washed with 1 M aq HCl (500 mL), brine (500 mL), dried over Na_2SO_4, filtered, and evaporated in *vacuo*. Yield 233 g (98%). Yellowish liquid. ^1H NMR (500 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.39 – 3.18 (m, 2H), 2.14 – 2.07 (m, 4H), 1.41 (s, 9H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 174.2, 172.8, 80.5, 51.7, 41.5, 40.1, 28.0, 21.9, 21.5. MS (ESI): m/z = 237 [M+Na]$^+$. GC/MS (EI): m/z = 141 [M–Ot-Bu]$^+$, 183 [M–OMe]$^+$. Anal. Calcd. for $C_{11}H_{18}O_4$: C 61.66; H 8.47. Found: C 61.86; H 8.57.

(1*R,2*R**)-2-(*tert*-Butoxycarbonyl)cyclobutanecarboxylic acid (16).** Compound **15** (233 g, 1.09 mol) was dissolved in THF – H_2O (2.4 L, 2:1, v/v), and the solution was cooled to 0 °C. Then, 4 M aq NaOH (545 mL, 2.18 mol) was added dropwise at 0 °C (NOTE: the temperature should not exceed 5 °C). The resulting mixture was stirred at 0 °C for 2 h, then diluted with H_2O (1 L), and washed with CH_2Cl_2 (1 L). The aqueous layer was acidified to pH = 2 with 2 M HCl and extracted with CH_2Cl_2 (3×1 L). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated in *vacuo*. Yield 212 g (97%). Colorless crystals; mp 49–52 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 11.30 (s, 1H), 3.57 – 3.01 (m, 2H), 2.18 – 2.06 (m, 4H), 1.40 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 179.6, 172.8, 80.8, 41.3, 40.2, 28.0, 21.8, 21.5. MS (ESI): m/z = 157 [M–CO_2+H]$^+$, 199 [M–H]$^+$. Anal. Calcd. for $C_{10}H_{16}O_4$: C 59.98; H 8.05. Found: C 60.18; H 8.18.

(1*R,2*R**)-*tert*-Butyl 2-(hydroxymethyl)cyclobutanecarboxylate (17).** A solution of **16** (212 g, 1.06 mol) in THF (2 L) was cooled to 0 °C, and 10 M BH_3SMe_2 (159 mL, 1.59 mol) was added at 0 °C under argon atmosphere (NOTE: the temperature should not exceed 5 °C). Then, the reaction mixture was warmed up to rt, then carefully poured into pre-cooled MeOH (1 L), and the resulting mixture was evaporated in *vacuo*. The residue was diluted with MeOH (1 L) and evaporated in *vacuo*. Yield 159 g (81%). Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 3.63 (dd, J = 10.8, 5.2 Hz, 1H), 3.57 (dd, J = 10.8, 7.6 Hz, 1H), 2.85 – 2.76 (m, 1H), 2.63 (dtd, J = 17.0, 8.5, 5.1 Hz, 1H), 2.15 – 2.08 (m, 2H), 1.99 (tdd, J = 11.4, 8.3, 2.4 Hz, 1H), 1.89 – 1.81 (m, 1H), 1.70 – 1.61 (m, 1H), 1.43 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 174.3, 80.5, 66.1, 42.5, 41.5, 28.0, 21.1, 20.3. MS (ESI): m/z = 209 [M+Na]$^+$. GC/MS (EI): m/z = 113 [M–Ot-Bu]$^+$, 131 [M–H_2C=$C(CH_3)_2$]$^+$. Anal. Calcd. for $C_{10}H_{18}O_3$: C 64.49; H 9.74. Found: C 64.34; H 9.84.

(1*R,2*R**)-*tert*-Butyl 2-formylcyclobutanecarboxylate (18).** A solution of DMSO (43.3 g, 0.554 mol) in CH_2Cl_2 (50 mL) was added dropwise to a solution of $(COCl)_2$ (64.9 g, 0.511 mol) in CH_2Cl_2 (1 L) at –78 °C under argon atmosphere. After stirring at –78 °C for 5 min, a solution of **17** (79.3 g, 0.426 mol) in CH_2Cl_2 (50 mL) was added dropwise maintaining the temperature below –65 °C. The resulting mixture was stirred for 5 min, and Et_3N (108 g, 1.07 mol) was added dropwise at –70 °C. The reaction mixture was warmed up to 0 °C and quenched with H_2O (500 mL). The organic layer was separated, washed with 1 M aq HCl (500 mL), brine (500 mL), and dried over Na_2SO_4. The compound was used in the next step as a solution in CH_2Cl_2 (1 L), while a small aliquot was evaporated in *vacuo* to dryness to obtain the spectral data. Yellowish oil. ^1H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 3.46 – 3.31 (m, 1H), 3.31 – 3.04 (m, 1H), 2.22 – 2.04 (m, 4H), 1.39 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 200.4, 172.8, 80.7, 47.8, 38.8, 28.0, 21.6, 18.8.

(1*R,2*R**)-*tert*-Butyl 2-(difluoromethyl)cyclobutanecarboxylate (19).** A solution of **18** in CH_2Cl_2 (1 L) was cooled to 0 °C, and a solution of morph-DAST (112 g, 0.639 mol) in CH_2Cl_2 (150 mL) was added dropwise at 0 °C (NOTE: the temperature should not exceed 5 °C). Then, the reaction mixture was warmed up to rt, stirred for 1 h, then carefully poured into saturated aq $NaHCO_3$ (2 L), and the resulting mixture was stirred until the gas evolution ceased. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (500 mL). THE combined organic layers were washed with brine (250 mL), dried over Na_2SO_4, filtered, and evaporated in *vacuo*. The crude product was

purified by distillation in *vacuo* (bp 33–34 °C / 0.5 mbar). Yield 62.3 g (71% from **17**). Colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (td, *J* = 56.9, 1.8 Hz, 1H), 3.22 – 3.05 (m, 1H), 3.05 – 2.90 (m, 1H), 2.27 – 2.13 (m, 2H), 2.10 – 1.95 (m, 2H), 1.49 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 177.2, 120.4 (t, *J* = 240 Hz), 85.0, 44.5 (t, *J* = 22.6 Hz), 42.6 (t, *J* = 5.8 Hz), 32.4, 25.9, 21.2 (t, *J* = 5.8 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ –124.1 (ddd, *J* = 283, 56.9, 14.0 Hz), –125.3 (ddd, *J* = 283, 56.9, 17.1 Hz). GC/MS (EI): *m/z* = 151 [M–H_2C=$C(CH_3)_2$]$^+$, 191 [M–Me]$^+$. Anal. Calcd. for $C_{10}H_{16}F_2O_2$: C 58.24; H 7.82. Found: C 58.38; H 7.81.

(1*R,2*R**)-2-(Difluoromethyl)cyclobutanecarboxylic acid (7).** *tert*-Butyl ester **19** (62.3 g, 0.302 mol) was dissolved in 1,4-dioxane (500 mL) and 4 M HCl – 1,4-dioxane (100 mL) was added. The resulting solution was stirred at rt for 48 h and evaporated in *vacuo*. The residue was purified by distillation in *vacuo* (66–68 °C, 0.5 mbar) followed by dissolving in CH_2Cl_2 (500 mL) and extraction with saturated aq. $NaHCO_3$ (2×500 mL). The combined aqueous phases were washed with CH_2Cl_2 (500 mL), acidified with 6 M aq HCl to pH = 1, extracted with CH_2Cl_2 (2×500 mL), dried over Na_2SO_4, filtered, and evaporated in *vacuo*. Yield 39.9 g (88%). Colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.91 (s, 1H), 5.79 (td, *J* = 56.8, 3.1 Hz, 1H), 3.34 – 3.14 (m, 1H), 3.14 – 2.93 (m, 1H), 2.37 – 2.13 (m, 2H), 2.13 – 1.90 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 179.8, 115.6 (t, *J* = 240 Hz), 39.8 (t, *J* = 22.8 Hz), 36.8 (t, *J* = 6.0 Hz), 21.7, 17.0 (t, *J* = 5.6 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ –125.00 (ddd, *J* = 265, 56.8, 15.5 Hz), –125.41 (ddd, *J* = 265, 56.8, 16.1 Hz). MS (ESI): *m/z* = 149 [M–H]$^-$. Anal. Calcd. for $C_6H_8F_2O_2$: C 48; H 5.37. Found: C 48.07; H 5.22.

***tert*-Butyl ((1*R**,2*R**)-2-(Difluoromethyl)cyclobutyl)carbamate (20).** Et_3N (29.6 g, 0.293 mol) was added to a solution of **7** (39.9 g, 0.266 mol) in *t*-BuOH (400 mL), and the resulting mixture was warmed up to 75 °C. DPPA (73.2 g, 0.266 mol) was added dropwise at 75 °C, the reaction mixture was stirred at 80 °C overnight and then evaporated in *vacuo* to dryness. The residue was partitioned between saturated aq K_2CO_3 (500 mL) and CH_2Cl_2 (500 mL), the organic phase was separated, the aqueous phase was extracted with CH_2Cl_2 (250 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and evaporated in *vacuo*. Yield 53.6 g (91%). Beige solid, mp 50–52 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (t, *J* = 56.8 Hz, 1H), 4.71 (s, 1H), 4.13 – 3.96 (m, 1H), 2.65 – 2.44 (m, 1H), 2.25 (dt, *J* = 8.7, 4.4 Hz, 1H), 1.86 – 1.75 (m, 3H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 154.8, 115.9 (t, *J* = 240 Hz), 79.7, 46.9, 45.3, 28.3, 26.7, 13.8 (t, *J* = 5.4 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ –126.5 (dd, *J* = 285, 56.8 Hz), –129.4 (ddd, *J* = 285, 56.8, 19.2 Hz). MS (ESI): *m/z* = 244 [M+Na]$^+$. Anal. Calcd. for $C_{10}H_{17}F_2NO_2$: C 54.29; H 7.75; N 6.33. Found: C 54.42; H 7.59; N 6.56.

(1*R,2*R**)-2-(Difluoromethyl)cyclobutan-1-aminium chloride (10).** 4 M HCl – 1,4-dioxane (100 mL) was added to a solution of **20** (53.6 g, 0.242 mol) in Et_2O (500 mL), and the resulting mixture was stirred at rt overnight. The precipitate formed was filtered, washed with Et_2O (500 mL), and dried in *vacuo* (0.5 mbar). Yield 29.8 g (78%). Greyish powder, mp 221–223 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (s, 3H), 6.20 (td, *J* = 56.8, 3.3 Hz, 1H), 3.71 – 3.51 (m, 1H), 3.14 – 2.87 (m, 1H), 2.17 – 1.99 (m, 2H), 1.95 – 1.84 (m, 1H), 1.84 – 1.72 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 115.5 (t, *J* = 238 Hz), 43.6 (dd, *J* = 9.6, 5.4 Hz), 41.7 (t, *J* = 22.9 Hz), 23.2, 14.0 (t, *J* = 5.4 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ –122.9 (d, *J* = 284 Hz), –125.8 (d, *J* = 284 Hz). MS (ESI): *m/z* = 122 [M–HCl+H]$^+$. Anal. Calcd. for $C_5H_{10}ClF_2N$: C 38.11; H 6.40; N 8.89; Cl 22.50. Found: C 38.41; H 6.28; N 9; Cl 22.28.

(1*R,2*R**)-*tert*-Butyl 2-(((methylsulfonyl)oxy)methyl)cyclobutanecarboxylate (21).** Et_3N (47.9 g, 0.473 mol) was added to a solution of **17** (80.0 g, 0.430 mol) in CH_2Cl_2 (1 L), and the resulting mixture was cooled to –30°C. A solution of MsCl (51.7 g, 0.452 mol) in CH_2Cl_2 (100 mL) was added dropwise under argon atmosphere while maintained at –30°C (NOTE: the temperature should not exceed –20°C). The resulting mixture was warmed up to rt, washed with water (500 mL), brine (500 mL), dried over Na_2SO_4, filtered, and evaporated in *vacuo*. The compound was used in the next step without additional purification. Yield 107 g (94%). Yellowish solid; mp 58–61 °C (the compound decomposed upon heating). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.18 (d, *J* = 4.9 Hz, 2H), 3.01 – 2.99 (m, 3H), 2.98 – 2.76 (m, 2H), 2.16 – 2.03 (m, 2H), 2.00 – 1.92 (m, 1H), 1.84 – 1.77 (m, 1H), 1.42 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 173.1, 80.5, 71.6, 41.1, 37.5, 37.3, 28.0, 21.4, 20.5. MS (ESI): *m/z* = 287 [M+Na]$^+$.

(1*R,2*R**)-*tert*-Butyl 2-(fluoromethyl)cyclobutanecarboxylate (22).** TMAF (48.9g, 0.525 mol) was added to a solution of **21** (107 g, 0.404 mol) in *t*BuOH (1 L, pre-distilled over CaH_2). The resulting mixture was refluxed for 18 h and then evaporated in *vacuo* to dryness. The residue was dissolved in CH_2Cl_2 (1 L), washed with H_2O (2×500 mL), brine (500 mL), dried over Na_2SO_4, filtered, and evaporated in *vacuo*. The residue was purified by distillation in *vacuo* (bp 36–37 °C / 0.5 mbar). Yield 52.4 g (69%). Colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.33 (dt, *J* = 47.9, 4.0 Hz, 2H), 3.02 – 2.85 (m, 1H), 2.83 – 2.66 (m, 1H), 2.12 – 1.97 (m, 2H), 1.91 – 1.81 (m, 2H), 1.40 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 173.6, 84.6 (d, *J* = 167 Hz), 80.0, 40.1 (d, *J* = 5.7 Hz), 39.0 (d, *J* = 20.4 Hz), 28.0, 21.2, 19.5 (d, *J* = 5.6 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ –226.4 (td, *J* = 47.9, 26.7 Hz). GC/MS (EI): *m/z* = 133 [M–H_2C=$C(CH_3)_2$]$^+$, 173 [M–Me]$^+$. Anal. Calcd. for $C_{10}H_{17}FO_2$: C 63.81; H 9.10. Found: C 63.43; H 8.81.

(1*R,2*R**)-2-(Fluoromethyl)cyclobutanecarboxylic acid (8).** *tert*-Butyl ester **21** (52.4 g, 0.279 mol) was dissolved in 1,4-dioxane (500 mL), and 4 M HCl – 1,4-dioxane (100 mL) was added. The resulting solution was stirred at rt for 48 h and evaporated in *vacuo*. The residue was purified by distillation in *vacuo* (73–75 °C, 0.5 mbar). Yield 32.0 g (87%). Colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.70 (s, 1H), 4.38 (dddd, *J* = 47.6, 22.2, 9.7, 4.3 Hz, 2H), 3.19 – 3.00 (m, 1H), 2.86 (dqt, *J* = 26.3, 8.6, 4.2 Hz, 1H), 2.23 – 2.09 (m, 2H), 1.95 (dd, *J* = 11.0, 7.4 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 180.8, 84.3 (d, *J* = 167 Hz), 39.0 (d, *J* = 1.3 Hz), 38.9 (d, *J* = 13.5 Hz), 21.2, 19.5 (d, *J* = 5.7 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ –226.8 (td, *J* = 47.6, 26.8 Hz). GC/MS (EI): *m/z* = 113 [M–F]$^+$, 132 [M]$^+$. Anal. Calcd. for $C_6H_9FO_2$: C 54.54; H 6.87. Found: C 54.61; H 6.91.

***tert*-Butyl ((1*R**,2*R**)-2-(fluoromethyl)cyclobutyl)carbamate (23).** Et_3N (26.9 g, 0.266 mol) was added to a solution of **8** (32.0 g, 0.242 mol) in *t*-BuOH (350 mL), and the resulting mixture was warmed up to 75 °C. DPPA (66.6 g, 0.242 mol) was added dropwise at 75 °C, the resulting mixture was stirred at 80 °C overnight and then evaporated in *vacuo* to dryness. The residue was partitioned between saturated aq K_2CO_3 (500 mL) and CH_2Cl_2 (500 mL), the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (250 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and evaporated in *vacuo*. Yield 44.8 g (91%). Colorless solid, mp 56–58 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.73 (s, 1H), 4.42 (dd, *J* = 47.6, 4.8 Hz, 2H), 4.01 – 3.87 (m, 1H), 2.54 – 2.37 (m, 1H), 2.27 – 2.19 (m, 1H), 1.86 – 1.70 (m, 2H), 1.62 – 1.54 (m, 1H), 1.42 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.9, 84.2 (d, *J* = 166 Hz), 79.3, 47.0, 45.1 (d, *J* = 19.7 Hz), 28.3, 27.2, 16.9. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –224.7. MS (ESI): *m/z* = 226 [M+Na]$^+$. Anal. Calcd. for $C_{10}H_{18}FNO_2$: C 59.09; H 8.93; N 6.89. Found: C 58.70; H 8.55; N 6.94.

(1*R,2*R**)-2-(Fluoromethyl)cyclobutanaminium chloride (11).** 4 M HCl – 1,4-dioxane (100 mL) was added to a solution of **23** (44.8 g, 0.221 mol) in Et_2O (500 mL), and the resulting mixture was stirred at rt overnight. The precipitate formed was filtered, washed with Et_2O (500 mL), and dried in *vacuo* (0.5 mbar). Yield 23.4 g (76%). Colorless solid, mp 186–189 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.44 (s, 3H), 4.56 – 4.35 (m, 2H), 3.50 – 3.43 (m, 1H), 2.86 – 2.67 (m, 1H), 2.09 – 1.96 (m, 2H), 1.91 – 1.82 (m, 1H), 1.69 – 1.58 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 83.6 (d, *J* = 163 Hz), 45.4 (d, *J* = 7.5 Hz), 40.7 (d, *J* = 20.4 Hz), 23.8, 17.5 (d, *J* = 5.2 Hz). ^{19}F NMR (470 MHz, DMSO-d_6) δ –225.7 (td, *J* = 47.6, 26.2 Hz). MS (ESI): *m/z* = 104 [M–HCl+H]$^+$. Anal. Calcd. for $C_5H_{11}ClFN$: C 43.02; H 7.94; N 10.03; Cl 25.39. Found: C 43.28; H 8.13; N 10.34; Cl 24.99.

(1*R,2*R**)-2-(Trifluoromethyl)cyclobutanecarbonitrile (25).** A solution of bromocyclobutane (300 g, 2.22 mol) in DMSO (100 mL) was added dropwise at 75 °C for 40 min under argon atmosphere to a vigorously stirred suspension of *t*-BuOK (660 g, 2.66 mol) in DMSO (2.5 L) placed in the 5 L reaction vessel with a water-cooled condenser attached to a transfer manifold. Then, the reaction mixture was stirred at 70 °C for 2 h, the manifold system was closed off from the reaction vessel, and the material collected in the first trap was slowly warmed. Cyclobutene was distilled at 2–3 °C into the second cooled trap.[51] A solution of TMSCN (74.0 g, 0.746 mol) and cyclobutene (32.3 g, 0.596 mol) in DMSO (100 mL) was added dropwise to a solution of Togni II reagent (157 g, 0.497 mol) and $Cu(OTf)_2$ (8.99 g, 24.9 mmol) in DMSO (1 L) under argon atmosphere maintaining the temperature below 60 °C (CAUTION: highly exothermic reaction occured upon addition of the solution of TMSCN and cyclobutene). The reaction mixture was stirred at 60 °C for 2 h, then extracted with Et_2O (3×400 mL). Combined organic layers were washed with H_2O (500 mL), brine, dried and evaporated in *vacuo*. Yield 74.1 g (61%). The compound was obtained with satisfactory purity after distillation in *vacuo* and used in the next step without additional purification. Brownish liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 3.35 – 3.17 (m, 2H), 2.44 – 2.30 (m, 2H), 2.20 (td, *J* = 8.6, 6.1 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 124.9 (q, *J* = 276 Hz), 119.2, 41.4 (q, *J* = 32.2 Hz), 22.6, 21.9 (q, *J* = 4.1 Hz), 19.3 (q, *J* = 3.0 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –74.8. GC/MS (EI): *m/z* = 122 [M–HCN]$^+$, 149 [M]$^+$.

(1*R,2*R**)-*N*-Phenyl-2-(trifluoromethyl)cyclobutanecarboxamide (27).** CDI (1.16 g, 7.14 mmol) was added in portions to a solution of **6** (1.00 g, 5.95 mmol) in CH_2Cl_2 (15 mL) at rt. When the gas evolution ceased, $PhNH_2$ (720 mg, 7.74 mmol) was added in one portion at rt, and the resulting mixture was stirred at rt overnight. Then, the reaction mixture was washed with 1 M aq HCl (10 mL), brine (10 mL), dried over Na_2SO_4, and evaporated in *vacuo*. Yield 1.23 g (85%). Colorless solid; mp 95–98 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.9 Hz, 2H), 7.47 (s, 1H), 7.29 (t, *J* = 7.9 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 3.42 – 3.30 (m, 1H), 3.29 – 3.16 (m, 1H), 2.40 – 2.25 (m, 1H), 2.21 – 2.03 (m, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 170.3, 137.5, 129.0, 126.3 (q, *J* = 276 Hz), 124.6, 120.2, 40.1 (q, *J* = 3.0 Hz), 39.2 (q, *J* = 30.8 Hz), 21.0, 17.7 (q, *J* = 3.4 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –73.6. MS (ESI): *m/z* = 244 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{12}F_3NO$: C 59.26; H 4.97; N 5.76. Found: C 58.98; H 5.12; N 5.95.

(1*R,2*R**)-2-(Difluoromethyl)-*N*-phenylcyclobutanecarboxamide (28).** CDI (1.30 g, 7.99 mmol) was added in portions to a solution of **7** (1.00 g, 6.66 mmol) in CH_2Cl_2 (15 mL) at rt. Since the gas evolution ceased, $PhNH_2$ (806 mg, 8.66 mmol) was added in one portion at rt, and the resulting mixture was stirred at rt overnight. Then, the reaction mixture was washed with 1 M aq HCl (10 mL), brine (10 mL), dried over Na_2SO_4, and evaporated in *vacuo*. Yield 1.22 g (81%). Colorless solid; mp 102–105 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.10 (t, *J* = 7.2 Hz, 1H), 5.83 (t, *J* = 56.9 Hz, 1H), 3.29 – 3.19 (m, 1H), 3.19 – 3.01 (m, 1H), 2.41 – 2.30 (m, 1H), 2.17 – 2.08 (m, 1H), 2.03 – 1.96 (m, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 171.2, 137.8, 129.0, 124.4, 119.9, 116.4 (t, *J* = 239 Hz), 40.1 (t, *J* = 21.8 Hz), 39.1 (t, *J* = 5.2 Hz), 21.0, 17.1 (dd, *J* = 7.1, 4.8 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –122.3 (d, *J* = 283 Hz), –125.1 (d, *J* = 283 Hz). MS (ESI): *m/z* = 226 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{13}F_2NO$: C 63.99; H 5.82; N 6.22. Found: C 63.68; H 5.61; N 5.85.

(1*R,2*R**)-2-(Fluoromethyl)-*N*-phenylcyclobutanecarboxamide (29).** CDI (1.47 g, 9.08 mmol) was added in portions to a solution of **8** (1.00 g, 7.57 mmol) in CH_2Cl_2 (15 mL) at rt. Since the gas evolution ceased, $PhNH_2$ (916 mg, 9.84 mmol) was added in one portion at rt, and the resulting mixture was stirred at rt overnight. Then, the reaction mixture was washed with 1 M aq HCl (10 mL), brine (10 mL), dried over Na_2SO_4, and evaporated in *vacuo*. Yield 1.35 g (86%). Colorless solid; mp 108–109 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 9.79 (s, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.28 (t, *J* = 7.7 Hz, 2H), 7.02 (t, *J* = 7.5 Hz, 1H), 4.42 (dd, *J* = 47.8, 4.8 Hz, 2H), 3.14 – 3.03 (m, 1H), 2.86 (dtd, *J* = 27.6, 8.6, 3.9 Hz, 1H), 2.17 – 1.98 (m, 2H), 1.97 – 1.74 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 172.2, 139.7, 129.0, 123.5, 119.6, 85.5 (d, *J* = 164.3 Hz), 41.7 (d, *J* = 5.7 Hz), 37.9 (d, *J* = 19.6 Hz), 21.7, 19.7 (d, *J* = 6.7 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ –223.0. MS (ESI): *m/z* = 208 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{14}FNO$: C 69.55; H 6.81; N 6.76. Found: C 69.38; H 6.47; N 6.74.

***N*-((1*R**,2*R**)-2-(Trifluoromethyl)cyclobutyl)benzamide (30).** Et_3N (633 mg, 6.27 mmol) was added to a suspension of **9** (1.00 g, 5.70 mmol) in CH_2Cl_2 (15 mL) at rt. Then, BzCl (841 mg, 5.99 mmol) was added dropwise at rt (NOTE: the temperature should not exceed 25 °C). The resulting mixture was stirred at rt for 2 h, then washed with 1 M aq HCl (10 mL), brine (10 mL), dried over Na_2SO_4, and evaporated in *vacuo*. Yield 1.32 g (95%). Colorless solid; mp 148–149 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.83 (d, *J* = 8.4 Hz, 1H), 7.89 – 7.78 (m, 2H), 7.60 – 7.51 (m, 1H), 7.48 (t, *J* = 7.3 Hz, 2H), 4.70 – 4.53 (m, 1H), 3.33 – 3.21 (m, 1H), 2.32 – 2.15 (m, 1H), 2.15 – 2.03 (m, 1H), 2.03 – 1.89 (m, 1H), 1.87 – 1.61 (m, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 165.8, 134.4, 131.8, 128.7, 127.6, 126.7 (q, *J* = 276 Hz), 44.30 (q, *J* = 29.0 Hz), 44.0 (q, *J* = 3.9 Hz), 26.3, 14.9 (q, *J* = 2.9 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ –71.2. MS (ESI): *m/z* = 244 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{12}F_3NO$: C 59.26; H 4.97; N 5.76. Found: C 59.58; H 4.80; N 5.49.

***N*-((1*R**,2*R**)-2-(Difluoromethyl)cyclobutyl)benzamide (31).** Et_3N (641 mg, 6.99 mmol) was added to a suspension of **10** (1.00 g, 6.35 mmol) in CH_2Cl_2 (15 mL) at rt. Then, BzCl (937 mg, 6.67 mmol) was added dropwise at rt (NOTE: the temperature should not exceed 25 °C). The resulting mixture was stirred at rt for 2 h, then washed with 1 M aq HCl (10 mL), brine (10 mL), dried over Na_2SO_4, and evaporated in *vacuo*. Yield 1.31 g (92%). Beige solid; mp 100–102 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, *J* = 7.6 Hz, 1H), 7.85 (d, *J* = 7.4 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.4 Hz, 2H), 6.13 (td, *J* = 57.0, 3.7 Hz, 1H), 4.50 – 4.36 (m, 1H), 2.87 (tdd, *J* = 21.1, 8.8, 4.0 Hz, 1H), 2.30 – 2.11 (m, 1H), 2.11 – 1.90 (m, 1H), 1.91 – 1.75 (m, 1H), 1.76 – 1.48 (m, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 165.9, 134.6, 131.7, 128.7, 127.7, 117.2 (t, *J* = 238 Hz), 45.4 (t, *J* = 21.2 Hz), 44.2, 26.4, 14.3 (t, *J* = 5.7 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ –121.6 (d, *J* = 282 Hz), –123.6 (d, *J* = 282 Hz). MS (ESI): *m/z* = 226 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{13}F_2NO$: C 63.99; H 5.82; N 6.22. Found: C 64.11; H 5.47; N 6.30.

***N*-((1*R**,2*R**)-2-(Fluoromethyl)cyclobutyl)benzamide (32).** Et_3N (795 mg, 7.88 mmol) was added to a suspension of **11** (1.00 g, 7.16 mmol) in CH_2Cl_2 (15 mL) at rt. Then, BzCl (1.06 g, 7.52 mmol) was added dropwise at rt (NOTE: the temperature should not exceed 25 °C). The resulting mixture was stirred at rt for 2 h, then washed with 1 M aq HCl (10 mL), brine (10 mL), dried over Na_2SO_4, and evaporated in *vacuo*. Yield 1.34 g (90%). Colorless solid; mp 114–116 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.71 (m, 2H), 7.47 (td, *J* = 7.2, 1.5 Hz, 1H), 7.43 – 7.37 (m, 2H), 6.33 (s, 1H), 4.59 – 4.52 (m, 1H), 4.47 – 4.36 (m, 2H), 2.64 – 2.52 (m, 1H), 2.39 – 2.31 (m, 1H), 1.96 – 1.88 (m, 2H), 1.74 – 1.65 (m, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 166.4, 133.8, 131.9, 128.0, 126.4, 84.1 (d, *J* = 166 Hz), 46.1 (d, *J* = 7.9 Hz), 44.4 (d, *J* = 19.6 Hz), 26.6, 16.9 (d, *J* = 5.9 Hz). ^{19}F NMR (470 MHz $CDCl_3$) δ –223.8 (td, *J* = 47.5, 22.3 Hz). MS (ESI): *m/z* = 208 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{14}FNO$: C 69.55; H 6.81; N 6.76. Found: C 69.15; H 6.92; N 6.48.

Acknowledgements

The work was funded by Enamine Ltd. O.O.G. was also funded by Ministry of Education and Science of Ukraine (Grant No.19BF037-03). The authors thank Prof. Andrey A. Tolmachev for his encouragement and support, Ms. Margarita Bolgova and Ms. Olga Kovalenko for pK_a titrations.

Keywords: fluorine • cyclobutane • building blocks • amines carboxylic acids

[1] D. Cahard, J.-A. Ma, Eds. , *Emerging Fluorinated Motifs Synthesis, Properties and Applications*, Wiley-VCH, **2020**.

[2] E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315–8359.

[3] H. Mei, J. Han, S. Fustero, M. Medio-Simon, D. M. Sedgwick, C. Santi, R. Ruzziconi, V. A. Soloshonok, *Chem. Eur. J.* **2019**, *25*, DOI 10.1002/chem.201901840.

[4] K. Müller, *Chim. Int. J. Chem.* **2014**, *68*, 356–362.

[5] S. Swallow, *Prog. Med. Chem.* **2015**, *54*, 65–133.

[6] K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886.

[7] D. O'Hagan, Y. Wang, M. Skibinski, A. M. Z. Slawin, *Pure Appl. Chem.* **2012**, *84*, 1587–1595.

[8] Q. A. Huchet, B. Kuhn, B. Wagner, H. Fischer, M. Kansy, D. Zimmerli, E. M. Carreira, K. Müller, *J. Fluorine Chem.* **2013**, *152*, 119–128.

[9] Q. A. Huchet, B. Kuhn, B. Wagner, N. A. Kratochwil, H. Fischer, M. Kansy, D. Zimmerli, E. M. Carreira, K. Müller, *J. Med. Chem.* **2015**, *58*, 9041–9060.

[10] Q. A. Huchet, N. Trapp, B. Kuhn, B. Wagner, H. Fischer, N. A. Kratochwil, E. M. Carreira, K. Müller, *J. Fluorine Chem.* **2017**, *198*, 34–46.

[11] R. Vorberg, N. Trapp, D. Zimmerli, B. Wagner, H. Fischer, N. A. Kratochwil, M. Kansy, E. M. Carreira, K. Müller, *ChemMedChem* **2016**, *11*, 2216–2239.

[12] B. Linclau, Z. Wang, G. Compain, V. Paumelle, C. Q. Fontenelle, N. Wells, A. Weymouth-Wilson, *Angew. Chem. Int. Ed.* **2016**, *55*, 674–678.

[13] K. Müller, in *Fluorine in Life Sciences: Pharmaceuticals, Medicinal Diagnostics, and Agrochemicals*, Elsevier, **2019**, pp. 91–139.

[14] Y. Zhu, S. H. Olson, D. Graham, G. Patel, A. Hermanowski-Vosatka, S. Mundt, K. Shah, M. Springer, R. Thieringer, S. Wright, J. Xiao, H. Zokian, J. Dragovic, J. M. Balkovec, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3412–3416.

[15] T. T. Wager, B. A. Pettersen, A. W. Schmidt, D. K. Spracklin, S. Mente, T. W. Butler, H. Howard, D. J. Lettiere, D. M. Rubitski, D. F. Wong, F. M. Nedza, F. R. Nelson, H. Rollema, J. W. Raggon, J. Aubrecht, J. K. Freeman, J. M. Marcek, J. Clanfrogna, K. W. Cook, L. C. James, L. A. Chatman, P. A. Iredale, M. J. Banker, M. L. Homiski, J. B. Munzner, R. Y. Chandrasekaran, *J. Med. Chem.* **2011**, *54*, 7602–7620.

[16] I. O. Feskov, B. O. Golub, B. V. Vashchenko, V. V. Levterov, I. S. Kondratov, O. O. Grygorenko, G. Haufe, *Eur. J. Org. Chem.* **2020**, *2020*, 4755–4767.

[17] D. S. Radchenko, O. M. Michurin, O. O. Grygorenko, K. Scheinpflug, M. Dathe, I. V. Komarov, *Tetrahedron* **2013**, *69*, 505–511.

[18] D. S. Radchenko, A. Tkachenko, O. O. Grygorenko, I. V. Komarov, *Synth. Commun.* **2011**, *41*, 1644–1649.

[19] A. V. Chernykh, D. S. Radchenko, O. O. Grygorenko, D. M. Volochnyuk, S. V. Shishkina, O. V. Shishkin, I. V. Komarov, *RSC Adv.* **2014**, *4*, 10894–10902.

[20] D. S. Radchenko, S. O. Pavlenko, O. O. Grygorenko, D. M. Volochnyuk, S. V. Shishkina, O. V. Shishkin, I. V. Komarov, *J. Org. Chem.* **2010**, *75*, 5941–5952.

[21] W. Yu, L. Williams, V. M. Camp, E. Malveaux, J. J. Olson, M. M. Goodman, *Bioorg. Med. Chem.* **2009**, *17*, 1982–1990.

[22] L. Martarello, J. McConathy, V. M. Camp, E. J. Malveaux, N. E. Simpson, C. P. Simpson, J. J. Olson, G. D. Bowers, M. M. Goodman, *J. Med. Chem.* **2002**, *45*, 2250–2259.

[23] A. W. Wong, M. J. Adam, S. G. Withers, *J. Label. Compd. Radiopharm.* **2001**, *44*, 385–394.

[24] I. O. Feskov, A. V. Chernykh, I. S. Kondratov, M. Klyachina, C. G. Daniliuc, G. Haufe, *J. Org. Chem.* **2017**, *82*, 12863–12868.

[25] A. Avenoza, H. Busto, N. Canal, J. M. Peregrina, *J. Org. Chem.* **2005**, *70*, 330–333.

[26] J. Lee, H. J. Seo, S. H. Lee, J. Kim, M. E. Jung, S. H. Lee, K. S. Song, J. Lee, S. Y. Kang, M. J. Kim, M. S. Kim, E. J. Son, M. Lee, H. K. Han, *Bioorg. Med. Chem.* **2010**, *18*, 6377–6388.

[27] G. S. Basarab, D. R. Rayner, D. B. Jordan, J. F. Okonya, G. S. Basarab, D. K. Amorose, B. M. Anaclerio, J. K. Lee, R. S. Schwartz, K. A. Whitmore, *Bioorg. Med. Chem.* **2000**, *8*, 897–907.

[28] L. D. Jennings, Z. Wawrzak, D. Amorose, R. S. Schwartz, D. B. Jordan, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2509–2514.

[29] B. Phillips, R. Cai, W. Delaney, Z. Du, M. Ji, H. Jin, J. Lee, J. Li, A. Niedziela-Majka, M. Mish, H. J. Pyun, J. Saugier, N. Tirunagari, J. Wang, H. Yang, Q. Wu, C. Sheng, C. Zonte, *J. Med. Chem.* **2014**, *57*, 2161–2166.

[30] W. R. Dolbier, T. A. Gray, J. J. Keaffaber, L. Celewicz, H. Koroniak, *J. Am. Chem. Soc.* **1990**, *112*, 363–367.

[31] M. Bugera, S. Trofymchuk, K. Tarasenko, O. Zaporozhets, Y. Pustovit, P. K. Mykhailiuk, *J. Org. Chem.* **2019**, *84*, 16105–16115.

[32] W. Dmowski, A. Wolniewicz, *J. Fluorine Chem.* **2000**, *102*, 141–146.

[33] W. R. Hasek, W. C. Smith, V. A. Engelhardt, *J. Am. Chem. Soc.* **1960**, *82*, 543–551.

[34] J. A. Kautzky, T. Wang, R. W. Evans, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2018**, *140*, 6522–6526.

[35] C. Dong, X. F. Bai, J. Y. Lv, Y. M. Cui, J. Cao, Z. J. Zheng, L. W. Xu, *Molecules* **2017**, *22*, 769.

[36] D. S. Radchenko, O. M. Michurin, A. V. Chernykh, O. Lukin, P. K. Mykhailiuk, *Tetrahedron Lett.* **2013**, *54*, 1897–1898.

[37] A. A. Homon, O. V. Hryshchuk, S. Trofymchuk, O. Michurin, Y. Kuchkovska, D. S. Radchenko, O. O. Grygorenko, *Eur. J. Org. Chem.* **2018**, *2018*, 5596–5604.

[38] D. J. P. Kornfilt, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2019**, *141*, 6853–6858.

[39] P. J. Sarver, V. Bacauanu, D. M. Schultz, D. A. DiRocco, Y. Lam, E. C. Sherer, D. W. C. MacMillan, *Nat. Chem.* **2020**, *12*, 459–467.

[40] Q. Wei, Y. Ma, L. Li, Q. Liu, Z. Liu, G. Liu, *Org. Lett.* **2018**, *20*, 7100–7103.

[41] M. Hanack, H. Meyer, *Justus Liebigs Ann. Chem.* **1968**, *720*, 81–97.

[42] X. Creary, *Beilstein J. Org. Chem.* **2019**, *15*, 1769–1780.

[43] Y. V. Tomilov, E. V. Guseva, I. V. Kostuchenko, B. I. Ugrak, E. V. Shulishov, O. M. Nefedov, *Eur. J. Org. Chem.* **2004**, *2004*, 3145–3153.

[44] P. Cao, J.-X. Duan, Q.-Y. Chen, *J. Chem. Soc. Chem. Commun.* **1994**, *204*, 737.

[45] A. M. Daly, D. G. Gilheany, *Tetrahedron Asymmetry* **2003**, *14*, 127–137.
[46] D. A. Bak, K. Conrow, *J. Org. Chem.* **1966**, *31*, 3608–3612.
[47] A. V. Chernykh, K. P. Melnykov, N. A. Tolmacheva, I. S. Kondratov, D. S. Radchenko, C. G. Daniliuc, D. M. Volochnyuk, S. V. Ryabukhin, Y. O. Kuchkovska, O. O. Grygorenko, *J. Org. Chem.* **2019**, *84*, 8487–8496.
[48] W. L. F. Armarego, C. Chai, *Purification of Laboratory Chemicals*, Elsevier: Oxford, **2003**.
[49] J. W. Wheeler, C. C. Shroff, W. S. Stewart, S. J. Uhm, *J. Org. Chem.* **1971**, *36*, 3356–3361.
[50] Unfortunately, all attempts to extend the developed methodologies to the preparation of *cis* isomers of the title building blocks were unfruitful.
[51] Salaün, A. Fadel, *Org. Synth.* **1986**, *64*, 50.

WILEY-VCH

RESEARCH ARTICLE

Mono- and Difluorinated Saturated Heterocyclic Amines for Drug Discovery: Systematic Study of Their Physicochemical Properties

Dr. Kostiantyn P. Melnykov,[a,b] Kostiantyn Nazar,[a,b] Oleh Smyrnov,[a,b] Artem Skreminskyi,[a] Serhii Pavlenko,[a] Oleksii Klymenko-Ulianov,[c] Prof. Dr. Svitlana Shishkina,[d] Prof. Dr. Dmitriy M. Volochnyuk,[a,b,d] and Dr. Oleksandr O. Grygorenko*[a,b]

Dedicated to the people of Ukraine

[a] Enamine Ltd.
Chervonotkatska Street 78, Kyiv 02094, Ukraine
URL: www.enamine.net
[b] Taras Shevchenko National University of Kyiv
Volodymyrska Street 60, Kyiv 01601, Ukraine
E-mail: gregor@univ.kiev.ua
[c] Bienta / Enamine Ltd.
Chervonotkatska Street 78, Kyiv 02094, Ukraine
URL: www.bienta.net
[d] Institute of Organic Chemistry, National Academy of Sciences of Ukraine
Akademik Kukhar Street 5, Kyiv 02660, Ukraine
Supporting information for this article is given via a link at the end of the document

Abstract: A comprehensive study of physicochemical properties (pK_a, Log*P*, and intrinsic microsomal clearance) within the series of mono- and difluorinated azetidine, pyrrolidine, and piperidine derivatives was performed. While the number of fluorine atoms and their distance to the protonation center were the major factors defining the compound's basicity, both pK_a and Log*P* values were affected considerably by the conformational preferences of the corresponding derivatives. For example, features of "Janus face" (facially polarized) cyclic compounds (i.e., unusually high hydrophilicity) were identified for *cis*-3,5-difluoropiperidine, prefering a diaxial conformation. Intrinsic microsomal clearance measurements demonstrated high metabolic stability of the compounds studied (with a single exception of the 3,3-difluoroazetidine derivative). According to pK_a – Log*P* plots, the title compounds provide a valuable extension of the fluorine-containing (e.g., fluoroalkyl-substituted) saturated heterocyclic amine series as building blocks for rational optimization studies in early drug discovery

Introduction

It is now widely recognized that fluorinated organic compounds have become extremely popular in the discovery and development of novel drugs, with numerous success stories occurring at an increasing rate over the last decades.[1–9] Introducing fluorine atoms into the molecules of interest can drastically change their physicochemical, biological, and other properties, which has been covered in several review articles.[10–12] While the general effects of such modifications are more or less understood, the rational application of fluorinated building blocks in design of potential drugs is still needs to be achieved in full.[13] Unlike their aromatic and acyclic aliphatic counterparts,[14–24] fluorine-containing saturated rings were among the least studied fluorinated chemotypes in terms of both synthetic accessibility and key in vitro properties relevant to drug discovery until recently. In a series of works, O'Hagan and co-workers showed that the fluorination typically increased polarity of saturated ring systems, and this effect was especially significant for all-*cis* derivatives ("Janus face" cycloalkanes) (Figure 1, *A*).[25–35] Linclau and co-workers observed similar effects for cyclopropylmethanols (*B*).[36] Our group has systematically studied the effect of *gem*-difluorination on pK_a, Log*P*, and metabolic stability of functionalized cycloalkane derivatives (*C*).[37,38] A similar study was performed by us for fluoroalkyl-substituted saturated heterocyclic amines and their derivatives (*D*).[39]

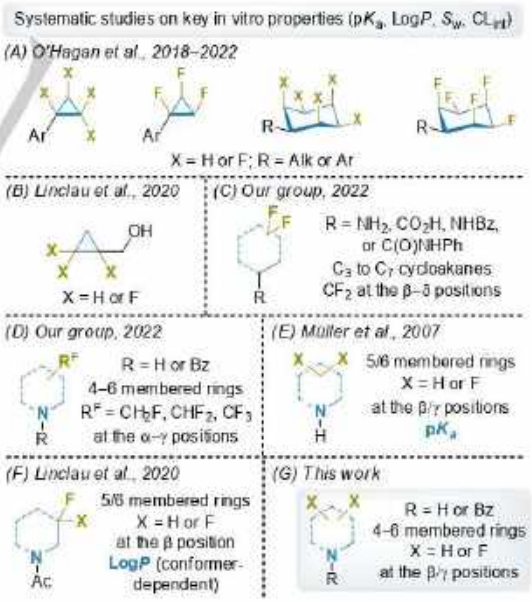


Figure 1. (*A–F*) Previous works on the impact of the fluorination on physicochemical properties of saturated cyclic compounds; (G) the chemotype studied in this work

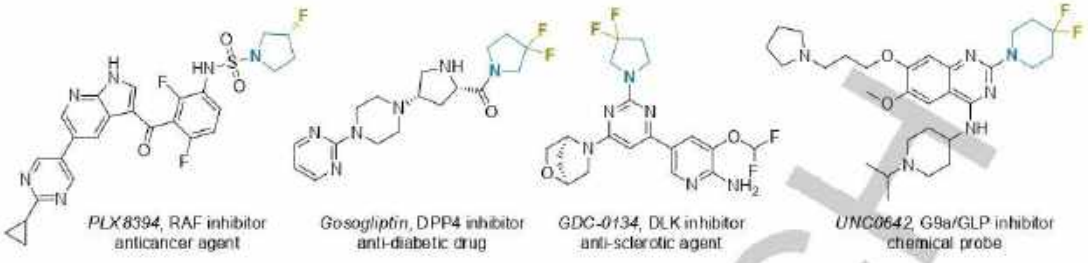


Figure 2. Examples of drug candidates and chemical probes containing fluorine-substituted pyrrolidine and piperidine moieties

To continue comprehensive exploration of fluorine-containing saturated cyclic compounds in terms of their experimental physicochemical properties, we have turned our attention to a series of mono- and difluorinated saturated heterocyclic amines and their derivatives (Figure 1, *G*). Remarkably, these building blocks have been widely used in medicinal chemistry, and several derivatives thereof have become investigational drugs or chemical probes, e.g. RAF kinase inhibitor and anticancer agent PLX8394, anti-diabetic drug Gosogliptin acting at dipeptidyl peptidase 4 (DPP4),[40] dual leucine zipper kinase (DLK) inhibitor GDC-0134 potentially useful to treat amyotrophic lateral sclerosis,[41] or UNC0642, an in vivo chemical probe for lysine methyltransferases G9a and GLP[42] (Figure 2). Furthermore, pK_a values of *mono-* and *gem*-difluorinated pyrrolidines and piperidines were reported in the literature; general trends were established for these series (Figure 1, *E*).[43] Also, conformer-dependent lipophilicity of 3-mono-/3,3-difluorinated pyrrolidine and piperidine derivatives was studied recently by Linclau and co-workers (Figure 1, *F*).[15]

Herein, we report a comprehensive study of mono- and difluorinated azetidine, pyrrolidine, and piperidine derivatives (Figure 3) including synthesis of the remaining unknown representatives, measurement of their basicity (pK_a(H), hereafter designated simply as pK_a), as well as lipophilicity (Log*P*) and metabolic stability (as defined by intrinsic microsomal clearance, CL_{int}) of the corresponding benzamides.

The following compound numbering system was adopted in this work to facilitate the discussion: x,y-F-**na** or x,y-F-**nb**, where **n** – ring size (**4**–**6**), **a** or **b** – compound series (**a** – free amines, **b** – their *N*-benzoyl derivatives), x,y – locant(s) of the fluorine atoms (3, 4, or 5); *cis* and *trans* stereochemical descriptors were also added where appropriate. The parent non-fluorinated amines and *N*-benzoyl derivatives were marked as **4**–**6a** and **4**–**6b**, respectively; most data for them were retrieved from the previous work.[39]

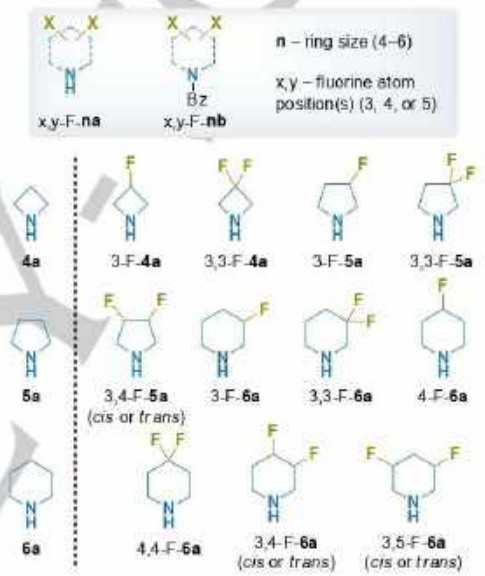


Figure 3. Fluorinated azetidine, pyrrolidine, and piperidine derivatives (and their non-fluorinated counterparts) studied in this work

Results and Discussion

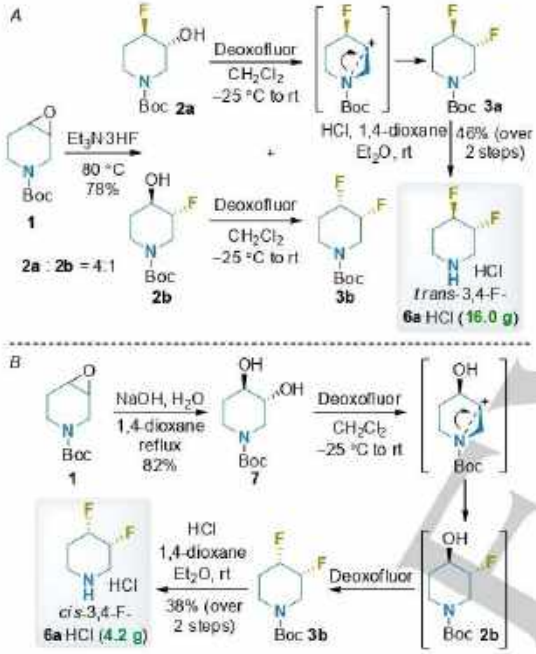
Synthesis

All the compounds shown in Figure 3 except *cis*-/*trans*-3,4-F-**6a** and *trans*-3,5-F-**6a** have been known in the literature and were either obtained from chemical vendors or synthesized according to the published procedures.[44,45]

Our approach to the synthesis of both *cis*- and *trans*-3,4-F-**6a** commenced from epoxide **1**.[46] Compound **1** reacted with $Et_3N{\cdot}3HF$ without a solvent at 80 °C to give a mixture of regioisomeric alcohols **2a** and **2b** (78% total isolated yield, **2a** : **2b** ~ 4:1) (Scheme 1, *A*). We could separate these compounds by column chromatography, but the mixture of **2a** and **2b** was used without additional purification when the experiment was repeated at the multigram scale. Intriguingly, both **2a** and **2b** reacted with $(MeOCH_2CH_2)_2NSF_3$ (Deoxofluor) in a diastereo-selective manner: **2a** – with retention of configuration (to give **3a**), and **2b** – with inversion (to give **3b**). Notably, stereoretentive deoxyfluorination of a similar piperidine-derived substrate was mentioned in the literature.[47] According to the previous authors, participation of the nitrogen atom lone pair was responsible for the regioselectivity observed in the reaction of compounds like **2a**.

Since the yield of intermediate **2b** was very low, an alternative reaction sequence was developed to obtain the *cis* isomer. In

particular, compound **1** was transformed into diol 7[48] (82% yield) upon reaction with aqueous NaOH in dioxane (Scheme 1, *B*). Compound **7** was subjected to double deoxyfluorination with Deoxofluor, which eventually led to desired *cis* isomer **3b**. Double deoxyflurination of 1,2-diols was documented in the literature,[35,49] but its stereochemical aspects did not receive sufficient attention. In our opinion, preferential formation of **3b** can be explained by initial deoxyfluorination at the 3-OH group, which is promoted by participation of the nitrogen lone pair and gives intermediate **2b** with retention of the stereochemical configuration. Further deoxyfluorination of alcohol **2b** follows S_N2 mechanism and results in the formation of **3b** with stereoinversion.



Scheme 1. Synthesis of *trans*-3,4-F-**6a**·HCl (*A*) and *cis*-3,4-F-**6a**·HCl (*B*) (relative configurations are shown).

After acid-promoted deprotection of **3a** and **3b**, target amines *trans*-3,4-F-**6a** and *cis*-3,4-F-**6a** were obtained as hydrochlorides in 46% and 38% yields (over two steps), respectively. Notably, both compounds were obtained on up to 16.0 g and 4.2 g scale, respectively, in a single run. Relative stereochemistry of these products was confirmed by X-Ray diffraction studies (Figure 4).

Synthesis of compound *trans*-3,5-F-**6a** commenced from chiral diol **8**, in turn obtained in three steps from 4-hydroxyproline ester **9** according to the published procedure (Scheme 2).[50] Diol **8** was subjected to double *O*-silylation, then deoxyfluorination with morph-DAST, and catalytic hydrogenolysis in acidic media. In this way, enantiopure compound *trans*-3,5-F-**6a** was obtained as a hydrochloride on up to 26.0 g in a single run. It should be stressed out that preliminary *O*-silylation of compound **8** was crucial to improve the yield of the target product and minimize the rearrangement of the corresponding cationic intermediates into pyrrolidine derivatives, which is observed for the non-protected diol.[51]

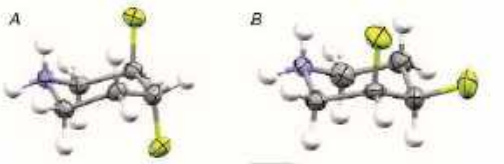
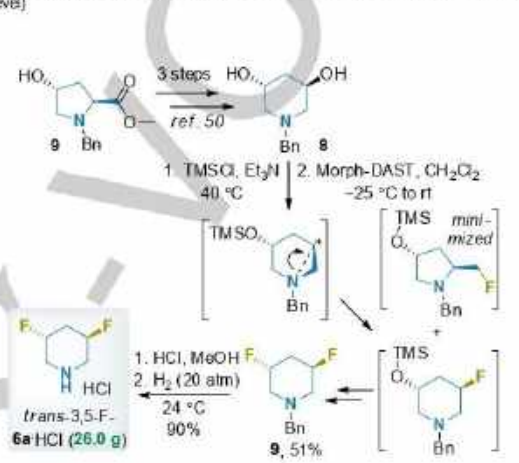


Figure 4. Molecular structure of *trans*-3,4-F-**6a**·HCl (*A*) and *cis*-3,4-F-**6a**·HCl (*B*) (chloride anions are omitted; thermal ellipsoids are shown at 50% probability level).



Scheme 2. Synthesis of *trans*-3,5-F-**6a**·HCl.

Amine Basicity

The pK_a values for the discussed fluorinated amine series were determined from acid-base titration following the previously reported protocol (Figure 5, Table 1).[37] The values were somewhat lower than those reported in the literature for some of the representatives,[43] presumably due to the differences in the titration conditions, but they followed the same general trends. In accordance with the previous data,[39,43] the ring size itself had a minor effect on the pK_a values obtained for mono- and *gem*-difluorinated derivatives; it was the number of the fluorine atoms and the distance to the fluorination site via both available bond pathways that was most definitive. Indeed, fluorination at the C-3 position of azetidine resulted in the most significant pK_a decrease (by 2.5 and 2.1 units for the first and the second fluorine atoms, respectively). For the pyrrolidine derivatives, the corresponding values were 2.3 and 2.1 (lit.[43] 1.9 in both cases). In the piperidine series, they were 2.4 (lit.[43] 1.8) and 1.8 (lit.[43] 1.9) for the C-3-fluorinated isomers, as well as 2.0 (lit.[43] 1.7) and 1.2 (lit.[43] 0.9) – for the C-4-fluorinated ones. Notably, addition of the first fluorine atom had somewhat greater impact on the basicity relatively to the second one, especially for the 4-fluorinated piperidine derivatives. The previous authors addressed the latter fact to a smaller absolute ΔpK_a increments for the fluorine atoms having axial (vs equatorial) orientation.[43]

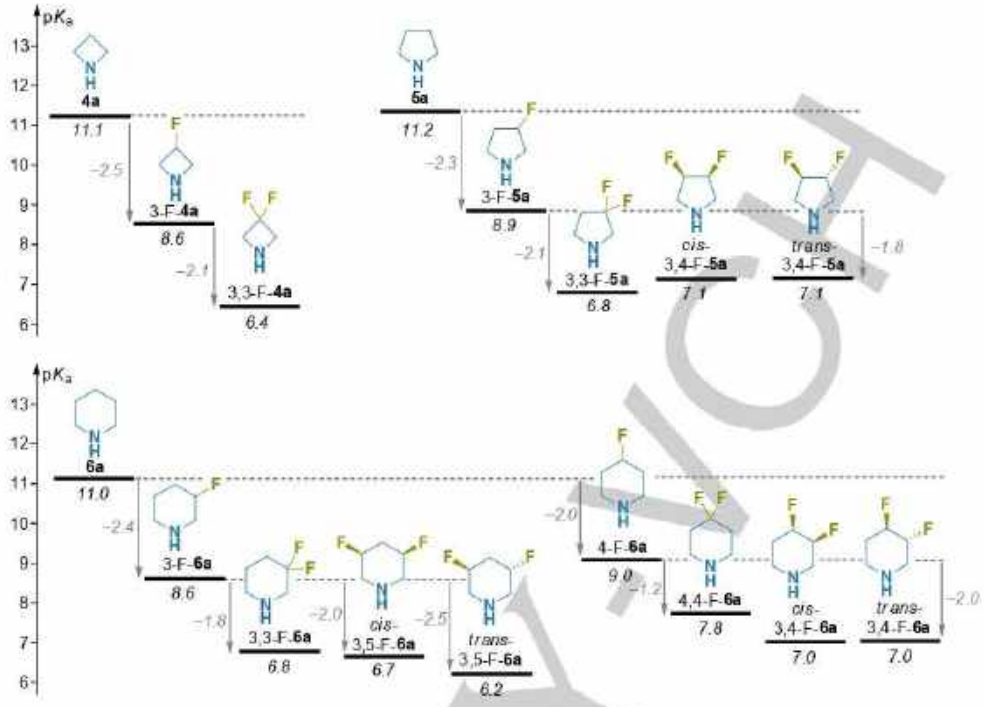


Figure 5. pK_a values of azeditine (**4a**), pyrrolidine (**5a**), piperidine (**6a**), and their mono- and difluorinated derivatives

Table 1. pK_a (21 °C), Log*P* (21 °C) and CL_{int} (37 °C) values for compounds **4–6a** or **4–6b** and their fluorinated analogs

Entry	Amine	pK_a	Amide	Log*P*	CL_{int}, µL·min^{-1}·(mg of protein)$^{-1}$ [a]
1	**4a**	11.13±0.07	**4b**	1.13±0.01[38]	≤5
2	3-F-**4a**	8.55±0.03	3-F-**4b**	0.94±0.04	≤5
3	3,3-F-**4a**	6.44±0.02	3,3-F-**4b**	1.34±0.03	19±4
4	**5a**	11.21±0.06	**5b**	1.19±0.01[38]	≤5
5	3-F-**5a**	8.87±0.02 (lit.[43] 9.4)	3-F-**5b**	0.91±0.02	≤5
6	3,3-F-**5a**	6.88±0.03 (lit.[43] 7.5)	3,3-F-**5b**	1.35±0.01	≤5
7	*cis*-3,4-F-**5a**	7.07±0.06	*cis*-3,4-F-**5b**	1.01±0.01	≤5
8	*trans*-3,4-F-**5a**	7.11±0.03	*trans*-3,4-F-**5b**	1.08±0.01	≤5
9	**6a**	10.98±0.06	**6b**	1.39±0.01[38]	≤5
10	3-F-**6a**	8.64±0.03 (lit.[43] 9.3)	3-F-**6b**	1.26±0.02	≤5
11	3,3-F-**6a**	6.79±0.08 (lit.[43] 7.4)	3,3-F-**6b**	1.65±0.01	≤5
12	4-F-**6a**	9.05±0.02 (lit.[43] 9.4)	4-F-**6b**	1.31±0.05	≤5
13	4,4-F-**6a**	7.75±0.04 (lit.[43] 8.5)	4,4-F-**6b**	1.51±0.03	≤5
14	*cis*-3,4-F-**5a**	7.01±0.04	*cis*-3,4-F-**5b**	1.15±0.01	≤5

WILEY-VCH

Entry	Amine	pK_a	Amide	Log*P*	CL_{int}, μL·min^{-1}·(mg of protein)$^{-1}$ [a]
15	*trans*-3,4-F-**5a**	7.02±0.02	*trans*-3,4-F-**5b**	1.26±0.01	≤5
16	*cis*-3,5-F-**6a**	6.74±0.06	*cis*-3,5-F-**6b**	0.58±0.01	≤5
17	*trans*-3,5-F-**6a**	6.22±0.10	*trans*-3,5-F-**6b**	1.35±0.03	≤5

[a] Human liver microsomes, NADPH as a cofactor, phosphate-buffered saline (PBS), 37°C. Due to the slow metabolism, the values are approximate. For the standards used, CL_{int} = 254±31 (diclofenac) and 22±4 (propranolol)

Both 3,4-difluorinated pyrrolidines *cis*- and *trans*-3,4-F-**5a** appeared to be somewhat more basic (pK_a = 7.1) than 3,3-difluorinated counterpart 3,3-F-**5a** (pK_a = 6.8): ΔpK_a = –1.8 and –2.1, respectively. These counter-intuitive results provide another illustration of the fact that simple additive models for inductive effect of the fluorine atom(s) spread through the existing σ bonds can provide only rough estimation of the compound's basicity.

A similar situation was observed for the 3,4-difluorinated piperidines: both *cis*- and *trans*-3,4-F-**6a** had pK_a = 7.0 (ΔpK_a = –2.0 relatively to 4-F-**6a**). Essentially the same result (ΔpK_a = –2.0 relatively to 3-F-**6a**) was obtained for *cis*-3,5-F-**6a**. Since it is known that axial orientation is preferable for the protonated (but not neutral) 3-fluorinated piperidine derivatives (Figure 6, *A*),[51–53] this orientation may be suggested for the fluorine atoms at the C-3 position in all protonated piperidines mentioned above (Figure 6, *B*). This hypothesis can explain the same pK_a decrease (–2.0) in this series. Notably, the proposed conformations were observed in the crystalline state for the protonated 3,4-difluorinated piperidines (Figure 4). Meanwhile, in the case of *trans*-3,5-F-**6a**, one of the fluorine atoms is forced to adopt equatorial orientation in both protonated and neutral forms (Figure 6, *C*), which might explain somewhat higher absolute ΔpK_a value (–2.5 relatively to 3-F-**6a**).

Lipophilicity

The Log*P* values for *N*-benzoylated derivatives of the title compounds were measured using a standard shake-flask method as described previously (Figure 7, Table 1).[37] The observed changes in Log*P* can be mostly explained through a qualitative analysis of the C–F bonds and amide moiety dipoles.

Ring size. As it was found, 3-mono- and 3,3-difluorinated azetidine and pyrrolidine derivatives had nearly the same lipophilicities. This might be partially rationalized through lower symmetry of the 3-fluorinated pyrrolidine ring, which counterbalances the effect of an additional CH_2 group (Figure 8, *A*). For the corresponding 3-fluorinated piperidine series, the Log*P* values were by ca. 0.3 units higher, which can be expected for the next higher homologue.

Fluorination at a single position. The following trend was observed for lipophilicity in the series studied:

gem-difluorinated > non-fluorinated > monofluorinated.

It should be noted that we have observed a similar effect previously in the spiro[3.3]heptane series.[54]

For the monofluorinated derivatives, the Log*P* decrease was ca. 0.1–0.3 units. We believe that this result can be explained by polarization of both C–F and neighboring C–H bonds (Figure 8, *B*). Notably, *gem*-difluorination of the saturated heterocyclic amides studied in this work increased their Log*P* by ca. 0.2 units. This is contrary to the results of our previous work on *gem*-difluorinated cycloalkane series where the CF_2 unit typically diminished the compound's lipophilicity (Figure 1, *C*).[37] One of the reasons behind this might be that a different functional group is present in the molecules of this study (i.e., tertiary vs secondary amide).

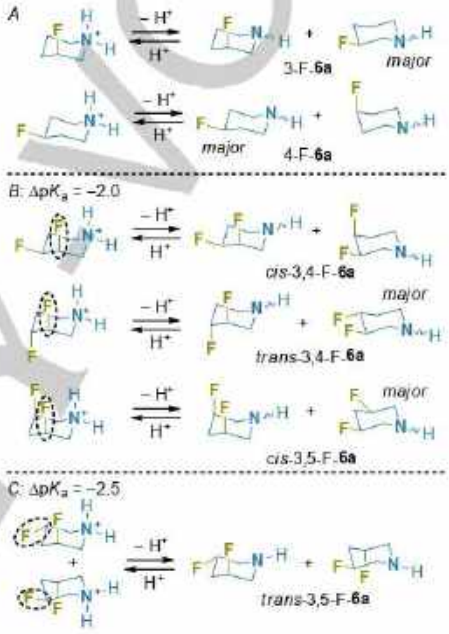


Figure 6. Putative conformational preferences of mono-, 3,4-, and 3,5-difluorinated piperidines

The difference between Log*P* values obtained for mono- and *gem*-difluorinated benzamides (ca. 0.4 units) showed a good correlation with the results obtained by Linclau and co-workers in their studies of the corresponding pyrrolidine and piperidine-derived acetamides.[19]

Fluorination at two different positions. In most cases, 3,4- and 3,5-difluorinated saturated heterocyclic benzamides had lipophilicity intermediate between their mono- and *gem*-difluorinated analogs. Thus, *cis*-3,4-**5b** and *cis*-3,4-**6b** were by 0.18–0.24 Log*P* units more lipophilic than the non-fluorinated counterparts, which correlates with partial compensation of the dipole moments (Figure 8, *C*). Meanwhile, *trans*-3,4-**5b**, *trans*-3,4-**6b**, and *trans*-3,5-**6b** had only slightly lower lipophilicity as compared to the parent compounds **5b** and **6b**, respectively (by 0.04–0.11 Log*P* units), which can be again explained by opposite orientation of the corresponding dipoles (Figure 8, *D*).

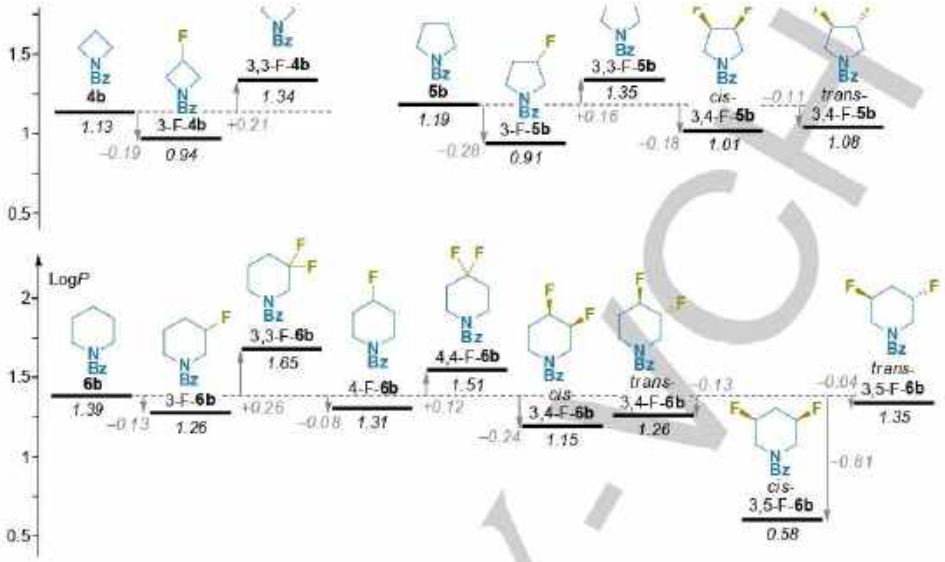


Figure 7. Log*P* values of *N*-benzoylated azetidine (**4b**), pyrrolidine (**5b**), piperidine (**6b**), and their mono- and difluorinated derivatives

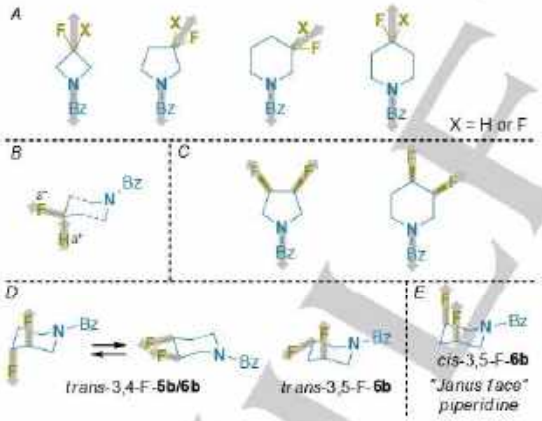


Figure 8. Qualitative analysis of the C–F bonds and amide moiety dipoles in the series of benzamides studied in this work

Perhaps the most interesting result was obtained for *cis*-3,5-**6b**, which was significantly more hydrophilic as compared to the parent non-fluorinated compound (by 0.81 Log*P* units). This result indicates considerable population of a conformer with diaxial orientation of the C–F bonds (Figure 8, ***E***) and correlates with the data obtained by O'Hagan and co-workers for facially polarized cycloalkane derivatives (Figure 1, *A*). In other words, *cis*-3,5-**6a** can be considered as a "Janus face" piperidine analog. The conformational preferences of protonated or *N*-acylated *cis*-3,5-difluoropiperidines has been studied thoroughly by Glorius and co-workers.[53] By a combination of experimental measurements and theoretical calculations, they have shown that in polar solvents like DMSO or H_2O, the diaxial conformers are by ca. 2 kcal/mol preferred over diequatorial ones.

Metabolic Stability

Metabolic stability of benzamides **4b**–**6b** and their fluorinated derivatives was evaluated by *in vitro* measurements of intrinsic human liver microsomal clearance (CL_{int}) following a previously reported protocol (human liver microsomes, NADPH as a cofactor, phosphate-buffered saline (PBS), 37 °C).[37] It was found that nearly all compounds were essentially stable under the conditions used (Table 1). Considerable (but still low) decomposition was observed only for 3,3-difluorinated azetidine 3,3-F-**6b**: CL_{int} = 19 $\mu L \cdot min^{-1} \cdot (mg\ of\ protein)^{-1}$.

Basicity vs Lipophilicity Plot

During medicinal chemistry optimization studies, it is advantageous to modulate the key physicochemical parameters of compounds in combination rather than separately. In this view, a pK_a – Log*P* plot (which is similar to the classical Craig plots[55]) for the compounds studied in this work can be useful for rational isosteric replacements within the series of saturated heterocyclic amines. As might be expected, the compounds studied in this work naturally grouped into three series in the pK_a – Log*P* plot corresponding to non-, mono-, and difluorinated saturated heterocyclic amines (with a single outlier corresponding to 4,4-difluoropiperidine), which is defined mainly by their pK_a value – ca. 11, 9, and 7 units, respectively (Figure 9). With a few exceptions,

the Log*P* variation for the corresponding amide series was not significant. Most data points could be found within a ±0.3 interval around the average value of 1.2 – compare these results with the much wider variation observed for fluoroalkyl-substituted saturated heterocycles.[39] The highest Log*P* window (1.07 units) was achieved for the difluorinated derivatives, which is clearly related to the specific properties of "Janus face" *cis*-3,5-difluoropiperidine mentioned above.

Importantly, nearly all mono- and difluorinated saturated heterocyclic amines occupy a different part of chemical space than their fluoroalkyl-substituted counterparts in terms of the pK_a – Log*P* coordinates. An interesting exception is provided by a 4,4-difluoropiperidine (4,4-F-**6**) and 2-(difluoromethyl)azetidine (2-CHF_2-**4**) pair having nearly the same physicochemical properties (pK_a = 7.8, Log*P* = 1.5) but very distinct chemical structures. An opposite example includes 3,3- and *cis*-3,5-difluoropiperidines (3,3- and *cis*-3,5-**6**) where a minor structural alteration results in a significant change in lipophilicity (Δ Log*P* = 1.07). These results demonstrate that the combined set of fluorine-containing saturated heterocyclic amines can be a valuable drug discovery tool for fine-tuning the compound's physicochemical properties while maintaining key interactions with the biological target and/or conformational preferences, and vice versa.

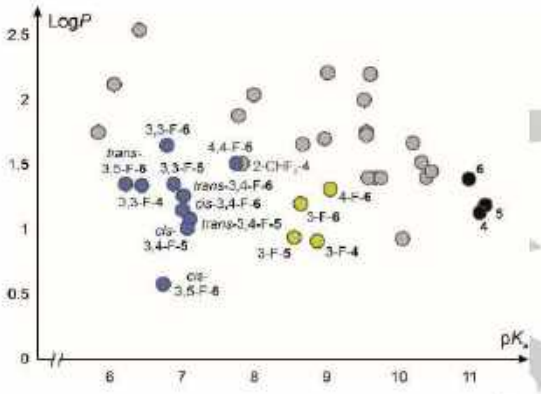


Figure 9. pK_a – Log*P* plot covered by fluorine-containing and non-fluorinated saturated nitrogen-containing heterocycles (color code: black – parent non-fluorinated, yellow – monofluorinated, blue – difluorinated, grey – fluoroalkyl-substituted heterocycles)

Conclusions

Mono- and difluorination of azetidine, pyrrolidine, and piperidine is a very useful tool to modulate physicochemical properties of biologically active compounds relevant to drug discovery (such as basicity and lipophilicity) in a rational manner. The resulting fluorinated analogs cover the pK_a and Log*P* ranges of 6.2–9.0 units (for the parent amines) and 0.6–1.6 units (for the *N*-benzoylated derivatives), respectively. Importantly, although these ranges are smaller than for the mono-, di- and trifluoromethyl-substituted counterparts studied in the previous work (6.4–10.5 and 0.9–2.5 units, respectively),[39] they are located in a different part of the chemical space (as defined by the pK_a and Log*P* coordinates). Furthermore, with a single exception, all mono- and difluorinated saturated heterocycles studied demonstrated metabolic stability towards human microsomes.

Within the series of mono- and difluorinated derivatives, both basicity and lipophilicity are affected by the compound's conformational preferences (although for pK_a, number of the fluorine atoms and their distance to the protonation site remain the major factors). Thus, the diaxial conformation preference documented previously for *cis*-3,5-difluoropiperidine[51–53] leads to unusually low Log*P* value for the corresponding *N*-benzoyl derivative (Δ Log*P* = –0.8 units as compared to the non-fluorinated counterpart). This fact which allows to classify this piperidine derivative as a representative of the so-called "Janus face" (facially polarized) saturated cyclic compounds, similar to the previously described cyclohexane derivatives.

The combined set of fluorinated and fluoroalkyl-substituted saturated heterocyclic amines provides extended possibilities for rational compound optimization during medicinal chemistry studies. In particular, it contains certain number of building block pairs where minimal structural alterations result in a significant change of physicochemical properties. On the contrary, there are also structurally distinct compounds having nearly the same basicity/lipophilicity, which allows affecting binding to the biological target without considerable changes in physicochemical properties.

Experimental Section

Compounds **7**[48] and **8**[50] were prepared according to the known methods. All other starting materials were available from Enamine Ltd. or purchased from other commercial sources. Compound *cis*-3,5-F-**6a** can be also prepared according to the reported methods.[45,51] Log*P* values for compounds **4–6b** were retrieved from the previously published work.[39] All other Log*P*, as well as pK_a values were measured as described previously.[37] Melting points were measured on MPA100 OptiMelt automated melting point system. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on an Agilent ProPulse 600 spectrometer (at 600 MHz for ^{1}H NMR, 151 MHz for ^{13}C NMR), Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR and 470 MHz for ^{19}F NMR) or Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-*d*$_6$. Coupling constants (*J*) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)). pK_a(H) measurements were performed using a SI Analytics TitroLine 7000 automated titrator. Agilent 1260 HPLC instrument equipped with diode-array detector (G1365A) and Agilent 6120B Quadrupole LC-MS with ESI ionisation (Zorbax SB C18 column (2.1×50 mm, 1.8 μm), gradient 0.1% HCO_2H in H_2O – 0.1% HCO_2H in MeCN (90:10 to 0:100) as eluent) was used for Log*P* measurements.

Metabolic stability measurements were performed using high performance liquid chromatography/tandem mass spectrometry (HPLC-MS/MS). Shimadzu HPLC system comprised of two isocratic pumps LC-10ADvp, an autosampler SIL-30ACMP, a system controller CBM-20A, a high-pressure switching valve FCV-20AH6, and a degasser DGU-14A and was equipped with Phenomenex Luna® C18 HPLC column, 2.1×50 mm, 5 μm. Mass spectrometric analysis was performed using an API 4000 QTRAP mass spectrometer from Applied Biosystems/ MDS Sciex (AB Sciex) with Turbo V ion source and Turbolonspray interface. The data acquisition and system control were performed using Analyst 1.6.3 software from AB Sciex. The TurbolonSpray ion source was used in both positive and negative ion

modes. Human liver microsomes (pooled, mixed gender) were obtained from XenoTech (H0630/lot N#1810003). Environmental incubator shaker G2, digital refrigerated incubator/shaker Innova 4330 (New Brunswick Scientific) were used for the microsomal incubation. Millipore Milli-Q Gradient A10 water purification system (Millipore, France) was used for the purification of water for the clearance measurements. Nitrogen gas was generated by Whatman N2-04-L1466 nitrogen generator, nitrogen purity 99%+.

(3*R,4*R**)-*tert*-Butyl 4-fluoro-3-hydroxypiperidine-1-carboxylate (2a) and (3*R**,4*R**)-*tert*-butyl 3-fluoro-4-hydroxypiperidine-1-carboxylate (2b).** *tert*-Butyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (**1**) (50 g, 0.251 mol) and $Et_3N{\cdot}3HF$ (55.0 mL, 0.337 mol) were mixed in a round-bottom flask. The reaction mixture was heated to 80 °C and stirred at that temperature overnight (monitored by ^1H NMR spectroscopy), then cooled to rt, and H_2O (650 mL) was added. The resulting mixture was extracted with EtOAc (3×300 mL). The combined organic extracts were washed with 1 M aq $NaHSO_4$ 300 mL), saturated aq $NaHCO_3$ (300 mL), and brine (200 mL), dried over Na_2SO_4, and evaporated in vacuo. The resulting mixture of compounds **2a** and **2b** (49.0 g, 4:1 by ^1H NMR spectrum) was used in the next step. A fraction from another run (1.20 g) was purified by column chromatography (hexanes – EtOAc (1:2) as eluent).

Compound 2a: yield 1.03 g (76%). Colorless powder, mp = 99–100 °C. R_f = 0.73. ^1H NMR (500 MHz, $CDCl_3$) δ 4.58 – 4.37 (m, 1H), 3.92 (s, 1H), 3.74 (s, 1H), 3.47 – 2.62 (m, 3H), 2.05 (s, 1H), 1.68 (s, 1H), 1.44 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0 (br), 93.0 (br), 80.3, 68.7 (br), 46.5 (br), 40.5 (br), 28.6 (d, *J* = 18.6 Hz), 28.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ –187.24 and –188.16. Anal. calcd. for $C_{10}H_{18}FNO_3$: C 54.78; H 8.28; N 6.39. Found: C 54.82; H 8.26; N 6.35.

Compound 2b: yield 30 mg (2%). Colorless oil. R_f = 0.49. ^1H NMR (500 MHz, $CDCl_3$) δ 4.38 – 4.21 (m, 1H), 4.20 – 4.04 (m, 1H), 3.95 – 3.87 (m, 1H), 3.85 – 3.70 (m, 1H), 3.07 – 2.97 (m, 1H), 2.93 (ddd, *J* = 13.8, 11.1, 3.0 Hz, 1H), 2.39 – 2.11 (m, 1H), 2.03 – 1.89 (m, 1H), 1.61 – 1.49 (m, 1H), 1.46 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.6, 90.8 (d, *J* = 177.5 Hz), 80.3, 70.7 (br), 44.9 (br), 40.8 (br), 30.5 (br), 28.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ –193.1. MS(APCI) *m/z* = 164 [M–*t*Bu+H]$^+$. Anal. calcd. for $C_{10}H_{18}FNO_3$: C 54.78; H 8.28; N 6.39. Found: C 54.82; H 8.25; N 6.39.

(3*R,4*R**)-3,4-Difluoropiperidine hydrochloride (*trans*-3,4-F-6a HCl).** A mixture of compounds **2a** and **2b** from the previous step (49.0 g, ca. 0.224 mol) was placed in a three-necked round-bottom flask equipped with a thermometer, a dropping funnel, and an argon inlet. CH_2Cl_2 (750 mL) was added under argon atmosphere. The mixture was cooled to –25 °C, and Deoxofluor (103 mL, 0.559 mol) was added dropwise at this temperature. The resulting mixture was kept at the above temperature for 1 h and then slowly warmed to rt overnight (monitored by ^1H NMR spectra). After the reaction was complete, the mixture was poured onto a mixture of saturated aq $NaHCO_3$ – ice (ca. 10:1, 1600 mL). The organic phase was separated and kept. The aqueous phase was extracted with EtOAc (3×500 mL). The organic phases were combined, washed with 1 M aq $NaHSO_4$ (2×200 mL) and brine (200 mL), dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by flash chromatography (hexanes – EtOAc (5:1) as eluent, R_f = 0.35) to give crude product **3a** used in the next step without additional purification.

Compound **3a** from the previous step was dissolved in Et_2O (200 mL), and 4 M HCl in 1,4-dioxane (200 mL) was added carefully. The resulting mixture was stirred overnight (monitored by ^1H NMR spectra). The precipitate was filtered, washed with *t*-BuOMe (300 mL), MeCN (2×200 mL), and *t*-BuOMe (200 mL), and then dried in vacuo to give *trans*-3,4-F-**6a** HCl. Yield 16.0 g (46% yield). White powder, mp = 190 °C. ^1H NMR (500 MHz, [D6]DMSO) δ 9.59 (br s, 2H), 5.13 – 4.95 (m, 1H), 4.95 – 4.78 (m, 1H), 3.58 – 3.40 (m, 1H), 3.27 – 3.11 (m, 2H), 3.07 – 2.93 (m, 1H), 2.34 – 2.12 (m, 1H), 2.05 – 1.87 (m, 1H). ^{13}C NMR (151 MHz, [D6]DMSO) δ 87.4 (dd, *J* = 175.9, 22.9 Hz), 85.9 (dd, *J* = 176.3, 24.3 Hz), 43.0 (dd, *J* = 26.8, 5.1 Hz), 39.6 (m), 25.4 (dd, *J* = 20.5, 4.7 Hz). ^{19}F NMR (376 MHz, [D6]DMSO) δ –189.5 (br), –194.2 (d, *J* = 14.2 Hz). MS(APCI) *m/z* = 122 [M+H]$^+$. Anal. calcd. for $C_5H_{10}ClF_2N$: C 38.11; H 6.40; N 8.89; Cl, 22.50. Found: C 38.07; H 6.38; N 8.89; Cl 22.50.

(3*R,4*S**)-3,4-Difluoropiperidine hydrochloride (*cis*-3,4-F-6a·HCl).** Compound *cis*-3,4-F-**6a**·HCl was obtained from (3*R**,4*R**)-*tert*-butyl 3,4-dihydroxypiperidine-1-carboxylate (**7**) (12.0 g, 55.4 mmol) and Deoxofluor (30.7 mL, 0.166 mol, 3 eq) following the procedure described above for the *trans* isomer. Yield 4.21 g (38%). White powder, mp = 144 °C. ^1H NMR (500 MHz, [D6]DMSO) δ 10.51 – 8.73 (m, 2H), 5.24 – 5.07 (m, 1H), 5.06 – 4.91 (m, 1H), 3.43 – 3.22 (m, 2H), 3.18 – 3.06 (m, 1H), 3.01 (dt, *J* = 13.1, 6.8 Hz, 1H), 2.07 (dq, *J* = 12.0, 5.8 Hz, 2H). ^{13}C NMR (126 MHz, [D6]DMSO) δ 85.9 (dd, *J* = 180.0, 17.5 Hz), 84.8 (dd, *J* = 178.8, 18.0 Hz), 43.1 (dd, *J* = 23.3, 6.1 Hz), 39.6 (d, *J* = 9.6 Hz), 23.6 (dd, *J* = 21.2, 4.2 Hz). ^{19}F NMR (376 MHz, [D6]DMSO) δ –193.2, –203.4. MS(APCI) *m/z* = 122 [M+H]$^+$. Anal. calcd. for $C_5H_{10}ClF_2N$: C 38.11; H 6.40; N 8.89; Cl, 22.50. Found: C 38.15; H 6.36; N 8.93; Cl 22.53.

(3*R*,5*R*)-1-benzyl-3,5-bis((trimethylsilyl)oxy)piperidine (10). To a solution of diol **8** (74.5 g, 0.358 mol) and triethylamine (175 mL, 1.283 mol) in dry CH_2Cl_2 (2.5 L), Me_3SiCl (114 mL, 0.896 mol) was added dropwise, and the mixture was heated in an oil bath (40 °C) with stirring for 12 h. Then the reaction mixture was cooled, washed with water (3×500 mL), brine (350 mL), dried over Na_2SO_4, and evaporated in vacuo to obtain compound **10** used in the next step without further purification. An analytical sample was prepared by flash chromatography (hexanes – EtOAc (8:1) as eluent). Yield 107 g (85%). Brownish oil. R_f = 0.75 (hexanes – EtOAc (8:1)). ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.14 (m, 5H), 4.06 (s, 2H), 3.73 (d, *J* = 13.5 Hz, 1H), 3.48 (d, *J* = 13.5 Hz, 1H), 2.46 (d, *J* = 10.1 Hz, 2H), 2.35 – 2.22 (m, 2H), 1.80 (s, 2H), 0.09 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.8, 128.8, 127.6, 126.5, 65.3, 62.2, 59.1, 41.1, –0.3. MS(APCI) *m/z* = 352 [M+H]$^+$. Anal. calcd. for $C_{18}H_{33}NO_2Si_2$: C 61.48; H 9.46; N 3.98. Found: C 61.47; H 9.49; N 3.97.

(3*R*,5*R*)-1-Benzyl-3,5-difluoropiperidine (9). To a solution of compound **10** (107 g, 0.305 mol) in CH_2Cl_2 (1.2 L), morph-DAST (110 mL, 0.903 mol) was added dropwise at 0 °C over 1 h, the cooling bath was removed, and the resulting mixture was stirred while slowly reaching rt for 14 h. The obtained solution was quenched with saturated aq $NaHCO_3$ (3.5 L) (added dropwise carefully). CAUTION! Vigorous gas evolution. The organic phase was separated, washed with saturated aq $NaHCO_3$ (400 mL), brine (400 mL), dried over Na_2SO_4 and evaporated in vacuo. The reside was purified by flash chromatography (hexanes – EtOAc (6:1) as eluent) to give compound **9** as reddish oil. Yield 38.6 g (60%). R_f = 0.55 (hexanes – EtOAc (6:1)). ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 – 6.97 (m, 5H), 5.03 – 4.75 (m, 2H), 3.77 – 3.58 (m, 2H), 2.86 – 2.65 (m, 2H), 2.65 – 2.52 (m, 2H), 2.17 – 1.93 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.6, 128.5, 127.9, 126.9, 86.1 (dd, *J* = 172.2, 6.9 Hz), 61.6, 55.8 (d, *J* = 22.4 Hz), 35.3 (t, *J* = 20.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –184.5. MS(APCI) *m/z* = 212 [M+H]$^+$. Anal. calcd. for $C_{12}H_{15}F_2N$: C 68.23; H 7.16; N 6.63. Found: C 68.24; H 7.18; N 6.65.

(3*R*,5*R*)-3,5-Difluoropiperidine hydrochloride (*trans*-3,5-F-6a HCl). To a solution of compound **9** (38.6 g, 0.183 mol) in dry MeOH (1 L), 2 M HCl in MeOH (100 mL) was added. The resulting solution was evaporated in vacuo. The residue was triturated with Et_2O (500 mL) and filtered. The resulting hydrochloride was dissolved in dry MeOH (1 L), 5% Pd-C (4.00 g, pre-washed with dry MeOH) was added, and the mixture was hydrogenated in a high-pressure vessel at 20 atm of H_2 and 24 °C for 12 h. The reaction was monitored by ^1H NMR; if it was incomplete after each 12 h, the catalyst was filtered off, a new portion was added, and the hydrogenation was repeated. After the complete conversion, the catalyst was filtered off, and the filtrate was evaporated in vacuo. The crude product was triturated with cold MeCN (100 mL), filtered, and dried in vacuo (1 mmHg) over P_2O_5 overnight. An analytical sample was obtained by recrystallization from MeCN. Yield 26.0 g (90%). Colorless solid. Mp 183–185 C (dec.). $[\alpha]_D$ = +10.2 (*c* 0.25, MeOH). *ee* > 99% (Chiralcel OJ-H (250×4.6 mm, 5 μm) column, hexane – *i*-PrOH – MeOH (50:25:25) as eluent, 0.6 mL/min flow). ^1H NMR (400 MHz, [D6]DMSO) δ 9.89 (s, 2H), 5.21 – 5.00 (m, 2H), 3.34 – 3.13 (m, 4H), 2.32 – 2.17 (m, 2H). ^{13}C NMR (151 MHz, [D6]DMSO) δ 84.8 (dd, *J* = 170.6, 7.6 Hz), 44.8 (d, *J* = 25.7 Hz), 33.5 (t, *J* = 20.1 Hz). ^{19}F NMR (376 MHz, [D6]DMSO) δ –186.3. MS(APCI)

m/z = 122 [M+H]+. Anal. calcd. for $C_5H_{10}ClF_2N$: C 38.11; H 6.40; N 8.89; Cl, 22.50. Found: C 38.10; H 6.43; N 8.87; Cl 22.47.

General procedure for the preparation of fluorinated amides x,y-F-4–6b. To a stirred solution of fluorinated amine x,y-F-**4–6a** (2.50 mmol as either free base, or hydrochloride, or trifluoroacetate, and NEt_3 (0.87 mL, 6.25 mmol) in CH_2Cl_2 (4 mL), a solution of benzoyl chloride (0.28 mL, 2.38 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise at 0 °C. The reaction mixture was stirred at rt for 18 h and then washed with 10% aq $NaHSO_4$ (2×2 mL), saturated aq $NaHCO_3$ (2 mL), and brine (2 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography (gradient hexanes – *t*-BuOMe as eluent unless noted otherwise).

1-Benzoyl-3-fluoroazetidine (3-F-4b). Yield 278 mg (62%) from 3-F-**4a**·HCl (279 mg, 2.50 mmol). Colorless solid, mp = 68–69 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.56 (m, 2H), 7.53 – 7.34 (m, 3H), 5.48 – 5.15 (m, 1H), 4.55 – 4.43 (m, 2H), 4.43 – 4.08 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2 (d, *J* = 1.9 Hz), 132.2, 130.9, 128.0, 127.4, 81.8 (d, *J* = 204.8 Hz), 60.2 (br), 56.1 (br). ^{19}F NMR (376 MHz, $CDCl_3$) δ –180.9. MS(APCI) *m/z* = 180 [M+H]+. Anal. calcd. for $C_{10}H_{10}FNO$: C 67.03; H 5.63; N 7.82. Found: C 67.01; H 5.60; N 7.85.

1-Benzoyl-3,3-difluoroazetidine (3,3-F-4b). Yield 313 mg (65%) from 3,3-F-**4a**·HCl (324 mg, 2.50 mmol). Colorless solid, mp = 99–100 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 – 7.37 (m, 5H), 4.53 (t, *J* = 12.0 Hz, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.9, 132.2, 131.8, 128.6, 127.9, 115.4 (t, *J* = 273.6 Hz), 64.3 (br), 60.7 (br). ^{19}F NMR (376 MHz, $CDCl_3$) δ –101.0. MS(APCI) *m/z* = 198 [M+H]+. Anal. calcd. for $C_{10}H_9F_2NO$: C 60.91; H 4.60; N 7.10. Found: C 60.89; H 4.59; N 7.13.

1-Benzoyl-3-fluoropyrrolidine (3-F-5b). Yield 340 mg (70%) from 3-F-**5a**·HCl (314 mg, 2.50 mmol). Orangish oil. The compound existed as a ca. 57:43 mixture of rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.30 (m, 5H), 5.52 – 5.04 (m, 1H), 4.32 – 3.46 (m, 4H), 2.42 – 1.67 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4, 136.0, 129.7 and 129.6, 127.9, 126.8 and 126.6, 92.0 (d, *J* = 178.8 Hz) and 91.2 (d, *J* = 175.6 Hz), 55.1 (d, *J* = 23.5 Hz) and 52.4 (d, *J* = 21.3 Hz), 46.6 and 43.5, 32.7 (d, *J* = 19.4 Hz) and 30.6 (d, *J* = 20.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –177.9 and –178.8. MS(APCI) *m/z* = 194 [M+H]+. Anal. calcd. for $C_{11}H_{12}FNO$: C 68.38; H 6.26; N 7.25. Found: C 68.39; H 6.22; N 7.25.

1-Benzoyl-3,3-difluoropyrrolidine (3,3-F-5b). Yield 329 mg (63%) from 3,3-F-**5a**·HCl (359 mg, 2.50 mmol). Colorless oil. The compound existed as a ca. 55:45 mixture of rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.38 (m, 5H), 4.12 – 3.50 (m, 4H), 2.62 – 2.26 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 168.6, 135.5 and 135.1, 130.3, 128.3, 127.8 (t, *J* = 245.7 Hz), 127.2 and 127.1, 54.5 (t, *J* = 31.7 Hz) and 52.3 (t, *J* = 31.4 Hz), 46.5 and 43.3, 34.0 (t, *J* = 24.2 Hz) and 31.9 (t, *J* = 23.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –102.0 and –102.4. MS(APCI) *m/z* = 212 [M+H]+. Anal. calcd. for $C_{11}H_{11}F_2NO$: C 62.55; H 5.25; N 6.63. Found: C 62.56; H 5.29; N 6.64.

1-Benzoyl-(3*R,4*S**)-3,4-difluoropyrrolidine (*cis*-3,4-F-5b).** Yield 314 mg (61%) from *cis*-3,4-F-**5a** TFA (552 mg, 2.50 mmol). Orangish oil. ^{1}H NMR (500 MHz, [D$_6$]DMSO) δ 7.60 – 7.21 (m, 5H), 5.55 – 5.10 (m, 2H), 4.04 – 3.75 (m, 2H), 3.73 – 3.57 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 168.9, 135.3, 130.3, 128.3, 127.3, 88.7 (dd, *J* = 188.7, 15.3 Hz), 88.4 (dd, *J* = 184.8, 14.3 Hz), 50.0 (d, *J* = 25.2 Hz), 48.1 (d, *J* = 22.9 Hz). ^{19}F NMR (376 MHz, [D$_6$]DMSO) δ –204.4 (d, *J* = 7.1 Hz), –206.2 (d, *J* = 7.2 Hz). MS(APCI) *m/z* = 212 [M+H]+. Anal. calcd. for $C_{11}H_{11}F_2NO$: C 62.55; H 5.25; N 6.63. Found: C 62.53; H 5.26; N 6.60.

1-Benzoyl-(3*S,4*S**)-3,4-difluoropyrrolidine (*trans*-3,4-F-5b).** Yield 355 mg (71%) from *trans*-3,4-F-**5a**·HCl (359 mg, 2.50 mmol). Orangish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.35 (m, 5H), 5.43 – 4.80 (m, 2H), 4.28 – 3.50 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 135.4, 130.0, 128.0, 126.8, 91.5 (dd, *J* = 180.4, 32.5 Hz), 90.5 (dd, *J* = 178.9, 31.9 Hz), 52.3 (d, *J* = 21.8 Hz), 49.7 (d, *J* = 22.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –188.8 (d, *J* = 13.0 Hz), –191.1 (d, *J* = 13.0 Hz). MS(APCI) *m/z* = 212 [M+H]+. Anal. calcd. for $C_{11}H_{11}F_2NO$: C 62.55; H 5.25; N 6.63. Found: C 62.57; H 5.29; N 6.67.

1-Benzoyl-3-fluoropiperidine (3-F-6b). Yield 375 mg (73%) from 3-F-**6a**·HCl (349 mg, 2.50 mmol). Yellowish solid, mp = 67–69 °C. The compound existed as a ca. 65:35 mixture of rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 9.9 Hz, 5H), 5.04 – 4.40 (m, 1H), 4.37 – 3.93 (m, 1H), 3.89 – 3.61 (m, 1H), 3.57 – 3.15 (m, 2H), 2.13 – 1.74 (m, 3H), 1.73 – 1.40 (m, 1H). ^{13}C NMR (126 MHz, DMSO) δ 169.7, 136.5 and 136.0, 129.4, 128.4 and 128.3, 126.9 and 126.5, 86.4 (d, *J* = 171.7 Hz), 50.8 (br) and 45.2 (br), 46.7 (br) and 41.3 (br), 28.8 (br), 21.1 (br) and 19.9 (br). ^{19}F NMR (376 MHz, $CDCl_3$) δ –184.8 and –186.4. MS(APCI) *m/z* = 208 [M+H]+. Anal. calcd. for $C_{12}H_{14}FNO$: C 69.55; H 6.81; N 6.76. Found: C 69.58; H 6.82; N 6.77.

1-Benzoyl-3,3-difluoropiperidine (3,3-F-6b). Yield 384 mg (68%) from 3,3-F-**6a**·HCl (394 mg, 2.50 mmol). Orangish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (s, 5H), 4.19 – 3.25 (m, 4H), 2.07 (tt, *J* = 13.1, 6.3 Hz, 2H), 1.97 – 1.73 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 134.7, 129.5, 128.1, 126.6, 118.6 (t, *J* = 244.2 Hz), 52.4 (br), 41.2 (br), 32.2 (t, *J* = 23.4 Hz), 21.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ –103.2, –104.1. MS(APCI) *m/z* = 226 [M+H]+. Anal. calcd. for C12H13F2NO: C 63.99; H 5.82; N 6.22. Found: C 63.95; H 5.81; N 6.23.

1-Benzoyl-4-fluoropiperidine (4-F-6b). Yield 320 mg (61%) from 4-F-**6a**·HCl (349 mg, 2.50 mmol). Beige solid, mp = 59–60 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.30 (m, 5H), 4.99 – 4.74 (m, 1H), 4.17 – 2.93 (m, 4H), 2.09 – 1.57 (m, 4H). ^{13}C NMR (126 MHz, DMSO) δ 169.0, 136.0, 129.4, 128.4, 126.6, 88.2 (d, *J* = 169.5 Hz), 43.3 (br), 37.8 (br), 31.1 (br), 30.7 (br). ^{19}F NMR (376 MHz, $CDCl_3$) δ –183.6. (APCI) *m/z* = 208 [M+H]+. Anal. calcd. for $C_{12}H_{14}FNO$: C 69.55, H 6.81; N 6.76. Found: C 69.56; H 6.84; N 6.80.

1-Benzoyl-4,4-difluoropiperidine (4,4-F-6b). Yield 426 mg (76%) from 4,4-F-**6a**·HCl (394 mg, 2.50 mmol). Yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.34 (m, 5H), 4.31 – 3.24 (m, 4H), 2.41 – 1.83 (m, 4H). ^{13}C NMR (126 MHz, [D$_6$]DMSO) δ 169.2, 135.6, 129.6, 128.4, 126.7, 122.7 (t, *J* = 241.3 Hz), 43.9 (br), 38.4 (br), 33.3 (br). ^{19}F NMR (376 MHz, $CDCl_3$) δ –98.4. MS(APCI) *m/z* = 226 [M+H]+. Anal. calcd. for $C_{12}H_{13}F_2NO$: C 63.99; H 5.82; N 6.22. Found: C 64.02; H 5.81; N 6.18.

1-Benzoyl-(3*S,4*R**)-3,4-difluoropiperidine (*cis*-3,4-F-6b).** Yield 342 mg (61%) from *cis*-3,4-F-**6a**·HCl (394 mg, 2.50 mmol). Orangish oil. The compound existed as a ca. 65:35 mixture of rotamers. ^{1}H NMR (500 MHz, [D$_6$]DMSO) δ 7.48 – 7.33 (m, 5H), 5.21 – 4.59 (m, 2H), 4.40 – 3.99 (m, 1H), 3.90 – 3.35 (m, 2H), 3.25 – 2.98 (m, 1H), 2.07 – 1.65 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 170.1 (br), 135.6, 129.6, 128.4, 127.0 and 126.7, 88.3 (dd, *J* = 176.6, 18.2 Hz), 86.1 (dd, *J* = 180.1, 16.8 Hz), 48.2 (br) and 43.0 (br), 42.0 (br) and 38.2 (br), 27.0 (br) and 26.0 (br). ^{19}F NMR (376 MHz, [D$_6$]DMSO) δ –189.0 and –192.9, –203.0 and –205.2. MS(APCI) *m/z* = 226 [M+H]+. Anal. calcd. for $C_{12}H_{13}F_2NO$: C 63.99; H 5.82; N 6.22. Found: C 63.96; H 5.81; N 6.25.

1-Benzoyl-(3*S,4*S**)-3,4-difluoropiperidine (*trans*-3,4-F-6b).** Yield 548 mg (73%) from *trans*-3,4-F-**6a**·HCl (394 mg, 2.50 mmol). Beige solid, mp = 97–98 °C. The compound existed as a ca. 55:45 mixture of rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (s, 5H), 4.93 – 4.71 (m, 1H), 4.70 – 4.36 (m, 1H), 4.32 – 3.21 (m, 4H), 2.53 – 1.71 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 169.6, 135.3, 129.7, 128.4, 126.8, 88.4 (br), 87.4 (br), 47.3 (br) and 42.1 (br), 43.2 (br) and 37.3 (br), 28.5 (br) and 27.5 (br). ^{19}F NMR (376 MHz, $CDCl_3$) δ –191.9 and –194.3, –195.0 and –195.7. MS(APCI) *m/z* = 226 [M+H]+. Anal. calcd. for $C_{12}H_{13}F_2NO$: C 63.99; H 5.82; N 6.22. Found: C 63.96; H 5.80; N 6.20.

1-Benzoyl-(3*S,5*R**)-3,5-difluoropiperidine (*cis*-3,5-F-6b).** Yield 469 mg (64%) from *cis*-3,5-F-**6a**·HCl (394 mg, 2.50 mmol). Beige solid, mp = 128–

130 °C. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.05 – 7.34 (m, 5H), 5.02 – 4.32 (m, 3H), 4.14 – 3.70 (m, 1H), 3.59 – 3.21 (m, 2H), 2.64 – 2.31 (m, 1H), 2.28 – 1.83 (m, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 171.4, 134.6, 129.5, 128.0, 127.0, 83.8 (d, J = 177.6 Hz), 50.0 (br), 45.2 (br), 34.0 (t, J = 21.1 Hz). ^{19}F NMR (376 MHz, CDCl$_3$) δ –183.3. MS(APCI) m/z = 226 [M+H]$^+$. Anal. calcd. for $C_{12}H_{13}F_2NO$: C 63.99; H 5.82; N 6.22. Found: C 64.02; H 5.85; N 6.21.

1-Benzoyl-(3*R*,5*R*)-3,5-difluoropiperidine (*trans*-3,5-F-6b). Yield 531 mg (69%) from *trans*-3,5-F-**6a**·HCl (394 mg, 2.50 mmol). Colorless solid, mp = 60–61 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO) δ 7.63 – 6.98 (m, 5H), 5.25 – 4.69 (m, 2H), 4.39 – 4.09 (m, 1H), 3.74 – 3.39 (m, 3H), 2.36 – 1.88 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 170.4, 135.3, 129.8, 128.4, 127.0, 86.5 (d, J = 197.8 Hz), 85.0 (d, J = 192.6 Hz), 49.9 (br), 44.8 (br), 35.0 (t, J = 20.2 Hz). ^{19}F NMR (376 MHz, [D$_6$]DMSO) δ –184.8, –185.1. MS(APCI) m/z = 226 [M+H]$^+$. Anal. calcd. for $C_{12}H_{13}F_2NO$: C 63.99; H 5.82; N 6.22. Found: C 64.00; H 5.85; N 6.22. $[\alpha]_D$ = –12.8 (*c* 0.25, CHCl$_3$). *ee* > 99% (Chiralcel OJ-H (250×4.6 mm, 5 μm) column, hexane – *i*-PrOH – MeOH (70:15:15) as eluent, 0.6 mL/min flow).

X-ray diffraction studies. The colourless crystals of *trans*-3,4-F-**6a**·HCl ($C_9H_{10}F_2NCl$) are monoclinic. At 173 K, a = 9.6890(10), b = 9.5641(8), c = 7.83217) Å, β = 101.399(4)°, V = 711.46(11) Å^3, M_r = 157.59, Z = 4, space group $P2_1/c$, d_{calc} = 1.471 g/cm^3, μ(MoK$_\alpha$) = 0.486 mm^{-1}, F(000) = 328. Intensities of 23126 reflections (1256 independent, R_{int} = 0.074) were measured on the Bruker APEX II diffractometer (graphite monochromated MoK$_\alpha$ radiation, CCD detector, φ- and ω-scanning, $2\Theta_{max}$ = 50°). The structure was solved by direct method using SHELXTL package.[56] Positions of the hydrogen atoms were located from electron density difference maps and refined using "riding" model with U_{iso} = 1.2U_{eq} of the carrier atom. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 1256 reflections was converged to wR_2 = 0.113 (R_1 = 0.046 for 1079 reflections with F>4σ(F), S = 1.080).

The colourless crystals of *cis*-3,4-F-**6a**·HCl ($C_9H_{10}F_2NCl$) are orthorhombic. At 173 K, a = 7.1864(7), b = 28.014(2), c = 10.6335(9) Å, V = 2140.8(3) Å^3, M_r = 157.59, Z = 12, space group *Pnma*, d_{calc} = 1.467 g/cm^3, μ(MoK$_\alpha$) = 0.485 mm^{-1}, F(000) = 984. Intensities of 28395 reflections (1931 independent, R_{int} = 0.089) were measured on the Bruker APEX II diffractometer (graphite monochromated MoK$_\alpha$ radiation, CCD detector, φ- and ω-scanning, $2\Theta_{max}$ = 50°). The structure was solved by direct method using SHELXTL package.[56] The asymmetric unit cell contains one molecule in the general position (molecule A) and half a molecule in the special position (molecule B). The large ADP of the F1B atom is due to the location of the B molecule in a special position. The disordering of the F1B atom does not have an adequate model. The location of molecule B in a special position causes the disorder of the substituent at the C2b atom. The fluorine or hydrogen atoms with occupancies of 50 % are found in this position. The C2B–F2B and C2B–H2Ba bond lengths were restricted as 1.40 Å and 0.99 Å. Positions of the hydrogen atoms were located from electron density difference maps and refined using "riding" model with U_{iso} = 1.2U_{eq} of the carrier atom. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 1931 reflections was converged to wR_2 = 0.231 (R_1 = 0.100 for 1723 reflections with F>4σ(F), S = 1.083).

Deposition Numbers <url href="https://www.ccdc.cam.ac.uk/services/structures?id=doi:10.1002/chem.202301383">> 2248713 (for *trans*-3,4-F-**6a**·HCl), 2248712 (for *cis*-3,4-F-**6a**·HCl)</url> contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe <url href="http://www.ccdc.cam.ac.uk/structures">Access Structures service</url>.

Acknowledgements

The work was supported by Enamine Ltd. and Ministry of Education and Science of Ukraine (Grants No. 0121U100387 (21BF037-01M) and 0122U001962 (22BF037-02)). The authors thank Ms. Olga Kovalenko and Ms. Margarita Bolgova for pK_a measurements, Oleksandr S. Liashuk for his help with manuscript preparation, Prof. Andrey A. Tolmachev for his encouragement and support, and all the brave people of Ukraine for making this publication possible.

Conflict of Interest

Most authors are / have been employees, trainees, or consulting scientists of Enamine Ltd. that offers all the amine building blocks described in this paper in the company's catalog.

Keywords: basicity • fluorine • lipophilicity • nitrogen heterocycles • saturated compounds

[1] Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422–518.

[2] J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506.

[3] S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330.

[4] C. Isanbor, D. O'Hagan, *J. Fluorine Chem.* **2006**, *127*, 303–319.

[5] M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633–10640.

[6] Y. Yu, A. Liu, G. Dhawan, H. Mei, W. Zhang, K. Izawa, V. A. Soloshonok, J. Han, *Chinese Chem. Lett.* **2021**, *32*, 3342–3354.

[7] H. Mei, A. M. Remete, Y. Zou, H. Moriwaki, S. Fustero, L. Kiss, V. A. Soloshonok, J. Han, *Chinese Chem. Lett.* **2020**, *31*, 2401–2413.

[8] H. Mei, J. Han, S. Fustero, M. Medio-Simon, D. M. Sedgwick, C. Santi, R. Ruzziconi, V. A. Soloshonok, *Chem. Eur. J.* **2019**, *25*, 11797–11819.

[9] D. Cahard, J.-A. Ma, Eds., *Emerging Fluorinated Motifs: Synthesis, Properties and Applications*; Wiley-VCH, Weinheim, **2020**, pp. 1–838.

[10] E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315–8359.

[11] N. A. Meanwell, *J. Med. Chem.* **2018**, *61*, 5822–5880.

[12] O. O. Grygorenko, K. P. Melnykov, S. Holovach, O. Demchuk, *ChemMedChem* **2022**, *17*, e202200365.

[13] K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886.

[14] Y. Zafrani, G. Sod-Moriah, D. Yeffet, A. Berliner, D. Amir, D. Marciano, S. Elias, S. Katalan, N. Ashkenazi, M. Madmon, E. Gershonov, S. Saphier, *J. Med. Chem.* **2019**, *62*, 5628–5637.

[15] N. Erdeljac, G. Kehr, M. Ahlqvist, L. Knerr, R. Gilmour, *Chem. Commun.* **2018**, *54*, 12002–12005.

[16] R. I. Troup, B. Jeffries, R. E.-B. Saudain, E. Georgiou, J. Fish, J. S. Scott, E. Chiarparin, C. Fallan, B. Linclau, *J. Org. Chem.* **2021**, *86*, 1882–1900.

[17] Y. Zafrani, G. Parvari, D. Amir, L. Ghindes-Azaria, S. Elias, A. Pevzner, G. Fridkin, A. Berliner, E. Gershonov, Y. Eichen, S. Saphier, S. Katalan, *J. Med. Chem.* **2021**, *64*, 4516–4531.

[18] A. V. Chernykh, D. S. Radchenko, A. V. Chernykh, I. S. Kondratov, N. A. Tolmachova, O. P. Datsenko, M. A. Kurkunov, S. X. Zozulya, Y. P. Kheylik, K. Bartels, C. G. Daniliuc, G. Haufe, *Eur. J. Org.*

Chem. **2015**, 6466–6471.

[19] B. Linclau, Z. Wang, B. Jeffries, J. Graton, R. J. Carbajo, D. Sinnaeve, J. Y. Le Questel, J. S. Scott, E. Chiarparin, *Angew. Chem. Int. Ed.* **2022**, *61*, e202114862.

[20] K. Müller, *Chim. Int. J. Chem.* **2014**, *68*, 356–362.

[21] Q. A. Huchet, B. Kuhn, B. Wagner, N. A. Kratochwil, H. Fischer, M. Kansy, D. Zimmerli, E. M. Carreira, K. Müller, *J. Med. Chem.* **2015**, *58*, 9041–9060.

[22] R. Vorberg, N. Trapp, D. Zimmerli, B. Wagner, H. Fischer, N. A. Kratochwil, M. Kansy, E. M. Carreira, K. Müller, *ChemMedChem* **2016**, *11*, 2216–2239.

[23] B. Jeffries, Z. Wang, J. Graton, S. D. Holland, T. Brind, R. D. R. Greenwood, J.-Y. Le Questel, J. S. Scott, E. Chiarparin, B. Linclau, *J. Med. Chem.* **2018**, *61*, 10602–10618.

[24] B. Jeffries, Z. Wang, H. R. Felstead, J. Y. Le Questel, J. S. Scott, E. Chiarparin, J. Graton, B. Linclau, *J. Med. Chem.* **2020**, *63*, 1002–1031.

[25] Z. Fang, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan, *Chem. Commun.* **2019**, *55*, 10539–10542.

[26] C. J. Thomson, Q. Zhang, N. Al-Maharik, M. Bühl, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan, *Chem. Commun.* **2018**, *54*, 8415–8418.

[27] T. J. Poskin, B. A. Piscelli, K. Yoshida, D. B. Cordes, A. M. Z. Slawin, R. A. Cormanich, S. Yamada, D. O'Hagan, *Chem. Commun.* **2022**, *58*, 7968–7971.

[28] Z. Fang, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan, *Chem. Commun.* **2019**, *55*, 10539–10542.

[29] D. O'Hagan, *Chem. Eur. J.* **2020**, *26*, 7981–7997.

[30] J. L. Clark, R. M. Neyyappadath, C. Yu, A. M. Z. Slawin, D. B. Cordes, D. O'Hagan, *Chem. Eur. J.* **2021**, *27*, 16000–16005.

[31] A. Rodil, S. Bosisio, M. S. Ayoup, L. Quinn, D. B. Cordes, A. M. Z. Slawin, C. D. Murphy, J. Michel, D. O'Hagan, *Chem. Sci.* **2018**, *9*, 3023–3028.

[32] J. L. Clark, R. M. Neyyappadath, C. Yu, A. M. Z. Slawin, D. B. Cordes, D. O'Hagan, *Chem. Eur. J.* **2021**, *27*, 16000–16005.

[33] Z. Fang, N. Al-Maharik, A. M. Z. Slawin, M. Bühl, D. O'Hagan, *Chem. Commun.* **2016**, *52*, 5116–5119.

[34] J. L. Clark, A. Taylor, A. Geddis, R. M. Neyyappadath, B. A. Piscelli, C. Yu, D. B. Cordes, A. M. Z. Slawin, R. A. Cormanich, S. Guldin, D. O'Hagan, *Chem. Sci.* **2021**, *12*, 9712–9719.

[35] N. S. Keddie, A. M. Z. Slawin, T. Lebl, D. Philp, D. O'Hagan, *Nat. Chem.* **2015**, *7*, 483–488.

[36] B. Jeffries, Z. Wang, R. I. Troup, A. Goupille, J. Y. Le Questel, C. Fallan, J. S. Scott, E. Chiarparin, J. Graton, B. Linclau, *Beilstein J. Org. Chem.* **2020**, *16*, 2141–2150.

[37] S. Holovach, K. P. Melnykov, A. Skreminskiy, M. Herasymchuk, O. Tavlui, D. Aloshyn, P. Borysko, A. B. Rozhenko, S. V. Ryabukhin, D. M. Volochnyuk, O. O. Grygorenko, *Chem. Eur. J.* **2022**, *28*, e202200331.

[38] A. V. Chernykh, K. P. Melnykov, N. A. Tolmacheva, I. S. Kondratov, D. S. Radchenko, C. G. Daniliuc, D. M. Volochnyuk, S. V. Ryabukhin, Y. O. Kuchkovska, O. O. Grygorenko, *J. Org. Chem.* **2019**, *84*, 8487–8496.

[39] K. P. Melnykov, O. Tavlui, A. Skreminskiy, Y. O. Kuchkovska, O. O. Grygorenko, *Chem. Eur. J.* **2022**, *28*, e202201601.

[40] D. S. Wishart, Y. D. Feunang, A. C. Guo, E. J. Lo, A. Marcu, J. R. Grant, T. Sajed, D. Johnson, C. Li, Z. Sayeeda, N. Assempour, I. Iynkkaran, Y. Liu, A. Maciejewski, N. Gale, A. Wilson, L. Chin, R. Cummings, Di. Le, A. Pon, C. Knox, M. Wilson, *Nucleic Acids Res.* **2018**, *46*, D1074–D1082.

[41] J. S. Katz, J. D. Rothstein, M. E. Cudkowicz, A. Genge, B. Oskarsson, A. B. Hains, C. Chen, J. Galanter, B. L. Burgess, W. Cho, G. A. Kerchner, F. L. Yeh, A. S. Ghosh, S. Cheeti, L. Brooks, L. Honigberg, J. A. Couch, M. E. Rothenberg, F. Brunstein, K. R. Sharma, L. van den Berg, J. D. Berry, J. D. Glass, *Ann. Clin. Transl. Neurol.* **2022**, *9*, 50–66.

[42] F. Liu, D. Barsyte-Lovejoy, F. Li, Y. Xiong, V. Korboukh, X. P. Huang, A. Allali-Hassani, W. P. Janzen, B. L. Roth, S. V. Frye, C. H. Arrowsmith, P. J. Brown, M. Vedadi, J. Jin, *J. Med. Chem.* **2013**, *56*, 8931–8942.

[43] M. Morgenthaler, E. Schweizer, A. Hoffmann-Röder, F. Benini, R. E. Martin, G. Jaeschke, B. Wagner, H. Fischer, S. Bendels, D. Zimmerli, J. Schneider, F. Diederich, M. Kansy, K. Müller, *ChemMedChem* **2007**, *2*, 1100–1115.

[44] R. Mondal, M. Agbaria, Z. Nairoukh, *Chem. Eur. J.* **2021**, *27*, 7193–7213.

[45] Z. Nairoukh, M. Wollenburg, C. Schlepphorst, K. Bergander, F. Glorius, *Nat. Chem.* **2019**, *11*, 264–270.

[46] X. Li, R. K. Russell, J. Spink, S. Ballentine, C. Teleha, S. Branum, K. Wells, D. Beauchamp, R. Patch, H. Huang, M. Player, W. Murray, *Org. Process Res. Dev.* **2014**, *18*, 321–330.

[47] S. Chen, Y. Ruan, J. L. Lu, L. Hunter, X. G. Hu, *Org. Biomol. Chem.* **2020**, *18*, 8192–8198.

[48] C. J. Oswood, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2022**, *144*, 93–98.

[49] K. Shanmuganathan, T. Koudriakova, S. Nampalli, J. Du, J. M. Gallo, R. F. Schinazi, C. K. Chu, *J. Med. Chem.* **1994**, *37*, 821–827.

[50] J. Cossy, C. Dumas, D. G. Pardo, *Eur. J. Org. Chem.* **1999**, 1693–1699.

[51] J. P. Snyder, N. S. Chandrakumar, H. Sato, D. C. Lankin, *J. Am. Chem. Soc.* **2000**, *122*, 544–545.

[52] D. C. Lankin, N. S. Chandrakumar, S. N. Rao, D. P. Spangler, J. P. Snyder, *J. Am. Chem. Soc.* **1993**, *115*, 3356–3357.

[53] Z. Nairoukh, F. Strieth-Kalthoff, K. Bergander, F. Glorius, *Chem. Eur. J.* **2020**, *26*, 6141–6146.

[54] A. Malashchuk, A. V. Chernykh, A. V. Dobrydnev, O. O. Grygorenko, *Eur. J. Org. Chem.* **2021**, 4897–4910.

[55] P. N. Craig, *J. Med. Chem.* **1971**, *14*, 680–684.

[56] G. M. Sheldrick, *Acta Crystallogr. Sect. A* **2007**, *64*, 112–122.

RESEARCH ARTICLE

Impact of Fluoroalkyl Substituents on Physicochemical Properties of Saturated Heterocyclic Amines

Dr. Kostiantyn P. Melnykov,[a,b] Olha Tavlui,[a,b] Artem Skreminskiy,[a] Yuliya O. Kuchkovska,[a,c] and Prof. Dr. Oleksandr O. Grygorenko *[a,b]

Dedicated to the memory of all Ukrainian scientists who have died because of the conflict in 2022

[a] Enamine Ltd.
Chervonotkatska Street 78, Kyiv 02094, Ukraine.
URL: www.enamine.net
[b] Taras Shevchenko National University of Kyiv
Volodymyrska Street 60, Kyiv 01601, Ukraine
E-mail: gregor@univ.kiev.ua
Supporting information for this article is given via a link at the end of the document
[c] Current address: Biozentrum, University of Basel
Spitalstrasse 41, 4056 Basel, Switzerland

Abstract: Profiling of the physicochemical properties (pK_a(H), log*P*, and aqueous solubility) of fluoroalkyl-substituted heterocyclic amines was carried out to facilitate their rational application in medicinal chemistry research. The corresponding features of fluorine-containing compounds were compared to the parent non-fluorinated heterocycles and the corresponding fluorinated *n*-alkylamines. Amine basicity was observed to change in a monotonic fashion depending on the fluorination pattern. Although the introduction of fluoroalkyl groups had complex effects on lipophilicity and aqueous solubility of the compounds, possible contributions of the fluorination pattern, ring size, and conformation of the substituent in the ring were addressed for a series of derivatives. The summarized data provides a useful guideline for application of fluorinated motifs for fine-tuning the compound's properties related to drug discovery.

Introduction

Introducing fluorine atoms and fluorine-containing motifs into the structures of bioactive compounds has become a widely implemented practice in drug optimization programs.[1–4] Such modification can provide considerable changes in a compound's physicochemical and conformational properties depending on the number of introduced fluorine atoms, their spatial arrangement, and the local molecular environment. The resulting capacity of fluorinated groups to tune potency, bioavailability, and pharmacokinetic parameters of drugs has been highlighted in a number of reviews.[5,6]

Given that fluorine-containing compounds constitute at least one-third of drugs that are approved each year,[7–10] the supply of novel fluorinated motifs (especially the ones with sp^3-enriched, conformationally restricted backbone, bearing commonly used functional groups) gives options to diversify screening libraries and to introduce new possibilities for late optimization of lead compounds. Although multiple academic and industrial groups put significant efforts into providing fluorinated building blocks in all shapes and forms,[11–13] there is still a lack of understanding of how to utilize these motifs rationally[14] instead of exhaustive enumeration and testing of multiple bioactive derivatives.

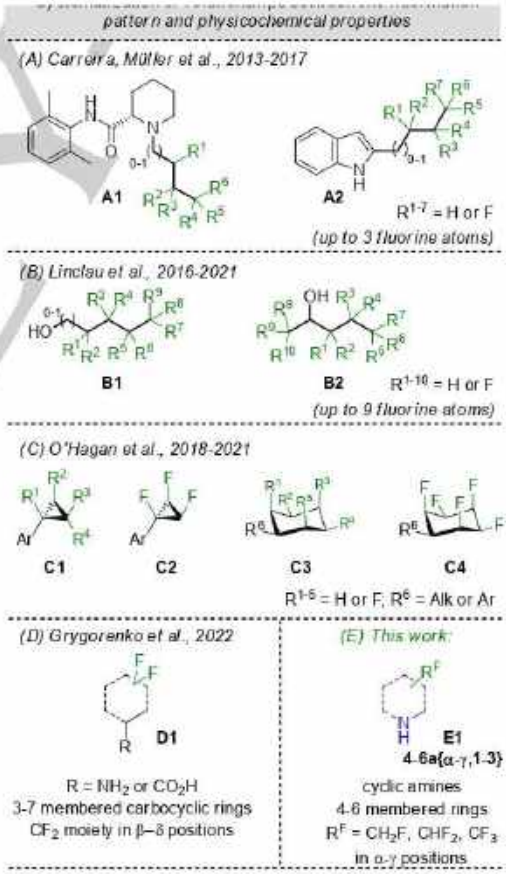


Figure 1. (*A–D*) Previous work systematizing the impact of the fluorination pattern on a compounds' physicochemical properties; (*E*) the structural type studied in this work

NOT PEER REVIEWED

A number of insightful studies that summarize the impact of various fluorination patterns on the compound's physicochemical and pharmacokinetic parameters started to emerge over the last decade.[15–19] In one of their contributions, Müller and co-authors suggested that the dipole moment of the *vic*-difluoro moiety is 1.4 times higher than that of the *gem*-difluoro moiety based on a simple vector analysis approach.[20] Later on, this assumption was experimenttally confirmed by showing a lipophilicity decrease in *vic*-difluoro-substituted derivatives **A1** and **A2**, and a basicity decrease in **A1** compared to their *gem*-difluoro-substituted counterparts (Figure 1, *A*).[21,22]

Another prominent contribution involved comprehensive screening of the Log*P* changes resulting from the introduction of additional fluorine atoms, their spatial rearrangement, and elongation of carbon chain in **B1**, **B2** or their derivatives (Figure 1, *B*).[23–25] This study by the Linclau group delivered helpful guidelines facilitating fine-tuning of lipophilicity in (hetero-)aliphatic chains.

Conformational restriction of carbocyclic rings provides better control over the direction of C–F bonds and hence the overall dipole moment of the motif. This property was masterly used by the O'Hagan group to design and synthesize polarized 'Janus face' derivatives of 1,2,3-trifluorocyclopropane (**C1**–**2**), all-*cis* tetra-, and all-*cis* pentafluorocyclohexanes (**C3**–**4**) that exhibit lowered lypophilicity (Figure 1, *C*).[26–29] In a different paper, our group scanned the impact of introduction of *gem*-CF_2 group in β–δ positions of 3 to 7 carbocyclic rings on pK_a, Log*P*, and aqueous solubility (Figure 1, *D*).[30,31]

In this work, we focus on the impact of introducing the fluoroalkyl substituents into saturated cyclic amines **E1** on the compound's physicochemical properties. Several representatives of chemotype **E1** have already found their applications in drug development. Among those are the selective estrogen receptor degrader GDC-0927[32] (**7**) and $Na_v1.7$ voltage-gated sodium ion channel inhibitor GNE-616[33] (**8**) (Figure 2). Yet, there are no restrictions on the accessibility of other building blocks of type **E1** since they are available from commercial sources and for ready use by medicinal chemists. Therefore, we aimed to deliver insights to facilitate rational fine-tuning of basicity, lipophilicity, and water solubility of small saturated *N*-heterocycles by introduction of fluoroalkyl groups. In particular, we focused on the substitution of azetidines **4a**, pyrrolidines **5a**, and piperidines **6a** (Figure 3) with CH_2F, CHF_2, and CF_3 moieties and compared the observed changes in their physicochemical parameters with a series of acyclic representatives **1**–**3a**.

The following compound numbering system was adopted to facilitate the discussion: **na{m,k}** or **nb{m,k}**, where **n** – ring or chain size (**4**–**6** or **1**–**3**, respectively), **a** or **b** – compound series (**a** – free amines, **b** – their *N*-benzoyl derivatives), **m** – position of the substituent (**α**–*γ*); **k** – number of the fluorine atoms in the fluoroalkyl substituent R^F (**1** – CH_2F, **2** – CHF_2, **3** – CF_3).

Results and Discussion

Amine Basicity

For all the derivatives of amines **4**–**6a**, a stepwise substitution of hydrogen atoms in the alkyl group by fluorine atoms changed pK_a(H) in a monotonic fashion (Figure 4, *A*–*C* and Table 1).

Impact of the ring size. The measured pK_a(H) values for the cyclic amines of different ring sizes bearing the R^F group at the same position and with the same number of F-atoms were very similar (typically within the 0.1–0.2 pK_a unit range) for most of the derivatives except the α-CF_3 substituted ones (**4**–**6a{α,3}**). Therefore, the ring size generally has a minor impact on the compound's basicity. The reasons behind the anomalous behavior of compounds **4**–**6a{α,3}** are not clear, but some conformational effects may influence outcomes.

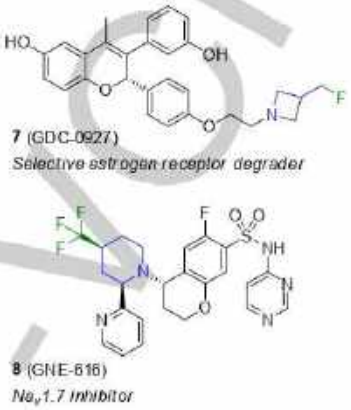


Figure 2. Examples of drug candidates containing fluoroalkyl-substituted azetidine (**7**) and piperidine (**8**) motif, respectively

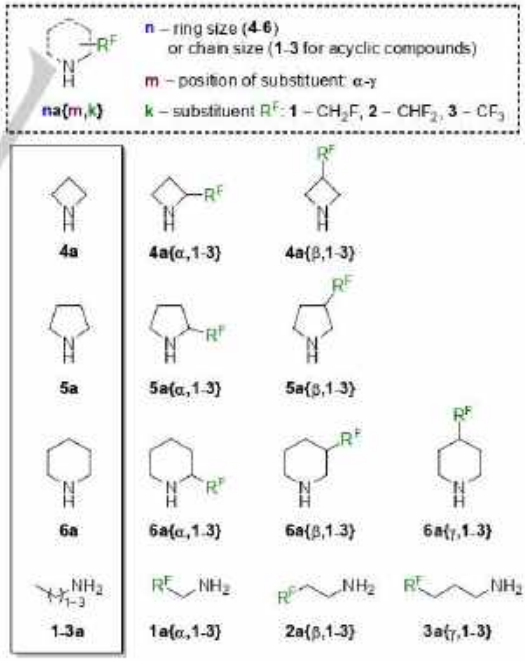


Figure 3. Non-substituted and fluoroalkyl-substituted amines studied in this work

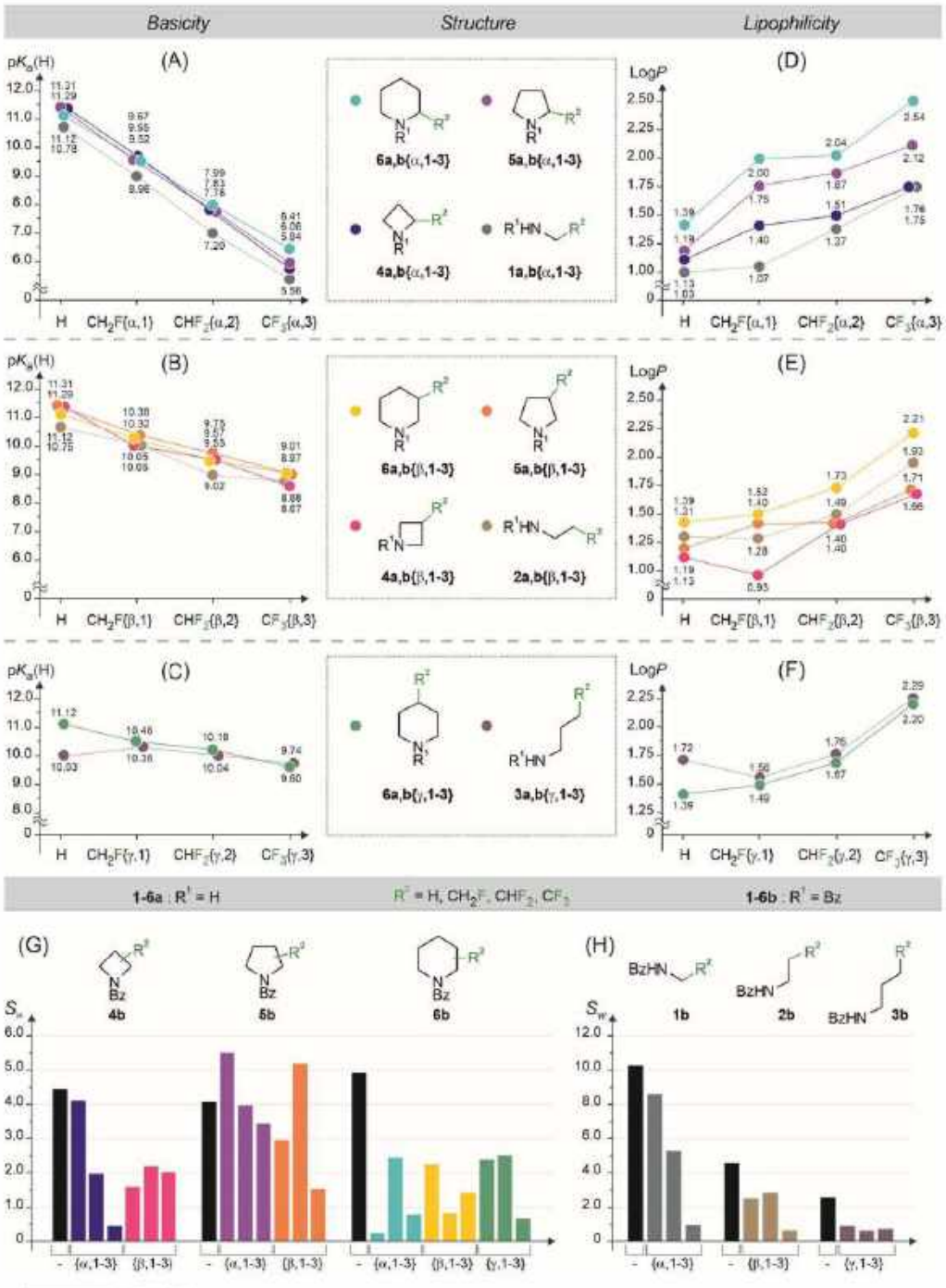


Figure 4. (*A–C*) Changes in pK_a(H) measured for amines **1,4–6a{α,1–3}**, **2,4–6a{β,1–3}**, and **3,6a{γ,1–3}**, respectively, as compared to pK_a(H) of non-fluorinated parent compounds **1–6a**; (*D–F*) changes in Log*P* measured for amides **1,4–6b{α,1–3}**, **2,4–6b{β,1–3}**, and **3,6b{γ,1–3}**, respectively, as compared to Log*P* of non-fluorinated parent compounds **1–6b**; (*G*) aqueous solubility of cyclic amides **4–6b** and **4–6{α–β,1–3}**; (*H*) aqueous solubility of acyclic amides **1–3b** and **1–3{α–β,1–3}**

Table 1. pK_a(H), Log*P* and S_w values for the compounds **1–6a,b** and their fluoroalkyl-substituted derivatives

Entry	R[a]	Amine	pK_a(H)	Amide	Log*P*	S_w, g/L
1	–	**4a**	11.29[b]	**4b**	1.13±0.01	4.44±0.36
2	CH_2F	**4a{α,1}**	9.67±0.03	**4b{α,1}**	1.40±0.01	4.09±0.12
3	CHF_2	**4a{α,2}**	7.83±0.03	**4b{α,2}**	1.51±0.01	1.96±0.16
4	CF_3	**4a{α,3}**	5.84±0.03	**4b{α,3}**	1.75±0.02	0.45±0.06
5	CH_2F	**4a{β,1}**	10.05±0.10	**4b{β,1}**	0.93±0.01	1.58±0.35
6	CHF_2	**4a{β,2}**	9.57±0.03	**4b{β,2}**	1.40±0.03	2.18±0.19
7	CF_3	**4a{β,3}**	8.67±0.03	**4b{β,3}**	1.66±0.01	2.01±0.12
8	–	**5a**	11.31[b]	**5b**	1.19±0.01	4.05±0.04
9	CH_2F	**5a{α,1}**	9.55±0.01	**5b{α,1}**	1.75±0.01	5.48±0.42
10	CHF_2	**5a{α,2}**	7.78±0.02	**5b{α,2}**	1.88±0.01	3.95±0.15
11	CF_3	**5a{α,3}**	6.06±0.03	**5b{α,3}**	2.12±0.01	3.42±0.02
12	CH_2F	**5a{β,1}**	10.38±0.03	**5b{β,1}**	1.40±0.01	2.94±0.17
13	CHF_2	**5a{β,2}**	9.75±0.01	**5b{β,2}**	1.40±0.02	5.17±0.27
14	CF_3	**5a{β,3}**	8.97±0.03	**5b{β,3}**	1.70±0.02	1.52±0.16
15	–	**6a**	11.12[b]	**6b**	1.39±0.01	4.88±0.02
16	CH_2F	**6a{α,1}**	9.52±0.01	**6b{α,1}**	2.00±0.01	0.24±0.02
17	CHF_2	**6a{α,2}**	7.99±0.03	**6b{α,2}**	2.04±0.01	2.42±0.01
18	CF_3	**6a{α,3}**	6.41±0.01	**6b{α,3}**	2.54±0.01	0.78±0.01
19	CH_2F	**6a{β,1}**	10.32±0.02	**6b{β,1}**	1.52±0.01	2.22±0.06
20	CHF_2	**6a{β,2}**	9.55±0.01	**6b{β,2}**	1.73±0.01	0.83±0.06
21	CF_3	**6a{β,3}**	9.01±0.04	**6b{β,3}**	2.21±0.01	1.42±0.16
22	CH_2F	**6a{γ,1}**	10.46±0.03	**6b{γ,1}**	1.45±0.01	2.37±0.16
23	CHF_2	**6a{γ,2}**	10.19±0.03	**6b{γ,2}**	1.67±0.01	2.50±0.30
24	CF_3	**6a{γ,3}**	9.60±0.02	**6b{γ,3}**	2.20±0.01	0.67±0.01
25	–	**1a**	10.78±0.03	**1b**	1.03±0.01	10.24±0.37
26	CH_2F	**1a{α,1}**	8.96±0.02	**1b{α,1}**	1.07±0.02	8.62±0.28
27	CHF_2	**1a{α,2}**	7.20±0.01	**1b{α,2}**	1.37±0.01	5.30±0.11
28	CF_3	**1a{α,3}**	5.56±0.01	**1b{α,3}**	1.76±0.01	0.98±0.02
29	–	**2a**	10.75±0.05	**2b**	1.31±0.01	4.57±0.38
30	CH_2F	**2a{β,1}**	10.05±0.03	**2b{β,1}**	1.28±0.01	2.55±0.24
31	CHF_2	**2a{β,2}**	9.02±0.05	**2b{β,2}**	1.49±0.01	2.88±0.12
32	CF_3	**2a{β,3}**	8.88±0.02	**2b{β,3}**	1.93±0.01	0.66±0.01
33	–	**3a**	10.03±0.06	**3b**	1.72±0.01	2.61±0.01
34	CH_2F	**3a{γ,1}**	10.36±0.04	**3b{γ,1}**	1.56±0.01	0.92±0.01
35	CHF_2	**3a{γ,2}**	10.04±0.02	**3b{γ,2}**	1.76±0.01	0.68±0.08
36	CF_3	**3a{γ,3}**	9.74±0.02	**3b{γ,3}**	2.28±0.01	0.77±0.12

[a] Values were retrieved from the literature data[34]

WILEY-VCH

Impact of the fluorination pattern. The following rule of thumb based on the R^F position and the number of F-atoms was derived from the obtained data: when R^F is introduced into amines **4–6a**, the pK_a(H) value is decreased by

$\Delta pK_a(H) = (1.68\pm0.10)\times\mathbf{k}$ for α-R^F substituted derivatives;
$\Delta pK_a(H) = (0.86\pm0.16)\times\mathbf{k}$ for β-R^F substituted derivatives;
$\Delta pK_a(H) = (0.54\pm0.10)\times\mathbf{k}$ for γ-R^F substituted derivatives;

where **k** corresponds to the number of F-atoms in the R^F group. These observations are in line with previously suggested rule of thumb for acyclic amines of type **1–3{α–β,1–3}**.[35] In particular, it was previously shown that pK_a(H) decreases by 1.7 and 0.7 units per fluorine atom for linear amines bearing CH_xF_y groups at α and β positions, respectively. However, for cyclic amines **4–6{γ,1–3}** the change of ca. 0.54 units appears to be slightly higher than reported 0.3 unit change for their acyclic counterparts.

Impact of the conformational restriction. The pK_a(H) decrease upon the R^F-substitution followed the same trends within the series of α-, β-, and γ-substituted derivatives for both cyclic (**4–6a{α–γ,1–3}**) and linear (**1–3a{α–γ,1–3}**) compounds. The pK_a(H) values for the cyclic amines bearing the α-R^F group were by 0.61 units (on average) higher than those of α-R^F substituted methylamine derivatives **1a{α,1–3}**. The observed pK_a(H) gap is in line with the expectedly higher basicity of secondary vs. primary amines (compare this value with an average 0.72 pK_a unit difference observed for the non-fluorinated compound series, **4–6a** and **1–3a**).

On the other hand, the average difference in the basicity of cyclic and linear amines in the series of β-R^F and γ-R^F derivatives was lower (0.27 and 0.13 pK_a units, respectively). Therefore, imposing the conformational restriction onto the *N*-γ-R^F-propyl and *N*-δ-R^F-butyl substituents by locking them into the 4–6-membered rings is expected to have little impact on the amine's basicity while possibly modulating the biological target affinity.

The above data reveal an effect of the cyclic backbone on the basicity of the studied compound series. This effect is opposite to the pK_a(H) increase caused by the primary – secondary amine difference. In other words, introducing the R_F group into β- or γ-positions of the small cyclic amines has a greater impact on the basicity as compared to acyclic ones. The effect might be explained by two alternative bond pathways of comparable lengths channeling the inductive effect of the fluorine atoms in the cyclic series.

Lipophilicity

Amides **1–6b** and their R^F-substituted derivatives were prepared by the standard reaction of corresponding amines **1–6a** (or their hydrochlorides) with benzoyl chloride in the presence of Et_3N. Log*P* and S_w of the compounds were measured using the classical shake-flask method combined with HPLC quantitative analysis. The results are shown in Figure 4, *D–F* and Table 1.

Impact of the ring size. The heterocyclic ring size of **4–6b** affected the lipophilicity in the series of α- and β-substituted compounds differently. In particular, an apparent Log*P* increase was observed in the series of α-R^F-substituted derivatives (**4b{α,1–3}** < **5b{α,1–3}** < **6b{α,1–3}**), which can be attributed merely to the increments of additional CH_2 units. Yet, irrespectively of ring size, the lipophilicity of β-CH_2F-pyrrolidine **5b{β,1}** approached the one for β-CH_2F-piperidine **6b{β,1}**. One more example is Log*P* of β-CHF_2-azetidine **4b{β,1}** that was the same as for β-CHF_2-pyrrolidine **5b{β,1}**. Likely, the relative orientation of the functional group dipoles that varied in different rings was important for the β-substituted derivatives, not merely the number of the carbon atoms in the heterocyclic ring.

Impact of the fluorination pattern. As might be anticipated, the lipophilicity increased in the series H < CH_2F ≤ CHF_2 < CF_3 for nearly all heterocyclic systems studied. Typically, the CH_2F- and CHF_2-substituted derivatives with the same ring size and R^F position had similar Log*P* values, whereas their CF_3-substituted counterpart was much more lipophilic – a trend that was also reported previously for acyclic compounds.[36] An exception to both regularities was β-CH_2F-substituted azetidine derivative **4b{β,1}**, for which Log*P* unexpectedly dropped by 0.2 units as compared to non-substituted *N*-benzoylazetidine **4b** (Figure 4, *E*). It was noted that the substituent position had a more pronounced impact on the Log*P* in the series of compounds bearing the same R^F group rather than the ring size (Figure 5). In particular, for the CH_2F- and CHF_2-substituted amides, introducing the R^F group into the α position resulted in a significant lipophilicity increase (Δlog*P*) that was above the average value for each of the series (depicted by dashed lines in Figure 5). On the contrary, the change in the lipophilicity for compounds **4–6b{β,1}** and **4–6b{β,2}** bearing β-R^F groups was below the average. However, a different trend was observed for the CF_3-substituted series. In this case, a greater impact of the CF_3 group on the Δlog*P* value was noted for α-CF_3-pyrrolidine **5b{α,3}** and all CF_3-substituted piperidines **6b{α–γ,3}**.

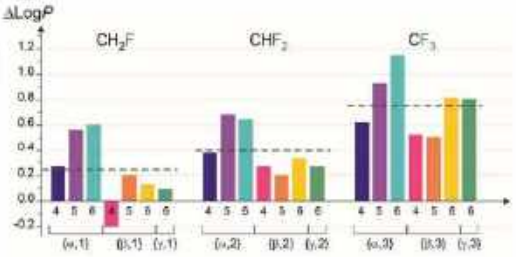


Figure 5. The Log*P* deviation of fluoroalkyl-substituted amides **4–6b{α–γ,1–3}** relatively to parent compounds **4–6b**. The compounds are grouped by the R^F substituent, and the impacts of the ring size and the substituent position on Δlog*P* are compared. The dashed lines correspond to mean Δlog*P* values within each group.

In general, the lipophilicity of the studied series changed in a non-monotonic fashion, and we were not able to generalize the log*P* changes and derive "the rule of thumb" similar to that for pK_a(H) values. Nevertheless, the obtained data is still useful for analysis of the Δlog*P* features and also as a reference.

Impact of the conformational restriction. Small and medium-sized rings are commonly used to impose a conformational restriction onto molecular fragments and fix the functional groups in a well-defined spatial arrangement. This strategy is especially beneficial for tuning the overall dipole moment of the molecule by controlling the angles of the between the separate polar moieties. In order to study impact of the conformational restriction on Log*P*, the relationship between the fluorination pattern and lipophilicity of **4–6b** was compared to acyclic amides **1–3b**. In general, there was a considerable change in the Log*P* values upon transition from non-fluorinated to CH_2F-substituted compounds **4–6b{α,1}** and **4–6b{β,1}** (0.27–0.61 units and 0.14–0.21 units, respectively). In contrast, the replacement of H with the CH_2F group in both

acyclic amides **1b** and **2b** changed Log*P* by only 0.03–0.04 units. However, the transition from CH_2F to CHF_2 followed the opposite trend. Whereas the lipophilicity of **1–2b{β,1}** increased by 0.21–0.30 units upon introduction of an additional fluorine atom, for the compounds **4–6b{α,1}**, only a minor change of 0.04–0.12 units was observed. Moreover, the lipophilicity of **5b{β,1}** was unaffected by an extra F-atom in the R^F group and remained the same. Nevertheless, the common increase in the lipophilicity was restored for the CHF_2 – CF_3 pairs in both series.

Finally, there was no significant gap between the Log*P* values of γ-R^F-substituted derivatives of piperidine (**6b**) and propylamine (**3b**) (Figure 4, *F*). This observation might be explained by the opposite orientations of the R^F and NBz group dipole moments that countervail each other in both series. In contrast, the proximity of α- and β-fluoroalkyl groups to amide substituent provided a notable shift of Log*P* values as compared to acyclic counterparts. This effect could be caused by the increased dipole moment that is induced by molecular geometry. Besides the role of the rotameric equilibria at the amide bonds and conformational equilibria of heterocyclic rings are also expected to impact the lipophilicity of the studied compounds. Conformation-specific lipophilicities of fluorine-containing piperidines and pyrrolidines were recently discussed in the literature.[19]

Aqueous Solubility

Aqueous solubility (S_W) was measured for both heterocyclic and acyclic fluoroalkyl-substituted amides **1–6b{α–γ,1–3}** and their non-fluorinated counterparts **1–6b** (Figure 4, *G* and *H*; Table 1). As expected, introducing the R^F group tends to decrease the S_W value in a series of *n*-alkylamides **1–3b{α–γ,1–3}** upon increasing the number of F-atoms. This effect goes in line with the lipophilicity increase for the corresponding compounds. However, a similar tendency was observed only for α-fluoroalkylazetidines **4b{α,1–3}** and α-fluoroalkylpyrrolidines **5b{α,1–3}**, whereas a non-monotonic change in S_W was noted for other cyclic derivatives. We also looked for the possible correlation between the Log*P* and S_W values for amides **1–6b{α–γ,1–3}** (Figure 6). Interestingly, no obvious correlation was observed in this case. Apparently, the equilibria in 1-octanol – water system and pure amide – water are quite different for the compounds studied.

Simultaneous Modulating Basicity and Lipophilicity

When optimizing physicochemical properties of potential drugs, it is advantageous to address the key parameters in combination rather than in isolation. The simultaneous mapping of pK_a(H) and log*P* values of the studied compounds (Figure 7) provides a straightforward guide to rational replacements of parent structures **4–6** with fluorinated building blocks. In this plot, four distinct areas were arbitrary outlined according to the R^F group (CH_2F, CHF_2, CF_3, or none).

The plot reveals a dense coverage of the pK_a(H) values ranging from *ca* 7.8 to 10.5 units, as well as three outliers **4–6a{α,3}** with basicity decreased about six orders of magnitude. On the other hand, the Log*P* values vary from 1.4 to 2.5, with the only outlier **(4b{β,1})** having log*P* = 0.93. Importantly, the discussed compounds provide a possibility to fine-tune the compound's basicity and lipophilicity even with alteration of a single structural feature: the size of the ring, the number of fluorine atoms in R^F, or its position in the ring.

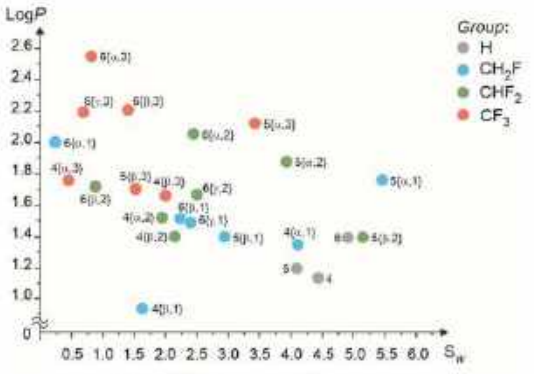


Figure 6. Compounds **1–6b{α–γ,1–3}** shown in Log*P* – S_W plot

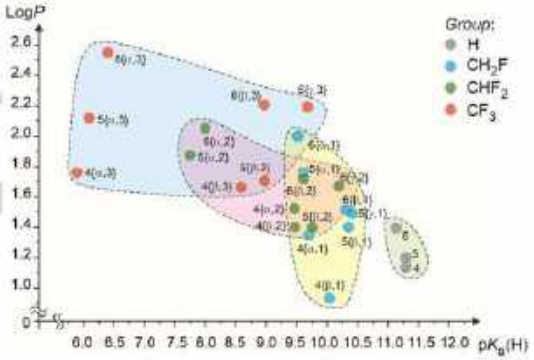


Figure 7. pK_a(H) and Log*P* value ranges covered by studied compounds. Area colors correspond to: yellow – R^F = CH_2F, pink – R^F = CHF_2, blue – R^F = CF_3, and grey – R^F is lacking

Interestingly, there is a significant overlap of physicochemical properties for the CH_2F- and CHF_2-substituted building blocks. Two remarkable examples are α-CH_2F-azetidine (**4{α,1}**) and β-CHF_2-pyrrolidine (**5{β,2}**) pair, as well as α-CH_2F-pyrrolidine (**5{α,1}**) and β-CHF_2-piperidine (**6{β,2}**) pair having nearly the same pK_a(H) and Log*P* values within the pairs. This observation highlights how two building blocks with different ring sizes, fluorinated groups, and their positions can be used interchangeably to retain physicochemical properties but modulate other characteristics (*e.g.*, conformational properties or binding affinity).

Results and Discussion

The replacement of azetidine, pyrrolidine, and piperidine with their fluoroalkyl-substituted analogs is an advantageous opportunity to modulate medicinal chemistry-related properties of biologically active compounds rationally. It can be achieved by alteration of the ring size, the substituent position, and the type of the fluoroalkyl group, either separately or in a combination. As a result,

physicochemical parameters of the discussed derivatives such as pK_a(H) and Log*P* cover the windows of 6.4–10.5 units and 0.9–2.5 units, respectively. Therefore, maximum shifts of ΔpK_a(H) = 4.9 and ΔLog*P* = 1.4 units can be achieved compared to the parent non-fluorinated heterocycles.

The most populated region of the discussed fluorinated compounds lies in the range of 7.8–10.5 pK_a(H) units and 1.4–2.5 Log*P* units, which allows using these building blocks interchangeably in order to carry out the precise tuning of the compound properties. Alternatively, the obtained data can provide helpful guidance when optimization of the compound's characteristics is required, but it is desirable to minimize the perturbation of physicochemical parameters.

In general, the basicity of the fluoroalkyl-substituted amines was dependent on the position and the nature of the fluorinated group, whereas the ring size had a lesser impact. A simple 'rule of thumb' was derived for the change in the pK_a(H) value per each fluorine atom in the substituent R^F: ΔpK_a(H) ca. 1.7 for α-R^F, 0.9 – for β-R^F, and 0.5 – for γ-R^F. On the other hand, the lipophilicity of the corresponding amide derivatives underwent a small increase going from CH_2F to CHF_2 group and a drastic increase going from CHF_2 to CF_3. Although the H < CH_2F ≤ CHF_2 < CF_3 trend was clearly discerned, the impact of the position of fluorinated substituents and the ring size was more complex. Similarly, the aqueous solubility of compounds changed in non-monotonic way and was affected by multiple factors.

We suggest that our physicochemical data analysis can be a helpful guidance for medicinal chemists to carry out hit-to-lead optimization in a more rational way. The building blocks studied in this work have small molecular weight, three-dimensional structure, and contain fluorinated moieties – all these have already proven to be advantageous for drug discovery and development. Together with other studies on impact of fluorination on the properties relevant to medicinal chemistry, our work provides a valuable perspective to comprehend a bigger picture of fluorination in drug discovery and encourages further exploration of other possibilities to rationally design novel fluorinated substituents.

Experimental Section

Amines **1–6a** (or their hydrochlorides) and amide **1b** were provided by Enamine Ltd. All other starting materials were available from Enamine Ltd. or purchased from other commercial sources. pK_a(H) values for compounds **4–6a** were retrieved from the previously published work.[34] All other pK_a(H), Log*P*, and S_w values were measured as described previously.[36] Melting points were measured on MPA100 OptiMelt automated melting point system. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on an Agilent ProPulse 600 spectrometer (at 600 MHz for ^{1}H NMR, 151 MHz for ^{13}C NMR), Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR and 470 MHz for ^{19}F NMR) or Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6. Coupling constants (*J*) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)). pK_a(H) measurements were performed using a SI Analytics TitroLine 7000 automated titrator. Agilent 1260 HPLC instrument equipped with diode-array detector (G1365A) and Agilent 6120B Quadrupole LC-MS with ESI ionisation (Zorbax SB C18 column (2.1×50 mm, 1.8 μm), gradient 0.1% HCO_2H in H_2O – 0.1% HCO_2H in MeCN (90:10 to 0:100) as eluent) was used for S_w and Log*P* measurements.

General procedure for the preparation of amides 2–6b. To a stirred solution of the corresponding amine **1–6a** (1.20 mmol) in CH_2Cl_2 (1.5 mL), a solution of benzoyl chloride (0.046 mL, 0.40 mmol) in CH_2Cl_2 (0.4 mL) was added dropwise at 0 °C. The reaction mixture was left to stir at rt for 18 h, and then was washed twice with 10% aq HCl. The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure.

General procedure for the preparation of amides 1–6b{α–γ,1–3}. To a stirred solution of the corresponding amine **1–6a{α–γ,1–3}** (2.50 mmol as either free base, or hydrochloride, or trifluoroacetate, and NEt_3 (0.87 mL, 6.25 mmol) in CH_2Cl_2 (4 mL), a solution of benzoyl chloride (0.28 mL, 2.38 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise at 0 °C. The reaction mixture was left to stir at rt for 18 h, and then was washed twice with 10% aq $NaHSO_4$. The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure.

***N*-(2-Fluoroethyl)benzamide (1b{α,1}).**[37] Yield 570 mg (88%) from **1a{α,1}**·HCl (385 mg, 3.87 mmol). Beige crystalline solid, mp = 50–52 °C (lit. 38–43 °C).[38] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.3 Hz, 2H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 6.64 (br s, 1H), 4.59 (dt, *J* = 47.4, 4.8 Hz, 2H), 3.77 (dq, *J* = 28.2, 5.1 Hz, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$)) δ 167.8, 134.2, 131.8, 128.7, 127.1, 82.9 (d, *J* = 166.4 Hz), 40.6 (d, *J* = 19.7 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –224.5 ppm. MS(APCI) *m/z* = 168 [M+H]$^+$. Elemental analysis calcd. (%) for $C_9H_{10}FNO$: C 64.66; H 6.03; N 8.38; found: C 65.01; H 6.06; N 8.78.

***N*-(2,2-Difluoroethyl)benzamide (1b{α,2}).**[39] Yield 750 mg (82%) from **1a{α,2}**·HCl (580 mg, 4.93 mmol). White crystalline solid, mp = 74–76 °C (lit. 68–69 °C).[39] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 6.56 (br s, 1H), 5.96 (tt, *J* = 56.1, 4.1 Hz, 1H), 3.82 (tdd, *J* = 14.8, 6.2, 4.1 Hz, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 133.6, 132.2, 128.8, 127.2, 113.8 (t, *J* = 241.4 Hz), 42.4 (t, *J* = 26.5 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –123.3 ppm. MS(APCI) *m/z* = 186 [M+H]$^+$. Elemental analysis calcd. (%) for $C_9H_9F_2NO$: C 58.38; H 4.90; N 7.56; found: C 58.59; H 5.13; N 7.69.

***N*-(2,2,2-Trifluoroethyl)benzamide (1b{α,3}).**[40] Yield 1.42 g (95%) from **1a{α,3}**·HCl (1.00 g, 7.38 mmol). White solid, mp = 116–118 °C (lit. 114–116 °C).[40] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.3 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 6.61 (br s, 1H), 4.11 (qd, *J* = 9.1, 6.4 Hz, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 133.3, 132.4, 128.9, 127.3, 124.3 (q, *J* = 278.5 Hz), 41.2 (q, *J* = 34.8 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –72.8 ppm. MS(APCI) *m/z* = 204 [M+H]$^+$. Elemental analysis calcd. (%) for $C_9H_8F_3NO$: C 53.21; H 3.97; N 6.89; found: C 52.85; H 4.08; N 6.86.

***N*-Ethylbenzamide (2b).**[41] Yield 750 mg (71%) from **2a** (321 mg, 7.11 mmol). Physical and spectral data were the same as previously reported in the literature.[41]

***N*-(3-Fluoropropyl)benzamide (2b{β,1}).**[42] Yield 510 mg (80%) from **2a{β,1}**·HCl (272 mg, 3.52 mmol). White crystalline solid, mp = 59–61 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.1 Hz, 2H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 2H), 6.61 (br s, 1H), 4.58 (dt, *J* = 47.3, 5.6 Hz, 2H), 3.60 (q, *J* = 6.2 Hz, 2H), 2.02 (dquint, *J* = 28.1, 6.1 Hz, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 134.6, 131.6, 128.7, 127.0, 82.9 (d, *J* = 164.0 Hz), 37.3 (d, *J* = 4.5 Hz), 30.3 (d, *J* = 19.2 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –220.4 ppm. MS(APCI) *m/z* = 182 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{10}H_{12}FNO$: C 66.28; H 6.68; N 7.73; found: C 66.58; H 6.56; N 7.72.

***N*-(3,3-Difluoropropyl)benzamide (2b{β,2}).**[43] Yield 510 mg (84%) from **2a{β,2}**·HCl (400 mg, 3.04 mmol). Beige solid, mp = 48–50 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.6 Hz, 2H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 6.58 (br s, 1H), 5.97 (tt, *J* = 56.2, 4.1 Hz, 1H), 3.65 (q, *J* = 6.4 Hz, 2H), 2.19 (tq, *J* = 17.7, 6.4, 4.1 Hz, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.9, 134.3, 131.8, 128.7, 127.0, 116.6 (t, *J* = 239.2 Hz), 34.1 (t, *J* = 20.6 Hz), 33.8 (t, *J* = 6.2 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –116.8 ppm. MS(APCI) *m/z* = 200 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{10}H_{11}F_2NO$: C 60.30; H 5.57; N 7.03; found: C 60.13; H 5.88; N 7.38.

***N*-(3,3,3-Trifluoropropyl)benzamide (2b{β,3}).**[44] Yield 490 mg (85%) from **2a{β,3}**·HCl (400 mg, 2.67 mmol). White solid, mp = 99–101 °C (lit. 96–97 °C).[44] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.3 Hz, 2H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 6.56 (br s, 1H), 3.71 (q, *J* = 6.4 Hz, 2H), 2.46 (qt, *J* = 10.8, 6.4 Hz, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 134.1, 131.9, 128.8, 127.0, 126.7 (q, *J* = 276.9 Hz), 33.8 (q, *J* = 27.7 Hz), 33.7 (q, *J* = 3.8 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –65.5 ppm. MS(APCI) *m/z* = 218 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{10}H_{10}F_3NO$: C 55.30; H 4.64; N 6.45; found: C 55.07; H 4.96; N 6.69.

***N*-propylbenzamide (3b).**[42] Yield 3.13 g (90%) from **3a** (1.26 g, 21.3 mmol). Physical and spectral data were the same as previously reported in the literature.[42]

***N*-(4-Fluorobutyl)benzamide (3b{γ,1}).** Yield 530 mg (87%) from **3a{γ,1}**·HCl (400 mg, 3.13 mmol). Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 6.42 (br s, 1H), 4.54 (t, *J* = 5.6 Hz, 1H), 4.45 – 4.39 (m, 1H), 3.49 (q, *J* = 6.4 Hz, 2H), 1.88 – 1.67 (m, 4H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.8, 134.7, 131.5, 128.7, 127.0, 83.9 (d, *J* = 164.5 Hz), 39.7, 28.0 (d, *J* = 19.8 Hz), 25.9 (d, *J* = 4.4 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –218.7 ppm. MS(APCI) *m/z* = 196 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{11}H_{14}FNO$: C 67.67; H 7.23; N 7.17; found: C 67.65; H 7.21; N 7.07.

***N*-(4,4-Difluorobutyl)benzamide (3b{γ,2}).**[30] Yield 520 mg (89%) from **3a{γ,2}**·HCl (400 mg, 2.75 mmol). Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.2 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 6.45 (br s, 1H), 5.86 (tt, *J* = 56.6, 4.2 Hz, 1H), 3.50 (q, *J* = 6.6 Hz, 2H), 2.08 – 1.71 (m, 4H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.9, 134.5, 131.7, 128.7, 127.0, 117.0 (t, *J* = 239.0 Hz), 39.3, 31.6 (t, *J* = 21.3 Hz), 22.5 (t, *J* = 5.2 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –116.5 ppm. MS(APCI) *m/z* = 214 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{11}H_{13}F_2NO$: C 61.96; H 6.15; N 6.57; found: C 61.63; H 5.86; N 6.44.

***N*-(4,4,4-Trifluorobutyl)benzamide (3b{γ,3}).**[45,46] Yield 508 mg (90%) from **3a{γ,3}**·HCl (400 mg, 2.45 mmol). White solid, mp = 58–60 °C (lit. 47–48 °C).[45] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.2 Hz, 2H), 7.50 (t, *J* = 7.1 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 2H), 6.48 (br s, 1H), 3.52 (q, *J* = 6.6 Hz, 2H), 2.27 – 2.10 (m, 2H), 1.89 (quint, *J* = 7.3 Hz, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.0, 134.4, 131.8, 128.7, 127.1 (q, *J* = 276.1 Hz), 127.0, 38.9, 31.5 (q, *J* = 29.1 Hz), 22.7 (q, *J* = 2.8 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.7 ppm. MS(APCI) *m/z* = 232 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{11}H_{12}F_3NO$: C 57.14; H 5.23; N 6.06; found: C 56.79; H 5.01; N 6.45.

Azetidin-1-yl(phenyl)methanone (4b).[47] The product was purified by column chromatography (Hexane–EtOAc = 1:2). For the preparation of the compound **4b**, NEt_3 (0.89 mL, 6.42 mmol) and benzoyl chloride (0.18 mL, 1.52 mmol) were used. Yield 450 mg (87%) from **4a**·HCl (300 mg, 3.21 mmol). Yellowish crystalline solid, m.p. 55–57 °C (lit. 61–62 °C).[48] ^{1}H NMR (500 MHz, CF_3CO_2D) δ 7.71 (t, *J* = 7.4 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 2H), 7.57 (t, *J* = 7.8 Hz, 2H), 4.66 (t, *J* = 8.0 Hz, 4H), 2.63 (quint, *J* = 7.7 Hz, 2H) ppm. ^{13}C NMR (126 MHz, CF_3CO_2D) δ 172.8, 137.2, 131.7, 129.8, 126.2, 56.5, 17.6 ppm. MS(APCI) *m/z* = 162 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{10}H_{11}NO$: C 74.51; H 6.88; N 8.69; found: C 74.20; H 6.63; N 8.69.

(2-(Difluoromethyl)azetidin-1-yl)(phenyl)methanone (4b{α,1}). Yield 330 mg (65%) from **4a{α,1}**·HCl (332 mg, 2.65 mmol). Colourless liquid. The compound existed as ca. 85:15 mixture of rotamers. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 – 7.59 (m, 2H), 7.55 – 7.48 (m, 1H), 7.48 – 7.43 (m, 2H), 4.95 – 4.43 (m, 3H), 4.35 – 4.18 (m, 1H), 4.14 – 3.93 (m, 1H), 2.40 (s, 1H), 2.21 (s, 1H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.4, 133.1, 131.0, 128.4, 127.5, 82.6 (d, *J* = 168.5 Hz), 60.2, 50.9, 17.8 (d, *J* = 5.2 Hz) ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ –233.1 (s, 0.85F) and –234.0 (s, 0.15F) ppm. MS(APCI) *m/z* = 194 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{11}H_{13}FNO$: C 68.38; H 6.26; N 7.25; found: C 68.37; H 6.14; N 7.24.

(2-(Fluoromethyl)azetidin-1-yl)(phenyl)methanone (4b{α,2}). Yield 90 mg (46%) from **4a{α,2}**·HCl (133 mg, 0.93 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.3 Hz, 2H), 7.52 – 7.46 (m, 1H), 7.45 – 7.39 (m, 2H), 6.31 (t, *J* = 56.6 Hz, 1H), 4.83 – 4.71 (m, 1H), 4.36 (q, *J* = 8.2 Hz, 1H), 4.12 (td, *J* = 8.8, 5.8 Hz, 1H), 2.59 – 2.48 (m, 1H), 2.47 – 2.35 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 132.5, 131.6, 128.6, 128.0, 113.0 (dd, *J* = 244.0, 240.8 Hz), 60.6, 52.2, 15.5 (d, *J* = 5.5 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –130.4 (d, *J* = 289.5 Hz, 1F), –136.3 (d, *J* = 289.5 Hz, 1F) ppm. MS(APCI) *m/z* = 212 [M+H]$^+$.

Phenyl(2-(trifluoromethyl)azetidin-1-yl)methanone (4b{α,3}). Yield 410 mg (87%) from **4a{α,3}** (258 mg, 2.06 mmol). Yellowish solid, mp = 88 – 90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.1 Hz, 2H), 7.54 – 7.47 (m, 1H), 7.42 (t, *J* = 7.4 Hz, 2H), 5.03 – 4.91 (m, 1H), 4.49 – 4.39 (m, 1H), 4.03 (ddd, *J* = 9.6, 8.3, 5.4 Hz, 1H), 2.60 (ddd, *J* = 12.4, 9.6, 6.7 Hz, 1H), 2.48 – 2.38 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 132.0, 128.6 (2C), 128.3, 124.8 (q, *J* = 279.6 Hz), 59.3 (q, *J* = 34.8 Hz), 52.2, 17.9 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –77.8 ppm. MS(APCI) *m/z* = 230 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{11}H_{10}F_3NO$: C 57.64; H 4.40; N 6.11; found: C 58.00; H 4.70; N 5.86.

(3-(Fluoromethyl)azetidin-1-yl)(phenyl)methanone (4b{β,1}). Yield 270 mg (81%) from **4a{β,1}**·HCl (217 mg, 1.73 mmol). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 2H), 7.48 – 7.37 (m, 3H), 4.56 (dd, *J* = 47.0, 5.6 Hz, 2H), 4.37 (t, *J* = 8.6 Hz, 1H), 4.29 (t, *J* = 9.0 Hz, 1H), 4.18 – 4.09 (m, 1H), 4.07 – 3.97 (m, 1H), 3.09 – 2.94 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 133.1, 131.2, 128.5, 128.0, 83.8 (d, *J* = 169.9 Hz), 54.9, 50.1, 29.6 (d, *J* = 20.8 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –226.8 ppm. MS(APCI) *m/z* = 194 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{11}H_{12}FNO$: C 68.38; H 6.26; N 7.25; found: C 68.74; H 6.64; N 6.90.

(3-(Difluoromethyl)azetidin-1-yl)(phenyl)methanone (4b{β,2}). Yield 240 mg (76%) from **4a{β,2}**·CF_3CO_2H (330 mg, 1.50 mmol). Beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 (d, *J* = 7.0 Hz, 2H), 7.56 – 7.50 (m, 1H), 7.49 – 7.43 (m, 2H), 6.35 (td, *J* = 56.3, 4.3 Hz, 1H), 4.41 (t, *J* = 8.9 Hz, 1H), 4.25 – 4.18 (m, 1H), 4.14 (t, *J* = 9.6 Hz, 1H), 3.97 (dd, *J* = 10.3, 5.6 Hz, 1H), 3.27 – 3.06 (m, 1H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.0, 132.6, 131.1, 128.4, 127.6, 116.7 (t, *J* = 238.0 Hz), 51.8, 47.5, 31.4 (t, *J* = 22.7 Hz) ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ –125.1 ppm. MS(APCI) *m/z* = 212 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{11}H_{11}F_2NO$: C 62.55; H 5.25; N 6.63; found: C 62.23; H 5.10; N 6.33.

Phenyl(3-(trifluoromethyl)azetidin-1-yl)methanone (4b{β,3}). Yield 400 mg (85%) from **4a{β,3}**·HCl (332 mg, 2.06 mmol). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.0 Hz, 2H), 7.53 – 7.46 (m, 1H), 7.45 – 7.39 (m, 2H), 4.45 – 4.21 (m, 4H), 3.32 (qt, *J* = 8.5, 5.6 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 132.4, 131.6, 128.7, 127.9, 126.2 (q, *J* = 275.5 Hz), 52.5, 48.4, 32.6 (q, *J* = 32.3 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –74.3 ppm. MS(APCI) *m/z* = 230 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{11}H_{10}F_3NO$: C 57.64; H 4.40; N 6.11; found: C 57.57; H 4.73; N 5.75.

Phenyl(pyrrolidin-1-yl)methanone (5b).[49] Yield 600 mg (96%) from **5a** (253 mg, 3.56 mmol). Colourless liquid. ^{1}H NMR (500 MHz, CF_3CO_2D) δ 7.68 – 7.63 (m, 1H), 7.55 (s, 2H), 7.54 (s, 2H), 3.93 (t, *J* = 7.4 Hz, 2H), 3.72 (t, *J* = 7.0 Hz, 2H), 2.20 – 2.14 (m, 2H), 2.09 – 2.02 (m, 2H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.46 (m, 2H), 7.41 – 7.35 (m, 3H), 3.63 (s, 2H), 3.42 (s, 2H), 2.01 – 1.78 (m, 4H) ppm. ^{13}C NMR (126 MHz, CF_3CO_2D) δ 173.1, 136.5, 131.6, 129.2, 128.7, 54.8 and 52.1, 27.0 and 25.7 ppm. MS(APCI) *m/z* = 176 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{11}H_{13}NO$: C 75.40; H 7.48; N 7.99; found: C 75.20; H 7.39; N 8.22.

(2-(Fluoromethyl)pyrrolidin-1-yl)(phenyl)methanone (5b{α,1}). Yield 230 mg (47%) from **5a{α,1}**·HCl (332 mg, 2.38 mmol). NMR spectra contain overlapping signals of both rotamers in ca. 95:5 ratio. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 6.8 Hz, 2H), 7.44 – 7.36 (m, 3H), 4.82 (ddd, *J* = 48.9, 9.0, 3.7 Hz, 1H), 4.66 – 4.37 (m, 2H), 3.57 – 3.38 (m, 2H), 2.17 – 2.02 (m, 2H), 2.01 – 1.90 (m, 1H), 1.84 – 1.69 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 136.9, 130.2, 128.4, 127.4, 83.1 (d, *J* = 171.4 Hz), 57.0 (d, *J* = 20.4 Hz), 50.8, 26.7 (d, *J* = 4.2 Hz), 25.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –226.0 (0.05F) and –233.3 (0.95F) ppm. MS(APCI) *m/z* = 208 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{12}H_{14}FNO$: C 69.55; H 6.81; N 6.76; found: C 69.83; H 6.45; N 6.85.

(2-(Difluoromethyl)pyrrolidin-1-yl)(phenyl)methanone (5b{α,2}). Yield 480 mg (84%) from **5a{α,2}**·HCl (399 mg, 2.53 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.48 (m, 2H), 7.47 – 7.35 (m, 3H), 6.34 (t, *J* = 57.2 Hz, 1H), 4.65 – 4.48 (m, 1H), 3.58 – 3.45 (m, 2H), 2.29 – 2.15 (m, 1H), 2.14 – 1.92 (m, 2H), 1.85 – 1.72 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 136.3, 130.5, 128.4, 127.4, 113.7 (t, *J* = 243.5 Hz), 58.3 (dd, *J* = 30.9, 21.3 Hz), 50.7, 25.3, 22.8 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –125.3 (d, *J* = 286.8 Hz, 1F), –135.9 (d, *J* = 286.8 Hz, 1F) ppm. MS(APCI) *m/z* = 226 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{12}H_{13}F_2NO$: C 63.99; H 5.82; N 6.22; found: C 64.31; H 5.67; N 6.35.

Phenyl(2-(trifluoromethyl)pyrrolidin-1-yl)methanone (5b{α,3}). Yield 460 mg (79%) from **5a{α,3}** (333 mg, 2.39 mmol). Yellowish oil. NMR spectra contain overlapping signals of both rotamers in *ca.* 85:15 ratio. ^{1}H NMR (500 MHz, CF_3CO_2D) δ 7.61 – 7.53 (m, 1H), 7.50 – 7.39 (m, 4H), 5.12 (q, *J* = 6.9 Hz, 0.85H) and 4.71 – 4.65 (m, 0.15H), 4.14 – 4.05 (m, 0.15H) and 3.79 – 3.69 (m, 0.85H), 3.89 – 3.81 (m, 0.15H) and 3.65 – 3.54 (m, 0.85H), 2.34 – 2.24 (m, 2H), 2.20 – 2.10 (m, 1H), 2.01 – 1.90 (m, 1H) ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 – 7.43 (m, 5H), 5.15 – 4.97 (m, 1H), 3.62 – 3.50 (m, 1H), 3.47 – 3.34 (m, 1H), 2.28 – 2.16 (m, 1H), 2.07 – 1.79 (m, 3H) ppm. ^{13}C NMR (126 MHz, CF_3CO_2D) δ 178.3 and 178.2, 135.3, 133.5 (q, *J* = 272.8 Hz) and 127.1 (q, *J* = 280.7 Hz), 131.3 and 131.2, 129.3, 128.6, 63.6 (q, *J* = 32.7, 32.1 Hz) and 60.9 (q, *J* = 32.8 Hz), 54.0 and 50.4, 27.2 and 26.2, 25.2 and 23.2 ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ –73.8 ppm. MS(APCI) *m/z* = 244 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{12}H_{12}F_3NO$: C 59.26; H 4.97; N 5.76; found: C 59.11; H 4.67; N 5.42.

(3-(Fluoromethyl)pyrrolidin-1-yl)(phenyl)methanone (5b{β,1}). Yield 350 mg (71%) from **5a{β,1}**·HCl (333 mg, 2.38 mmol). Yellowish oil. NMR spectra contain overlapping signals of both rotamers in *ca.* 1:1 ratio. ^{1}H NMR (500 MHz, CF_3CO_2D) δ 7.70 – 7.64 (m, 1H), 7.58 – 7.49 (m, 4H), 4.65 – 4.30 (m, 2H), 4.17 – 4.04 (m, 1H), 4.00 – 3.67 (m, 3H), 2.82 (d, *J* = 24.5 Hz, 0.5H) and 2.71 (d, *J* = 23.3 Hz, 0.5H), 2.38 – 2.27 (m, 0.5H) and 2.27 – 2.18 (m, 0.5H), 2.10 (dt, *J* = 13.4, 8.1 Hz, 0.5H) and 2.03 (dt, *J* = 13.4, 7.8 Hz, 0.5H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.47 (m, 2H), 7.43 – 7.36 (m, 3H), 4.53 – 4.31 (m, 2H), 3.80 – 3.36 (m, 4H), 2.71 – 2.55 (m, 1H), 2.12 – 1.99 (m, 1H), 1.80 (dq, *J* = 12.6, 8.1 Hz, 1H) ppm. ^{13}C NMR (126 MHz, CF_3CO_2D) δ 173.7, 136.8, 131.7, 129.2, 85.5 (d, *J* = 168.6 Hz) and 85.1 (d, *J* = 168.1 Hz), 55.9 (d, *J* = 4.7 Hz) and 53.3 (d, *J* = 4.2 Hz), 54.2 and 51.5, 41.3 (d, *J* = 19.2 Hz) and 40.1 (d, *J* = 19.7 Hz), 28.9 (d, *J* = 4.1 Hz) and 27.4 (d, *J* = 5.6 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –222.1 ppm. MS(APCI) *m/z* = 208 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{12}H_{14}FNO$: C 69.55; H 6.81; N 6.76; found: C 69.46; H 6.99; N 6.78.

(3-(Difluoromethyl)pyrrolidin-1-yl)(phenyl)methanone (5b{β,2}). Yield 355 mg (92%) from **5a{β,2}**·HCl (270 mg, 1.71 mmol). Yellowish oil. NMR spectra contain overlapping signals of both rotamers in *ca.* 1:1 ratio. ^{1}H NMR (500 MHz, CF_3CO_2D) δ 7.76 – 7.70 (m, 1H), 7.64 – 7.57 (m, 4H), 5.93 (t, *J* = 56.7 Hz, 0.5H) and 5.84 (t, *J* = 55.5 Hz, 0.5H), 4.18 – 4.00 (m, 2H), 3.96 – 3.81 (m, 2H), 3.00 (s, 0.5H) and 2.89 (s, 0.5H), 2.46 – 2.19 (m, 2H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.47 (m, 2H), 7.45 – 7.37 (m, 3H), 5.82 (t, *J* = 56.4 Hz, 0.5H) and 5.75 (t, *J* = 56.5 Hz, 0.5H), 3.91 – 3.43 (m, 4H), 2.80 – 2.59 (m, 1H), 2.18 – 1.89 (m, 2H) ppm. ^{13}C NMR (126 MHz, CF_3CO_2D) δ 174.3, 136.5, 131.7, 129.2, 128.9, 53.6 and 51.0, 52.6, and 50.3, 44.1 (t, *J* = 21.7 Hz) and 43.1 (t, *J* = 21.2 Hz), 26.6 and 25.3 ppm (^{13}C signal of CHF_2 group was not visible due to overlap with the solvent signal). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 136.6, 130.2, 128.5, 127.2, 117.0 (t, *J* = 241.5 Hz) and 116.6 (t, *J* = 241.8 Hz), 48.8 and 48.4, 45.6 and 45.5, 43.1 (t, *J* = 21.7 Hz) and 41.2 (t, *J* = 21.3 Hz), 26.1 and 24.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –119.7 – –122.7 (m) ppm. MS(APCI) *m/z* = 226 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{12}H_{13}F_2NO$: C 63.99; H 5.82; N 6.22; found: C 63.92; H 6.02; N 6.33.

Phenyl(3-(trifluoromethyl)pyrrolidin-1-yl)methanone (5b{β,3}). Yield 340 mg (70%) from **5a{β,3}**·HCl (353 mg, 2.00 mmol). Colourless oil. NMR spectra contain overlapping signals of both rotamers in *ca.* 2:3 ratio. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.47 (m, 2H), 7.45 – 7.38 (m, 3H), 4.00 – 3.46 (m, 4H), 3.05 – 2.87 (m, 1H), 2.27 – 2.05 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 136.3, 130.4, 128.5, 127.2, 48.5, 45.5 and 45.3, 43.1 (q, *J* = 28.3 Hz) and 41.4 (q, *J* = 29.0 Hz), 26.3 and 24.3 ppm (signal of C-atom in CF_3 group was not detected because of its low intensity). ^{19}F NMR (376 MHz, $CDCl_3$) δ –71.6 (s, 1.25F) and –71.7 (s, 1.75F) ppm. MS(APCI) *m/z* = 244 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{12}H_{12}F_3NO$: C 59.26; H 4.97; N 5.76; found: C 58.93; H 4.85; N 5.63.

Phenyl(piperidin-1-yl)methanone (6b).[30] Yield 3.20 g (98%) from **6a** (1.46 g, 17.18 mmol). Yellowish liquid. ^{1}H NMR (500 MHz, CF_3CO_2D) δ 7.60 (t, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.40 (d, *J* = 7.7 Hz, 2H), 3.95 (s, 2H), 3.58 (s, 2H), 1.86 – 1.80 (m, 2H), 1.77 – 1.65 (m, 4H) ppm. ^{13}C NMR (126 MHz, CF_3CO_2D) δ 173.9, 136.1, 131.8, 129.0, 127.9, 54.1, 50.2, 28.0, 27.2, 24.6 ppm. MS(APCI) *m/z* = 190 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{12}H_{13}NO$: C 76.16; H 7.99; N 7.40; found: C 75.97; H 8.05; N 7.78.

(2-(Fluoromethyl)piperidin-1-yl)(phenyl)methanone (6b{α,1}). Yield 120 mg (25%) from **6a{α,1}**·HCl (333 mg, 2.17 mmol). White solid. NMR spectra contain overlapping signals of both rotamers in *ca.* 3:2 ratio. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.32 (m, 5H), 5.19 – 4.35 (m, 2H), 4.66 (ddd, *J* = 47.5, 9.4, 7.0 Hz, 1H), 3.82 – 3.42 (m, 1H), 3.21 – 2.79 (m, 1H), 1.96 – 1.35 (m, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 136.5, 129.5, 128.6, 126.8, 82.4, 53.7 and 48.3, 45.0 and 38.1, 25.6, 25.3, 20.0 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –224.2 (0.4F) and –225.9 (0.6F) ppm. MS(APCI) *m/z* = 222 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{13}H_{16}FNO$: C 70.57; H 7.29; N 6.33; found: C 70.21; H 7.40; N 6.34.

(2-(Difluoromethyl)piperidin-1-yl)(phenyl)methanone (6b{α,2}). Yield 330 mg (88%) from **6a{α,2}**·HCl (269 mg, 1.57 mmol). Colourless oil. NMR spectra contain overlapping signals of both rotamers in *ca.* 65:35 ratio. ^{1}H NMR (500 MHz, CF_3CO_2D) δ 7.71 – 7.64 (m, 1H), 7.61 – 7.55 (m, 2H), 7.52 – 7.47 (m, 2H), 6.15 (td, *J* = 51.6, 4.3 Hz, 0.65H) and 6.18 – 5.90 (m, 0.35H), 5.20 – 5.10 (m, 0.65H) and 4.28 – 4.18 (m, 0.35H), 4.81 (d, *J* = 13.7 Hz, 0.35H) and 3.92 (d, *J* = 12.8 Hz, 0.65H), 3.55 (t, *J* = 13.7 Hz, 0.65H) and 3.37 (t, *J* = 12.8 Hz, 0.35H), 2.26 (d, *J* = 14.9 Hz, 0.65H) and 2.08 (d, *J* = 12.8 Hz, 0.35H), 2.05 – 1.98 (m, 0.35H) and 1.75 – 1.65 (m, 0.65H), 2.13 – 1.97 (m, 1H), 1.94 – 1.81 (m, 3H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.32 (m, 5H), 6.02 (t, *J* = 56.0 Hz, 1H), 5.23 – 4.55 (m, 1H), 4.19 – 3.49 (m, 1H), 3.30 – 2.77 (m, 1H), 2.35 – 1.88 (m, 1H), 1.83 – 1.34 (m, 5H) ppm. ^{13}C NMR (126 MHz, CF_3CO_2D) δ 178.3, 135.4 and 135.2, 131.6 and 131.6, 130.2, 128.8, 116.5 (t, *J* = 246.9 Hz), 60.7 (t, *J* = 23.6 Hz) and 56.0 (t, *J* = 22.8 Hz), 50.5 and 45.7, 26.5 and 26.2, 25.9 and 24.5, 20.3 and 20.2 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –121.05 (d, *J* = 294.1 Hz, 0.7F) and –124.95 (d, *J* = 284.0 Hz, 1.3F) ppm. MS(APCI) *m/z* = 240 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{13}H_{15}F_2NO$: C 65.26; H 6.32; N 5.85; found: C 65.12; H 6.34; N 5.75.

Phenyl(2-(trifluoromethyl)piperidin-1-yl)methanone (6b{α,3}). Yield 350 mg (78%) from **6a{α,3}**·HCl (332 mg, 1.75 mmol). NMR spectra contain overlapping signals of both rotamers in *ca.* 4:1 ratio. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 5H), 5.56 – 5.36 (m, 0.8H) and 4.74 – 4.57 (m, 0.2H), 4.34 – 4.16 (m, 0.2H) and 3.68 (d, *J* = 13.0 Hz, 0.8H), 3.27 (t, *J* = 13.4 Hz, 0.8H) and 3.06 – 2.89 (m, 0.2H), 2.18 – 2.06 (m, 0.8H) and 2.01 – 1.93 (m, 0.2H), 1.88 – 1.31 (m, 5H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.5 and 171.8, 135.6, 130.0, 128.7, 126.9, 55.2 (q, *J* = 26.1 Hz) and 48.5 (q, *J* = 29.8 Hz), 45.3 and 39.1, 25.3 and 24.5, 23.7 and 22.7, 19.5 ppm (signal of C-atom in CF_3 group was not detected because of the overlap with signals of aromatic C-atoms). ^{19}F NMR (376 MHz, $CDCl_3$) δ –69.2 (s, 0.6F) and –69.8 (s, 2.4F) ppm. MS(APCI) *m/z* = 258 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{13}H_{14}F_3NO$: C 60.70; H 5.49; N 5.44; found: C 60.56; H 5.46; N 5.49.

(3-(Fluoromethyl)piperidin-1-yl)(phenyl)methanone(6b{β,1}). Yield 410 mg (81%) from **6a{β,1}**·HCl (350 mg, 2.28 mmol). Yellowish oil. NMR spectra contain overlapping signals of both rotamers in *ca.* 1:1 ratio. ^{1}H NMR (500 MHz, CF_3CO_2D) δ 7.70 (t, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 7.7 Hz, 2H), 7.50 (d, *J* = 7.6 Hz, 2H), 4.71 (d, *J* = 13.2 Hz, 0.5H), 4.67 – 4.56 (m, 0.5H), 4.53 – 4.44 (m, 0.5H), 4.43 – 4.35 (m, 0.5H), 4.32 – 4.24 (m, 0.5H), 4.22 – 4.13 (m, 0.5H), 4.09 – 4.00 (m, 0.5H), 3.91 (d, *J* = 13.6 Hz, 0.5H), 3.49 – 3.34 (m, 2H), 2.32 – 2.04 (m, 1.5H), 2.04 – 1.81 (m, 2H), 1.81 – 1.51 (m, 1.5H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 5H), 4.81 – 4.02 (m, 3H), 3.89 – 3.42 (m, 1H), 3.11 – 2.65 (m, 2H), 2.04 – 1.60 (m, 3H), 1.59 – 1.19 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 136.2, 129.7, 128.6, 127.0, 85.4 (d, *J* = 176.9 Hz), 50.0 and 48.3, 44.4 and 42.9, 37.3, 26.3, 25.2 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –225.6 (s, 0.5F) and –227.3 (s, 0.5F) ppm. MS(APCI) *m/z* = 222 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{13}H_{16}FNO$: C 70.57; H 7.29; N 6.33; found: C 70.29; H 7.02; N 6.59.

(3-(Difluoromethyl)piperidin-1-yl)(phenyl)methanone (6b{β,2}). Yield 210 mg (43%) from **6a{β,2}**·HCl (350 mg, 2.04 mmol). Beige crystalline solid (mp = 71–73 °C). NMR spectra contain overlapping signals of both rotamers in *ca.* 1:1 ratio. ^{1}H NMR (500 MHz, CF_3CO_2D) δ 7.65 – 7.58 (m, 1H), 7.58 – 7.47 (m, 2H), 7.47 – 7.38 (m, 2H), 5.72 (t, *J* = 55.9 Hz, 0.5H), 5.54 (t, *J* = 55.3 Hz, 0.5H), 4.53 (d, *J* = 13.3 Hz, 0.5H), 4.46 (d, *J* = 13.3 Hz, 0.5H), 3.94 (d, *J* = 13.6 Hz, 0.5H), 3.80 (d, *J* = 13.6 Hz, 0.5H), 3.61 – 3.37 (m, 2H), 2.34 – 1.86 (m, 3H), 1.85 – 1.59 (m, 2H) ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 – 7.41 (m, 3H), 7.41 – 7.34 (m, 2H), 6.24 – 5.71 (m, 1H), 4.50 – 4.22 (m, 1H), 3.69 – 3.42 (m, 1H), 3.07 – 2.80 (m, 2H), 2.11 – 1.97 (m, 1H), 1.91 – 1.57 (m, 2H), 1.53 – 1.34 (m, 2H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.2, 136.1, 129.4, 128.4, 126.6, 117.7 (t,

J = 239.3 Hz), 47.4, 45.9, 40.4, 23.9, 23.1 ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ −123.7 – −124.1 (m) ppm. MS(APCI) *m/z* = 240 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{13}H_{15}F_3NO$: C 65.26; H 6.32; N 5.85; found: C 65.27; H 6.58; N 5.96.

Phenyl(3-(trifluoromethyl)piperidin-1-yl)methanone (6b{β,3}). Yield 250 mg (54%) from **6a{β,3}**·HCl (344 mg, 1.81 mmol). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.32 (m, 5H), 4.96 – 4.51 (m, 1H), 4.08 – 3.60 (m, 1H), 3.10 – 2.69 (m, 2H), 2.51 – 2.19 (m, 1H), 2.15 – 2.05 (m, 1H), 1.93 – 1.68 (m, 1H), 1.69 – 1.36 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 135.7, 130.0, 128.7, 127.0, 47.9, 41.4, 40.4, 24.6, 23.7 ppm (signal of C-atom in CF_3 group was not detected because of its low intensity). ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.9 ppm. MS(APCI) *m/z* = 258 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{13}H_{14}F_3NO$: C 60.70; H 5.49; N 5.44; found: C 60.60; H 5.58; N 5.38.

(4-(Fluoromethyl)piperidin-1-yl)(phenyl)methanone (6b{γ,1}). Yield 300 mg (69%) from **6a{γ,1}**·HCl (300 mg, 1.95 mmol). Yellowish oil. ^{1}H NMR (500 MHz, CF_3CO_2D) δ 7.70 (t, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 7.7 Hz, 2H), 7.51 (d, *J* = 7.5 Hz, 2H), 4.86 (d, *J* = 13.3 Hz, 1H), 4.39 (dd, *J* = 46.6, 5.2 Hz, 2H), 4.05 (d, *J* = 13.5 Hz, 1H), 3.47 (t, *J* = 13.3 Hz, 1H), 3.38 (t, *J* = 11.7 Hz, 1H), 2.21 – 2.05 (m, 2H), 1.96 (d, *J* = 13.9 Hz, 1H), 1.76 – 1.64 (m, 1H), 1.61 – 1.51 (m, 1H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 5H), 4.88 – 4.61 (m, 1H), 4.30 (dd, *J* = 47.3, 5.9 Hz, 2H), 3.99 – 3.64 (m, 1H), 3.12 – 2.65 (m, 2H), 2.36 – 1.65 (m, 3H), 1.54 – 1.16 (m, 2H) ppm. ^{13}C NMR (126 MHz, CF_3CO_2D) δ 174.8, 136.2, 131.8, 129.1, 128.1, 88.5 (d, *J* = 166.9 Hz), 52.5, 48.6, 37.7 (d, *J* = 19.6 Hz), 29.7, 28.8 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ −224.4 ppm. MS(APCI) *m/z* = 222 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{13}H_{16}FNO$: C 70.57; H 7.29; N 6.33; found: C 70.87; H 7.43; N 6.52.

(4-(Difluoromethyl)piperidin-1-yl)(phenyl)methanone (6b{γ,2}). Yield 250 mg (72%) from **6a{γ,2}**·HCl (250 mg, 1.46 mmol). Yellowish oil. ^{1}H NMR (500 MHz, CF_3CO_2D) δ 7.68 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 2H), 7.49 (d, *J* = 7.5 Hz, 2H), 5.62 (td, *J* = 56.0, 3.8 Hz, 1H), 4.85 (d, *J* = 13.3 Hz, 1H), 4.04 (d, *J* = 12.9 Hz, 1H), 3.50 – 3.39 (m, 1H), 3.38 – 3.28 (m, 1H), 2.25 – 2.07 (m, 2H), 2.01 – 1.92 (m, 1H), 1.84 – 1.69 (m, 1H), 1.69 – 1.57 (m, 1H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 5H), 5.62 (td, *J* = 56.4, 4.3 Hz, 1H), 5.01 – 4.68 (m, 1H), 4.05 – 3.72 (m, 1H), 3.11 – 2.67 (m, 2H), 2.40 – 1.67 (m, 3H), 1.64 – 1.33 (m, 2H) ppm. ^{13}C NMR (126 MHz, CF_3CO_2D) δ 175.3, 136.2, 131.8, 129.1, 128.4, 119.0 (t, *J* = 241.5 Hz), 51.8, 47.8, 40.9 (t, *J* = 21.3 Hz), 26.6, 26.0 ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 136.0, 129.8, 128.6, 127.0, 118.0 (t, *J* = 242.0 Hz), 47.0, 41.6, 40.4 (t, *J* = 20.3 Hz), 25.2 (2C) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ −123.9 (s, 1F), −124.1 (s, 1F) ppm. MS(APCI) *m/z* = 240 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{13}H_{15}F_2NO$: C 65.26; H 6.32; N 5.85; found: C 65.50; H 6.39; N 6.17.

Phenyl(4-(trifluoromethyl)piperidin-1-yl)methanone (6b{γ,3}).[51,52] Yield 401 mg (74%) from **6a{γ,3}**·HCl (400 mg, 2.11 mmol). White crystalline solid, mp = 80 – 82 °C. ^{1}H NMR (600 MHz, CF_3CO_2D) δ 7.62 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.43 (d, *J* = 7.5 Hz, 2H), 4.80 (d, *J* = 13.5 Hz, 1H), 3.99 (d, *J* = 13.7 Hz, 1H), 3.38 (t, *J* = 13.5 Hz, 1H), 3.27 (t, *J* = 13.7 Hz, 1H), 2.51 – 2.37 (m, 1H), 2.17 (d, *J* = 14.0 Hz, 1H), 2.01 (d, *J* = 14.0 Hz, 1H), 1.85 – 1.76 (m, 1H), 1.73 – 1.63 (m, 1H) ppm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 – 7.42 (m, 3H), 7.42 – 7.37 (m, 2H), 4.67 – 4.42 (m, 1H), 3.81 – 3.51 (m, 1H), 3.20 – 2.92 (m, 1H), 2.88 – 2.70 (m, 1H), 2.70 – 2.58 (m, 1H), 2.02 – 1.68 (m, 2H), 1.49 – 1.33 (m, 2H) ppm. ^{13}C NMR (151 MHz, CF_3CO_2D) δ 175.4, 135.9, 131.5, 128.9, 128.4, 128.1 (q, *J* = 277.0 Hz), 51.0, 47.0, 41.2 (q, *J* = 28.9 Hz), 26.5, 25.7 ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ −72.9 ppm. MS(APCI) *m/z* = 258 [M+H]$^+$. Elemental analysis calcd. (%) for $C_{13}H_{14}F_3NO$: C 60.70; H 5.49; N 5.44; found: C 60.66; H 5.42; N 5.22.

Acknowledgements

The work was supported by Enamine Ltd. and Ministry of Education and Science of Ukraine (Grants No. 0121U100387 (21BF037-01M) and 0122U001962 (22BF037-02)). The authors thank Ms. Olga Kovalenko and Ms. Margarita Bolgova for pK_a(H) measurements, Prof. Andrey A. Tolmachev for his encouragement and support, and all the brave people of Ukraine for making finalizing this publication possible.

Conflict of Interest

The authors are / have been employees, trainees, or consulting scientists of Enamine Ltd. that offers all the building blocks described in this paper in the company's catalog.

Keywords: basicity • fluorine • lipophilicity • nitrogen heterocycles • saturated compounds

[1] Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422–518.

[2] J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506.

[3] S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330.

[4] C. Isanbor, D. O'Hagan, *J. Fluor. Chem.* **2006**, *127*, 303–319.

[5] E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315–8359.

[6] N. A. Meanwell, *J. Med. Chem.* **2018**, *61*, 5822–5880.

[7] M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633–10640.

[8] Y. Yu, A. Liu, G. Dhawan, H. Mei, W. Zhang, K. Izawa, V. A. Soloshonok, J. Han, *Chinese Chem. Lett.* **2021**, *32*, 3342–3354.

[9] H. Mei, A. M. Remete, Y. Zou, H. Moriwaki, S. Fustero, L. Kiss, V. A. Soloshonok, J. Han, *Chinese Chem. Lett.* **2020**, *31*, 2401–2413.

[10] H. Mei, J. Han, S. Fustero, M. Medio-Simon, D. M. Sedgwick, C. Santi, R. Ruzziconi, V. A. Soloshonok, *Chem. Eur. J.* **2019**, *25*, 11797–11819.

[11] P. Richardson, *Expert Opin. Drug Discov.* **2016**, *11*, 983–999.

[12] T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264.

[13] Dominique Cahard and Jun-An Ma, **2020**, 1–837.

[14] K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886.

[15] Y. Zafrani, G. Sod-Moriah, D. Yeffet, A. Berliner, D. Amir, D. Marciano, S. Elias, S. Katalan, N. Ashkenazi, M. Madmon, E. Gershonov, S. Saphier, *J. Med. Chem.* **2019**, *62*, 5628–5637.

[16] N. Erdeljac, G. Kehr, M. Ahlqvist, L. Knerr, R. Gilmour, *Chem. Commun.* **2018**, *54*, 12002–12005.

[17] Y. Zafrani, G. Parvari, D. Amir, L. Ghindes-Azaria, S. Elias, A. Pevzner, G. Fridkin, A. Berliner, E. Gershonov, Y. Eichen, S. Saphier, S. Katalan, *J. Med. Chem.* **2021**, *64*, 4516–4531.

[18] A. V. Chernykh, D. S. Radchenko, A. V. Chernykh, I. S. Kondratov, N. A. Tolmachova, O. P. Datsenko, M. A. Kurkunov, S. X. Zozulya, Y. P. Kheylik, K. Bartels, C. G. Daniliuc, G. Haufe, *Eur. J. Org. Chem.* **2015**, *2015*, 6466–6471.

[19] B. Linclau, Z. Wang, B. Jeffries, J. Graton, R. J. Carbajo, D. Sinnaeve, J. Le Questel, J. S. Scott, E. Chiarparin, *Angew. Chem. Int. Ed.* **2022**, *61*, DOI 10.1002/anie.202114862.

[20] K. Müller, *Chim. Int. J. Chem.* **2014**, *68*, 356–362.

[21] Q. A. Huchet, B. Kuhn, B. Wagner, N. A. Kratochwil, H. Fischer, M. Kansy, D. Zimmerli, E. M. Carreira, K. Müller, *J. Med. Chem.* **2015**, *58*, 9041–9060.

[22] R. Vorberg, N. Trapp, D. Zimmerli, B. Wagner, H. Fischer, N. A.

Kratochwil, M. Kansy, E. M. Carreira, K. Müller, *ChemMedChem* **2016**, *11*, 2216–2239.

[23] B. Jeffries, Z. Wang, J. Graton, S. D. Holland, T. Brind, R. D. R. Greenwood, J.-Y. Le Questel, J. S. Scott, E. Chiarparin, B. Linclau, *J. Med. Chem.* **2018**, *61*, 10602–10618.

[24] B. Jeffries, Z. Wang, H. R. Felstead, J. Y. Le Questel, J. S. Scott, E. Chiarparin, J. Graton, B. Linclau, *J. Med. Chem.* **2020**, *63*, 1002–1031.

[25] R. I. Troup, B. Jeffries, R. E.-B. Saudain, E. Georgiou, J. Fish, J. S. Scott, E. Chiarparin, C. Fallan, B. Linclau, *J. Org. Chem.* **2021**, *86*, 1882–1900.

[26] Z. Fang, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan, *Chem. Commun.* **2019**, *55*, 10539–10542.

[27] D. O'Hagan, *Chem. – A Eur. J.* **2020**, *26*, 7981–7997.

[28] J. L. Clark, R. M. Neyyappadath, C. Yu, A. M. Z. Slawin, D. B. Cordes, D. O'Hagan, *Chem. – A Eur. J.* **2021**, *27*, 16000–16005.

[29] A. Rodil, S. Bosisio, M. S. Ayoup, L. Quinn, D. B. Cordes, A. M. Z. Slawin, C. D. Murphy, J. Michel, D. O'Hagan, *Chem. Sci.* **2018**, *9*, 3023–3028.

[30] S. Holovach, K. P. Melnykov, A. Skreminskiy, M. Herasymchuk, O. Tavlui, D. Aloshyn, P. Borysko, A. B. Rozhenko, S. V. Ryabukhin, D. M. Volochnyuk, O. O. Grygorenko, *Chem. – A Eur. J.* **2022**, *28*, e202200331.

[31] A. V. Chernykh, K. P. Melnykov, N. A. Tolmacheva, I. S. Kondratov, D. S. Radchenko, C. G. Daniliuc, D. M. Volochnyuk, S. V. Ryabukhin, Y. O. Kuchkovska, O. O. Grygorenko, *J. Org. Chem.* **2019**, *84*, 8487–8496.

[32] M. Kahraman, S. P. Govek, J. Y. Nagasawa, A. Lai, C. Bonnefous, K. Douglas, J. Sensintaffar, N. Liu, K. Lee, A. Aparicio, J. Kaufman, J. Qian, G. Shao, R. Prudente, J. D. Joseph, B. Darimont, D. Brigham, R. Heyman, P. J. Rix, J. H. Hager, N. D. Smith, *ACS Med. Chem. Lett.* **2019**, *10*, 50–55.

[33] S. J. McKerrall, T. Nguyen, K. W. Lai, P. Bergeron, L. Deng, A. DiPasquale, J. H. Chang, J. Chen, T. Chernov-Rogan, D. H. Hackos, J. Maher, D. F. Ortwine, J. Pang, J. Payandeh, W. R. Proctor, S. D. Shields, J. Vogt, P. Ji, W. Liu, E. Ballini, L. Schumann, G. Tarozzo, G. Bankar, S. Chowdhury, A. Hasan, J. P. Johnson, K. Khakh, S. Lin, C. J. Cohen, C. M. Dehnhardt, B. S. Safina, D. P. Sutherlin, *J. Med. Chem.* **2019**, *62*, 4091–4109.

[34] W. M. Haynes, *CRC Handbook of Chemistry and Physics (97th Ed.)*, CDC Press, **2017**.

[35] M. Morgenthaler, E. Schweizer, A. Hoffmann-Röder, F. Benini, R. E. Martin, G. Jaeschke, B. Wagner, H. Fischer, S. Bendels, D. Zimmerli, J. Schneider, F. Diederich, M. Kansy, K. Müller, *ChemMedChem* **2007**, *2*, 1100–1115.

[36] K. Müller, in *Fluorine in Life Sciences: Pharmaceuticals, Medicinal Diagnostics, and Agrochemicals*, Elsevier, **2019**, pp. 91–139.

[37] E. J. L. Stéen, V. Shalgunov, C. Denk, H. Mikula, A. Kjaer, J. L. Kristensen, M. M. Herth, *Eur. J. Org. Chem.* **2019**, 1722–1725.

[38] M. Glaser, E. Årstad, A. Gacta, J. Nairne, W. Trigg, E. G. Robins, *J. Label. Compd. Radiopharm.* **2012**, *55*, 326–331.

[39] V. Srivastava, P. K. Singh, P. P. Singh, *Tetrahedron Lett.* **2019**, *60*, 40–43.

[40] P. V. Ramachandran, H. J. Hamann, S. Choudhary, *Org. Lett.* **2020**, *22*, 8593–8597.

[41] Y.-P. Zhu, P. Mampuys, S. Sergeyev, S. Ballet, B. U. W. Maes, *Adv. Synth. Catal.* **2017**, *359*, 2481–2498.

[42] X. Zhang, T. Rovis, *J. Am. Chem. Soc.* **2021**, *143*, 21211–21217.

[43] P. Spieß, M. Berger, D. Kaiser, N. Maulide, *J. Am. Chem. Soc.* **2021**, *143*, 10524–10529.

[44] Y.-F. Yang, J.-H. Lin, J.-C. Xiao, *Org. Lett.* **2021**, *23*, 9277–9282.

[45] B. Cui, H. Sun, Y. Xu, L. Li, L. Duan, Y.-M. Li, *J. Org. Chem.* **2018**, *83*, 6015–6024.

[46] I. G. Logvinenko, Y. Markushyna, I. S. Kondratov, B. V. Vashchenko, M. Kliachyna, Y. Tokaryeva, V. Pivnytska, O. O. Grygorenko, G. Haufe, *J. Fluor. Chem.* **2020**, *231*, 109461.

[47] F. Bie, X. Liu, Y. Shi, H. Cao, Y. Han, M. Szostak, C. Liu, *J. Org. Chem.* **2020**, *85*, 15676–15685.

[48] Y. Iwakura, A. Nabeya, T. Nishiguchi, Y. Ichikawa, *J. Org. Chem.* **1965**, *30*, 3410–3413.

[49] N. F. Nikitas, M. K. Apostolopoulou, E. Skolia, A. Tsoukalo, C. G. Kokotos, *Chem. – A Eur. J.* **2021**, *27*, 7915–7922.

[50] S. M. Mali, R. D. Bhaisare, H. N. Gopi, *J. Org. Chem.* **2013**, *78*, 5550–5555.

[51] J. A. Kautzky, T. Wang, R. W. Evans, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2018**, *140*, 6522–6526.

[52] J. Xu, B. Xiao, C.-Q. Xie, D.-F. Luo, L. Liu, Y. Fu, *Angew. Chem. Int. Ed.* **2012**, *51*, 12551–12554.

RESEARCH ARTICLE

3,3-Difluorooxetane – A Versatile Functional Group for Bioisosteric Replacements in Drug Discovery

Oleksandr S. Liashuk,[a,b] Anastasiya Fedinchyk,[a,b] Kostiantyn P. Melnykov,[a,b] Maksym Herasymchuk,[a,b] Diana Alieksieieva,[c] Dmytro Lesyk,[b,c] Yuliia P. Bas,[b] Tetiana Ye. Keda,[b] Andriy V. Yatsymyrskiy,[b] Yuliia Holota,[c] Petro Borysko,[c] Volodymyr S. Yarmolchuk,[a,b] Oleksandr O. Grygorenko[a,b]*

Dedicated to the people of Ukraine

[a] O. S. Liashuk, A. Fedinchyk, Dr. K. P. Melnykov, M. Herasymchuk, Dr. V. S. Yarmolchuk, Dr. Prof. Dr. O. O. Grygorenko
Enamine Ltd., Winston Churchill Street 78, 02094, Kyiv, Ukraine
Web page: www.enamine.net

[b] O. S. Liashuk, A. Fedinchyk, Dr. K. P. Melnykov, M. Herasymchuk, Dr. Yu. P. Bas, Dr. T. Ye. Keda, Dr. A. V. Yatsymyrskiy, Dr. V. S. Yarmolchuk, Prof. Dr. O. O. Grygorenko
Taras Shevchenko National University of Kyiv, Volodymyrska Street 60, 01601, Kyiv, Ukraine
E-mail: gregori@univ.kiev.ua
Web page: www.grygorenko.com

[c] D. Alieksieieva, D. Lesyk, Y. Holota, Dr. P. Borysko
Bienta/Enamine Ltd., Winston Churchill Street 78, 02094, Kyiv, Ukraine
Web page: www.bienta.net

Supporting information for this article is given via a link at the end of the document.

Abstract: Functional group (FG) is one of the cornerstone concepts in organic chemistry and related areas. The wide spread of bioisosterism ideas in medicinal chemistry and beyond caused a striking rise in demand for novel FGs with a defined impact on the developed compound properties. In this work, the evaluation of the 3,3-difluorooxetane unit (3,3-*di*Fox) as a functional group for bioisosteric replacements is disclosed. A comprehensive experimental study (including multigram building block synthesis, quantification of steric and electronic properties, measurements of pK_a, Log*P*, chemical stability, and biological evaluation of the 3,3-*di*Fox-derived bioisostere of a drug candidate) revealed a prominent behavior of the 3,3-*di*Fox fragment as a versatile substituent for early drug discovery programs.

Introduction

Functional group (FG), an atom or a group of atoms with similar chemical properties whenever it occurs in different compounds, is a cornerstone concept in fundamental organic chemistry (Figure 1, *top*).[1,2] In medicinal chemistry and related areas, FGs usually play several important roles, being responsible not only for the chemical transformations of organic molecules but also for establishing specific ligand-target interactions and improving physicochemical parameters – key desirable features in drug design.[3] Examples of the classical FGs most often occurring in medicinal chemistry include the derivatives of carboxylic acids (*i.e.*, amides and esters), ethers, amines, or halogens.[4] For the last decade, increased attention to fluorinated moieties[5] was observed due to the unique properties of the Fluorine atom. Among them, one should mention enhanced resistance to metabolic degradation,[6] a striking effect on pK_a and Log*P*,[7] or amenability for establishing weak interactions with N–H, C–H, and C=O fragments.[8] The type of fluorination pattern has a profound impact on the overall effect of the Fluorine-containing substituent;[9] therefore, the design and implementation of novel fluorinated moieties are of special significance to modern drug discovery.

Recently, an overwhelmingly increased interest in potential drug substances enriched in sp^3-hybrid carbon atoms has led to increased exploitation of small cycloalkyl groups and their heterocyclic analogs in medicinal chemistry.[10–13] Oxetane, an oxa-analog of the cyclobutane ring, was unfairly omitted from the drug discovery campaigns until the early 2000s, when its application as hydrophilic *gem*-dimethyl[14] or metabolically stable carbonyl[15] surrogate was demonstrated.[16] Since then, a large (and still growing) number of oxetane-centered studies have been reported in the literature, revealing a special place of this ring as a promising core for bioisosteric replacements.[17–19]

A major bias that suspended the application of oxetanes in drug discovery is connected with its potential liability under certain conditions.[15,18] Refuting this statement, recent studies demonstrated the enhanced tolerance of 3,3-disubstituted oxetanes to external conditions[20,21] despite several reported exclusions related to the specific structural environment.[22]

With increased interest in 2-substituted oxetanes,[16,18,19,23] application of the Fluorine-containing substituents aimed at modulation of the stability and/or other molecular properties could be regarded as a promising approach to the development of novel oxetane-based functional groups (Figure 1, *bottom*). In this work, we have turned our attention to 3,3-difluorooxetane (3,3-*di*Fox) that potentially resembles many common FGs (e.g., ester or amide, acetal, small (cyclo)alkyl, etc.) and hence has a great potential for bioisosteric replacements. In view of that, we developed an approach to the multigram synthesis of 3,3-*di*Fox-containing building blocks and studied numerous

physicochemical (i.e. acidity/basicity, lipophilicity, Hammett constant), structural, and electronic properties, as well as chemical stability of model derivatives. Finally, we demonstrated the feasibility of bioisosteric replacement of the *tert*-butyl group with 3,3-difluorooxetane fragment by preparation and evaluation of 3,3-*di*Fox-substituted Tenovin-6 analog.

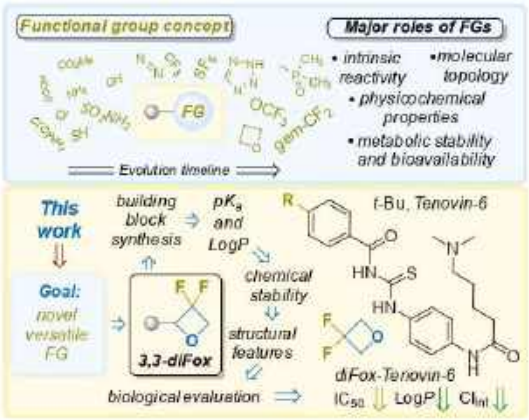
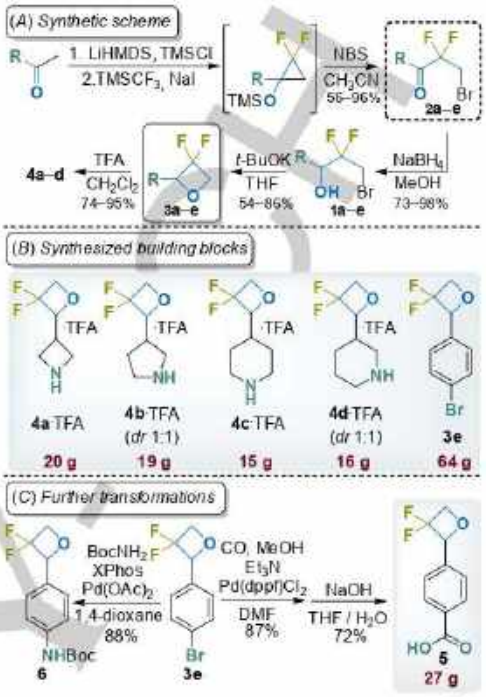


Figure 1. Functional group concept (*top*) and 3,3-difluoroxetane (3,3-*di*Fox) as studied in this work (*bottom*).

Results and Discussion

Synthesis. Previously, preparation of polyfluorinated oxetanes has been performed *via* formal [2+2] cycloaddition,[23–26] intramolecular radical cyclization,[27,28] or base-promoted reaction of fluorinated enolates and carbonyl compounds;[29,30] all these methods are hardly extendable to the synthesis of 3,3-difluorooxetanes. Construction of the target 3,3-difluoroxetane core could be achieved by the intramolecular nucleophilic substitution in 2,2-difluoro-3-haloalcohols of type **1** (Scheme 1); a few precedents of this transformation have been mentioned in the literature for the non-functionalized substrates.[31–33] This retrosynthetic disconnection is easily telescoped to ketones **2**, that can be obtained *via* the difluorocyclopropanation of silyl enolates according to the reported method.[34] Aiming at the multigram preparation of building blocks suitable for further functionalization by common chemical transformations, we synthesized α-bromoketones **2a–e** bearing an *N*-Boc-protected amine or aryl bromide moieties. Reduction of compounds **2a–e** with $NaBH_4$ cleanly produced alcohols **1a–e** in good to excellent yields (73–98%). After evaluating several reaction conditions for the key cyclization step, we have found that *t*-BuOK in THF[35] gave the best results (Table 1). In this way, *N*-Boc protected derivatives **3a–d** and aryl bromide **3e** were synthesized in 40–72% yield over two steps. Compounds **3a–d** were treated with TFA in CH_2Cl_2 giving target amine building blocks **4a–d** as trifluoroacetates in 74–95% yield.

Expectedly, both compounds **3b** and **3d** were synthesized as *ca.* 1:1 mixtures of diastereomers. While their bulk separation appeared to be difficult, we were able to isolate individual (*R**,*S**) and (*S**,*S**) isomers on a subgram scale after the column chromatography. The relative configuration of each product was established by 2D NMR spectroscopy and, in the case of (*S**,*S**)-**3d**, by X-ray diffraction studies.



Scheme 1. Synthesis of 3,3-difluoroxetane building blocks **3e**, **4a–d**, and **5**.

Table 1. Optimization of the heterocyclization step (**1c** → **3c**).[a]

Entry	Base	Temperature, °C	Yield of **3c**, %
1	K_2CO_3	60	0
2	LiHMDS	–78	31
3	NaH	0	25
4	*t*-BuOK	25	79

[a] Conditions: **6c** (1 mmol), base (1.5 mmol), THF

Pd-catalyzed carbonylation of aryl bromide **3e** followed by alkaline saponification of the ester formed produced carboxylic acid **5** in 63% overall yield (Scheme 1, *C*). Buchwald-Hartwig amination[36] of compound **3e** with $BocNH_2$ cleanly afforded *N*-Boc-protected aniline **6** in 88% yield. Unfortunately, all attempts to cleave the carbamate moiety in the molecule of **6** were accompanied by an oxetane ring opening, so the corresponding aniline derivative could not be obtained.

Acidity/basicity. The pK_a values of synthesized amine **4c** (trifluoroacetate) and carboxylic acid **5**, as well as their analogs **7a–n** and **8a–n**, respectively, were measured by standard acid-base titration (Figure 5, Table S1 in the Supporting Information). For the piperidine series, the effect of 3,3-*di*FOx substituent (**4c**)

was somewhat more pronounced (ΔpK_a = 1.1), thus illustrating the weak electron-acceptor properties of this group. The pK_a value (10.0) was similar to that of oxetane (**7b**, 10.2), 1,3-dioxolane (**7m**, 10.0), *gem*-difluorocyclopropane (**7k**, 10.1), and $CHF_2CH(OMe)$-substituted (**7l**, 9.9) derivatives. It was by 0.7–0.8 units lower than those of (cyclo)alkyl derivatives **7e–h**, and by 0.2–0.4 units higher than those for CF_3-, $C(O)NH_2$, or CO_2Me-substituted counterparts (**7i**, **7n**, and **7o**, respectively).

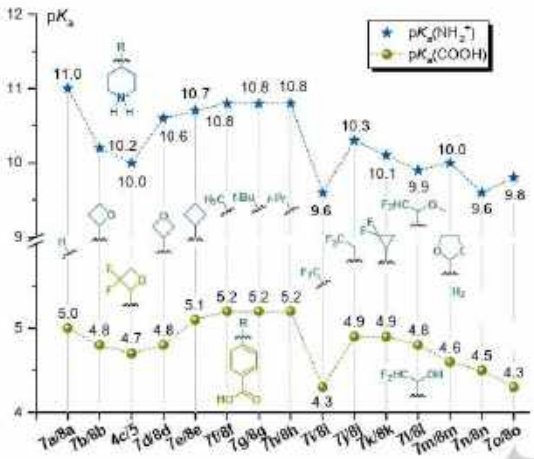


Figure 5. pK_a values for protonated 4-substituted piperidines **4c**, **7a–k** and benzoic acids **5**, **8a–k**.

In the benzoic acid series, similar trends were observed, albeit with lower ΔpK_a magnitude. In particular, difluorooxetanyl-substituted benzoic acid **5** had a pK_a value (4.7) comparable to those of oxetane (**8b** and **8d**, 4.8) 1,3-dioxolane- (**8m**, 4.6) and $CHF_2CH(OMe)$-substituted (**8l**, 4.8) analogs. The pK_a value of compound **5** was by 0.3 and 0.6 units lower than that of parent benzoic acid **8a** (5.0) and alkyl-substituted counterparts **8f–h** (5.2), respectively, and by 0.4 units higher than CF_3- or CO_2Me-substituted analogs **8i** and **8o** (4.3).

These data show that the 3,3-*di*FOx substituent is intermediate in terms of its effect on the pK_a value, and it can be used as a replacement for both (cyclo)alkyl groups and relatively strong acceptors to fine-tune the acidity/basicity of the compounds in the necessary direction.

Lipophilicity. Log*P* values were measured for benzamides **9a–o** (prepared by benzoylation of amines **4c** and **7a–o** under the standard reaction conditions) using the classical shake-flask method combined with HPLC quantitative analysis as reported previously (Figure 6).[7] The 3,3-*di*Fox substituent slightly increased the lipophilicity upon introduction into parent piperidine derivative **9a** (Log*P* = 1.6 vs 1.1, respectively); this effect was similar to those of methyl or $CHF_2CH(OMe)$ groups. Notably, *gem*-difluorination of the oxetane ring resulted in nearly the same Log*P* increase (1.6 vs 1.1 for **9c** and **9b**, respectively), which is contrary to the case cycloalkane derivatives where *gem*-difluorination typically led to increased hydrophilicity.[7] Analysis of the remaining data presented in Figure 6 revealed that the 3,3-*di*Fox substituent had intermediate position between lipophilic (cyclo)alkyl or CF_3-substituted compounds and hydrophilic derivatives bearing polar groups (*e.g.*, ester, amide, or 1,3-dioxolane). Therefore, according to these results, the 3,3-diFOx moiety can be considered as a possible replacement for both substituent types to fine-tune the compound's lipophilicity in the desired direction.

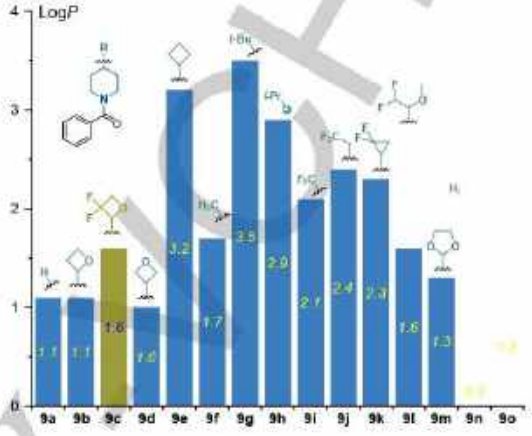


Figure 6. Log*P* values measured for benzamides **9a–k**.

Linear free energy relationships. A quantitative relationships between the structure and reactivity of benzene derivatives was formulated by L.P. Hammett in 1937[37] and is still actively used in QSAR studies.[38,39] In its essence, the Hammett equation states that there is a linear relation between the reaction rates and equilibrium constants for a similar series of compounds (e.g., benzoic acid derivatives):

$$\mathrm{Log}(k/k_H) = \rho\mathrm{Log}(K_a/K_{aH}) = \rho\sigma,$$

where k and k_H – rate constants for a model reaction of the studied compound and parent benzoic acid (**8a**) derivatives, K_a and K_{aH} – dissociation constants of the studied molecule and parent benzoic acid **8a**, ρ – reaction rate constant, $\sigma = \mathrm{Log}(K_a/K_{aH})$ – substituent constant (Hammett constant).

Hammett constants σ measure the magnitude of the substituent electronic effects, thus allowing the positioning of new functional groups among the known ones in terms of their electronic properties. To achieve this for the 3,3-*di*Fox moiety, we have studied 14 *p*-substituted benzoic acids **5**, **8a–p** (9 – with known σ values of the para substituent, and 5 – with yet unreported ones, Table S1 in the Supporting Information). Based on the previously established acidity data shown in Figure 5, the σ values were calculated. The obtained results for the compounds with known σ values were in good agreement with previously reported.[40] In addition to that, kinetic experiments were performed following the methodology reported by Keenan and colleagues.[41] For this purpose, *p*-nitrophenolate esters **10a–p** were synthesized from benzoic acids **8a–p** via acyl chloride activation, and the kinetics data of the ester hydrolysis upon the action of aq NaOH were studied by UV-Vis spectrophotometry. The obtained logarithmic relative rate constants $\mathrm{Log}(k/k_H)$ were plotted against calculated Hammett constant values σ and linearized using the least square method (Figure 7). A good linear correlation was found

(R^2=0.953); the obtained ρ value was slightly lower than the previously reported (1.7 *vs.* 2.1–2.4[41]), which can be related to differences in the experiment conditions.

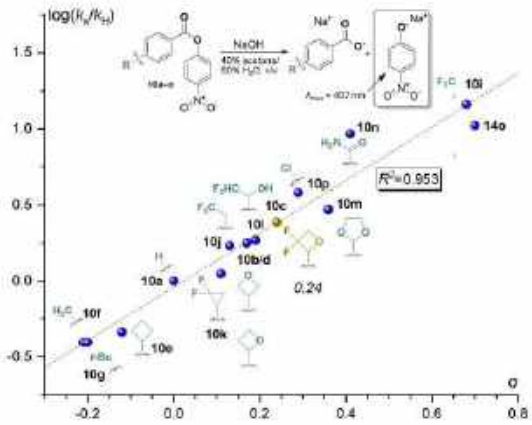


Figure 7. Linear free energy relationship graph.

According to the obtained Hammett constant value (σ = 0.24), the 3,3-*di*Fox functional group can be considered a weak electron acceptor, comparable to chlorine (**10p**, 0.29) and significantly less pronounced than CF_3 (**10i**, 0.68) or CO_2Me (**10o**, 0.70) groups. As might be expected, *gem*-difluorination results in a slight increase of electron-acceptor properties as compared to the parent oxetan-2-yl and oxetan-3-yl substituents (**10b/10d**, σ = 0.17). When the 3,3-*di*Fox is compared to the donor (cyclo)alkyl groups such as cyclobutyl (**10e**, σ = –0.12), a considerable increase of electron-withdrawing properties is observed. Therefore, it is the oxygen atom that is mainly responsible for the electron-acceptor properties of the 3,3-*di*FOx functional group.

Stability of the 3,3-difluorooxetane moiety. Full profiling of a novel drug candidate necessarily requires metabolic stability assaying as one of the key parameters.[42,43] At the same time, the chemical stability of the studied molecule often stays out of attention.[44,45] Considering the known oxetane reactivity,[16,18,46–48] as well as our unsuccessful experience with *N*-Boc cleavage from compound **6**, one could question the 3,3-diFox moiety stability. To overcome these biases, we evaluated compound **3e** as a model substrate under common organic transformation conditions.[49] We included highly acidic (TFA and anhydrous HCl), basic (LiOH), oxidative (Dess-Martin periodinane and 30% aq H_2O_2), and reductive agents (H_2 – Pd/C and $LiAlH_4$), irradiation (at 365 and 450 nm), and air.[50] The experiment included mixing the compound **3e** and indicated reagents at low (0 °C), ambient (24 °C), and elevated (60 °C) temperatures (or irradiation at the corresponding wavelengths) for 2 h, and work-up of the reaction mixture. Then, the recovery yields were measured by quantitative ^{1}H NMR spectroscopy against a control sample of **3e**. The results have been depicted as a radar diagram (Figure 8). It is apparent that the 3,3-diFox moiety is compatible with most common reaction conditions at 0 °C and 24 °C. As expected, elevated temperature was detrimental to the relative recovery ratio (42–88%); in this case, significant decomposition was observed in the presence of HCl and $LiAlH_4$ (but not LiOH). Notably, dehalogenation was the main decomposition pathway in the presence of reductants: while the oxetane fragment remained virtually intact, significant amounts of defluorinated products were detected (up to 11% for catalytic hydrogenation and 80% for $LiAlH_4$). Finally, the stability of the 3,3-*di*Fox fragment was illustrated by a five-year on-shelf storage with no detected loss of the sample quality (see Supporting Information). The observed results correlate with previously reported data on other 3,3-substituted oxetanes.[16] This effect was typically related to reduced ring strain[51] and/or sterically hindered access to C–O σ* antibonding orbital;[16] these explanations are less pertinent for the 3,3-*di*Fox fragment.

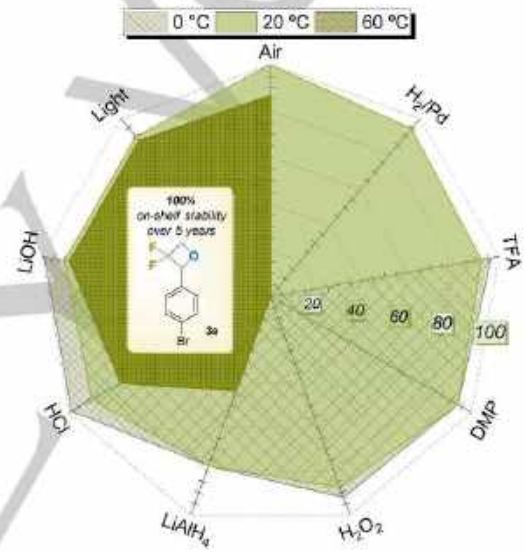


Figure 8. Stability assessment of compound **3e** (the recovery yields measured by quantitative ^{1}H NMR spectroscopy against a control sample are shown as a radar diagram).

Structural and electronic properties. An X-ray diffraction study of (*S*,S**)-**3d**[52] and comparison of the obtained results with the CCDC data for oxetane,[53] cyclobutane,[54] and 3,3-difluoro-cyclobutane[55] derivatives revealed several structural features of the 3,3-*di*Fox moiety (Figure 9, *A*). While the *gem*-CF_2 or O fragments had minor effects on the valent angles φ_1 and φ_2 as compared to the parent cyclobutane scaffold (1–2° difference), ring puckering angle θ was affected significantly. Thus, introducing an oxygen atom to the cyclobutane ring led to its significant flattening (θ = 26.9° and 6.9° for cyclobutane and oxetane, respectively), while *gem*-difluorination slightly increased puckering (26.9° and 29.7°, respectively). For the oxetane core, the latter effect of *gem*-difluorination was even more pronounced: the θ value was increased by 10°.

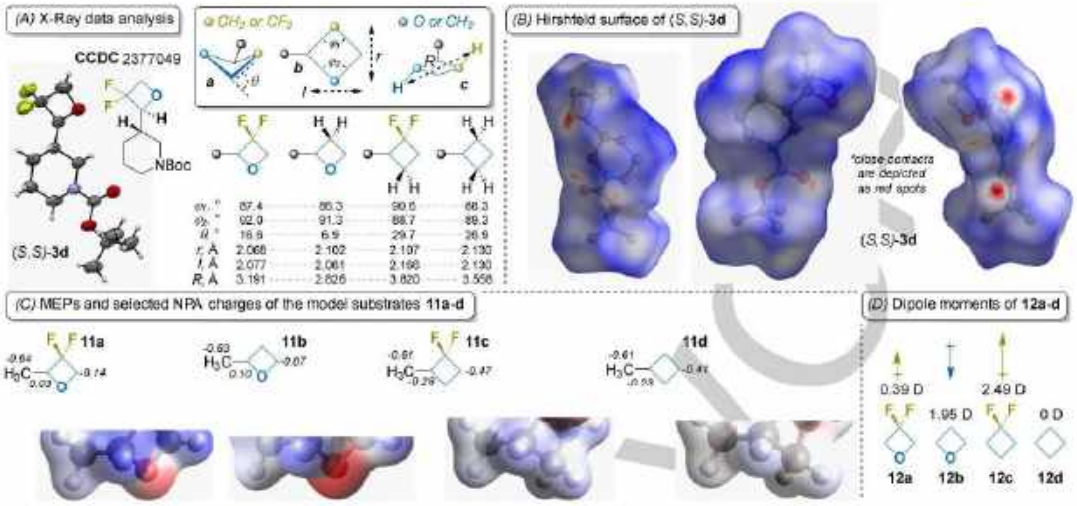


Figure 9. (*A*) X-Ray structure of (*S**,*S**)-**3d** and comparison of the geometric parameters of 3,3-*di*Fox fragment with its closest analogs. (*B*) The Hirshfeld surface of (*S**,*S**)-**3d**. (*C*) The molecular electrostatic potential (MEP) surfaces for the optimized geometry of **11a–d** and calculated NPA-derived partial atomic charges (DFT/PBE0/ma-def2-TZVP).[58] (*D*) Dipole moments calculated for parent cyclic compounds **12a–d**.

As for the relative size of the discussed moieties, introducing oxygen atom decreased both C1–C3 (*l*) and C2–C4/O (*r*) interatomic distances (numeration of the parent cyclobutane ring was preserved). For the CF_2 moiety, the corresponding effects were opposite, i.e., decrease for *r* and increase for *l*. Also, the 3,3-*di*FOx moiety had the second lowest value of maximum fragment diameter (*R*) within the series studied.

Analysis of the Hirshfeld surface[57] of (*S**,*S**)-**3d** (Figure 9, *B*) demonstrated high involvement of the Oxygen and Nitrogen atoms in the formation of intermolecular contacts in the solid state (red spots), whereas the Fluorine atoms did not participate in these interactions (blue areas).

To get a deeper insight into the structural and electronic features of the studied fragments, a DFT study of 2-methyl-3,3-difluoro-oxetane (**11a**), 2-methyloxetane (**11b**), 1,1-difluoro-2-methyl-cyclobutane (**11c**), and methylcyclobutane (**11d**) was performed. Molecular electrostatic potential (MEP) analysis was used to identify the reactive sites of the corresponding fragments (Figure 9, *C*). Negative (red) and positive (blue) regions of the electrostatic potential contour maps denote the sites of possible electrophilic and nucleophilic attack, respectively. Thus, the introduction of a single electron-withdrawing moiety (either O or CF_2) mainly affected α-Carbon atoms, inverting their electrostatic potentials from slightly negative to neutral or positive values (compare **11d** and **11b**/**11c**). At the same time, the combination of both CF_2 and O fragments in the molecule **11a** had a synergistic effect, significantly decreasing the electrostatic potential on all the Carbon atoms of the four-membered ring and hence creating an X-shaped electrostatic map with opposite potential signs.

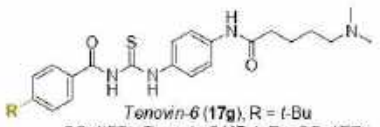
A closer look at the ***gem***-CF_2 fragment in **11a** offers a possible explanation for the lowered susceptibility of the fluorinated oxetane ring towards most chemical reagents studied. While the steric size of the Fluorine atom is relatively low, high Fluorine electronegativity causes the formation of a large negatively charged surface near the potential reaction centers. This, in turn, makes the nucleophilic attack at the oxetane ring less feasible, enhancing the chemical stability of the moiety.

The calculated dipole moments of parent cyclobutane **12a** and its fluorinated and/or oxygenated analogs **12b–d** revealed the higher effect of the ***gem***-CF_2 fragment on the overall polarization of 3,3-*di*Fox moiety, which compensated the effect of the Oxygen atom in the oxetane ring (Figure 9, *D*). In view of its relatively low dipole moment (0.39 D), the 3,3-*di*FOx group can be considered a better mimic of the non-polar cycloalkyl groups than the corresponding simple ***gem***-difluorinated or oxygen-containing counterparts.

Physicochemical and biological evaluation. To demonstrate the potential of 3,3-difluorooxetane for bioisosteric replacements in medicinal chemistry, we have prepared 3,3-*di*FOx-substituted analog **13c** of Tenovin-6 (**13g**, as a racemic mixture of enantiomers), a known selective inhibitor of histone deacetylases SirT1 and SirT2 (Table 1).[58-60] In this case, the 3,3-*di*FOx moiety was introduced instead of ***tert***-butyl group. The synthesis of compounds **13c** and **13g** commenced from corresponding benzoic acids **8g** and **5** and followed the procedure reported previously for compound **13g** (see the Supporting Information for more details).[59,61] Evaluation of the obtained products revealed that 3,3-*di*FOx-substituted analog **13c** retained most biological activity of original Tenovin-6 (**13g**) against histone deacetylase SIRT1 (only a 4-fold decrease of the IC_{50} value was observed). Furthermore, compound **13c** was by 0.7–1.3 LogP / Log$D_{7.4}$ units less lipophilic than parent Tenovin-6, while the aqueous solubility of both compounds was similar (370 and 350 μM, respectively). Caco-2 permeability test demonstrated moderate permeability through the cell membranes for both compounds. Nevertheless, the efflux of Tenovin-6 (**13g**) was strongly affected by P-glycoprotein (P-gp) inhibitor Verapamil, while 3,3-*di*FOx-Tenovin-6 (**13c**) was much less sensitive to the presence of this compound. In other words, introducing the 3,3-*di*FOx substituent decreased

affinity of Tenovin-6 towards P-gp. Finally, metabolic stability (measured as intrinsic clearance, CL_{int}) was somewhat improved for the 3,3-*di*FOx-substituted derivative (CL_{int} = 2 μL/min/mg vs 9 μL/min/mg for Tenovin-6). These results show that 3,3-difluorooxetane can be indeed used as a bioisostere of *tert*-butyl (and likely other) groups to improve the pharmacokinetic properties of optimized compounds.

Table 1. Physicochemical and biological assessment of Tenovin-6 (**13g**) and its 3,3-diFOx analog (**13c**).



Tenovin-6 (**17g**), R = *t*-Bu
3,3-diFOx-Tenovin-6 (**17c**), R = 3,3-*di*FOx

Compound	Log*P* / Log$D_{7.4}$	S_w, μM[a]	Efflux ratio,[b] without/with Verapamil	IC_{50}, μM[c]	CL_{int}, μL/min/mg[d]
Tenovin-6 (**13g**)	1.1 / 3.1	350	9.1 / 1.3	14	9
*3,3-di*FOx-*Tenovin-6* (**13c**)	0.4 / 1.8	370	0.9 / 0.3	58	2

[a] Kinetic solubility in phosphate-buffered saline, pH = 7.4 [b] In Caco-2 cells [c] Sirt Glo assay [d] In human liver microsomes.

Conclusion

With the wide spread of the bioisosteric replacement approach in medicinal chemistry, the demand for new functional groups allowing fine-tuning of desirable properties of potential drugs has increased considerably. We propose 3,3-difluoroxetan-2-yl (3,3-*di*FOx) as a promising fluorinated substituent and non-classical isostere of numerous functional groups. We have shown that functionalized derivatives with 3,3-*di*FOx moiety mounted onto an aromatic or saturated heterocyclic ring can be prepared in multigram quantities (up to 64 g scale in a single run). Measurement of pK_a values for model derivatives demonstrated that the 3,3-*di*FOx fragment is a weak acceptor that can be used to fine-tune acidity/basicity by replacing either donor alkyl groups or stronger acceptors like CF_3, CO_2Me, or $C(O)NH_2$. This was confirmed by linear free energy relationship studies, with the Hammet constant value of the title substituent (σ = 0.24) being close to that of chlorine (σ = 0.29).

Lipophilicity measurements for a series of model derivatives showed that the 3,3-*di*FOx moiety slightly increases the compound's lipophilicity when introduced into the parent molecule (ΔLog*P* = +0.5). Again, this effect was intermediate between those of (cyclo)alkyl groups and polar fragments like amide, ester, 1,3-dioxolane, or non-fluorinated oxetane, thus suggesting potential for isosteric replacements of both these categories.

In terms of three-dimensional structure, the 3,3-*di*FOx fragment showed intermediate ring puckering between oxetane and cyclobutane/*gem*-difluorocyclobutane and was the second smallest between these fragments. The molecular electrostatic potential (MEP) map of the 3,3-*di*FOx group was X-shaped, with opposite potential signs at the diagonal ring atoms. As a result, the overall dipole moment of 3,3-difluorooxetane was relatively low (0.39 D), suggesting that the proposed moiety can be a better mimic for (cyclo)alkyl groups than simpler *gem*-difluorinated or oxygen-containing counterparts.

Finally, the 3,3-*di*FOx moiety had reasonable stability towards common chemical reagents, excellent shelf storage stability (over 5 years), and good metabolic stability. The latter fact was confirmed by introducing the title functional group into the molecule of Tenovin-6, a known sirtuin inhibitor, instead of a *tert*-butyl group. This modification retained a significant fraction of the compound's biological activity, increased hydrophilicity, and reduced P-glycoprotein affinity. These data confirm bioisosteric replacement compatibility of the 3,3-*di*FOx moiety for the particular case studied. We hope that along with all other results presented in this work, they will promote applications of 3,3-difluorooxetane as a promising functional group in drug discovery and other areas of science.

Supporting Information

The solvents were purified according to the standard procedures.[82] Compounds **7,8a,b,d–o** were obtained from Enamine stock; all other starting materials were available commercially. Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR and 470 MHz for ^{19}F NMR) and Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR). NMR chemical shifts are reported in pp (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6. Coupling constants (*J*) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, and coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and Agilent 5890 Series II 5972 MS instrument (electron impact ionization (EI)). High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer.

General Procedure for the Synthesis of Bromoketones 2.

Corresponding ketones were prepared according to the previously reported procedure.[34] NEt_3 (8.62 mL, 0.0619 mol) and TMSCl (3.80 mL, 0.030 mol) were added to a solution of corresponding ketone (0.025 mol) in DMF (10 mL). The reaction mixture was stirred overnight at 80 °C. Then it was allowed to cool to r.t. and poured into an ice/water mixture (20 mL) and extracted with hexanes (2×20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to give crude ***O***-silyl enolate (*ca.* 0.022 mol) used in the next step without characterization.

$TMSCF_3$ (6.67 mL, 0.045 mol) and NaI (0.68 g, 0.004 mol) were added to the solution of crude enolate in THF (70 mL). The reaction mixture was stirred for 1 h at r.t and overnight at 50 °C. Then it was evaporated, diluted with *t*BuOMe (30 mL), filtered, and the filtrate was evaporated to give crude product (*ca.* 0.018 mol) used in the next step without purification.

NBS (4.29 g, 0.024 mol) was added to the solution of crude product (from the previous step) in MeOH (70 mL). The reaction mixture was stirred at r.t for 1 h and water (200 mL) was added. The mixture was extracted with hexane (2 × 200 mL), the combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (gradient hexanes – *t*BuOMe (95:5 to 0:100) as eluent) to give pure compound **5**.

3-Bromo-1-(4-bromophenyl)-2,2-difluoropropan-1-one (2e). Yield 126.7 g, 0.386 mol, 96%. Orange crystals, mp = 48 – 50 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 7.9 Hz, 2H), 3.88 (t, *J* = 14.5 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 186.2 (t, *J* = 31.0 Hz), 131.7, 131.0 (d, *J* = 3.3 Hz), 130.0, 129.7 (t, *J* = 3.3 Hz), 114.6 (t, *J* = 256.3 Hz), 28.2 (t, *J* = 27.9 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –100.2. Anal. calcd. for $C_9H_6Br_2F_2O$: C 32.96; H 1.84; Br 48.73. Found: C 33.05; H 2.00; Br 49.04.

General Procedure for the Synthesis of Bromoalcohols 1.

To a pre-cooled to 0 °C solution of ketone **2a**–**e** (10.0 mmol) in CH_3OH (70 mL) solid $NaBH_4$ (0.450 g, 12.0 mmol) was added in small portions. The resulting mixture was slowly warmed to rt (ca. 1 h) and evaporated under reduced pressure. Crude product was dissolved in H_2O (80 mL) and extracted with CH_2Cl_2 (3 × 50 mL). Combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to give pure product **1**.

***tert*-Butyl 3-(3-bromo-2,2-difluoro-1-hydroxypropyl)piperidine-1-carboxylate (1d).** Yield 28.8 g, 80.4 mmol, 95% (from 30.0 g of **2d**). Yellowish viscous oil. Mixture of diasteromers 1:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.01 (s, 1H), 3.97 – 3.70 (m, 3H), 3.63 (tt, *J* = 11.7, 6.6 Hz, 1H), 3.39 (s, 2H), 2.71 (s, 1H), 2.04 – 1.75 (m, 2H), 1.75 – 1.55 (m, 2H), 1.44 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 155.3 and 154.5, 120.8 (t, *J* = 249.1 Hz) and 120.1 (t, *J* = 248.6 Hz), 79.7 and 79.3, 71.3 (dd, *J* = 29.1, 25.8 Hz) and 69.6 (br), 46.4 and 45.6, 45.0 and 43.9, 36.1 and 35.6, 29.3 (br), 27.9, 26.4 and 24.8, 24.1 and 22.8. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –105.1 (d, *J* = 249.0 Hz), –106.4 (d, *J* = 240.1 Hz), –107.7 (d, *J* = 251.1 Hz), –111.5 (d, *J* = 244.3 Hz), –111.9 (d, *J* = 248.5 Hz), –113.8 (d, *J* = 258.6 Hz). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{23}BrF_2NO_3^+$: 358.0824; Found: 358.0818.

General Procedure for the Synthesis of Oxetanes 3.

To a pre-cooled to 0 °C solution of alcohol **1** (10.0 mmol) in THF (70 mL) solid *t*-BuOK (1.68 g, 15.0 mmol) was added in small portions. The resulting mixture was slowly warmed to rt (ca. 1 h) and stirred overnight. After the reaction was complete (concluded by ^{1}H NMR spectroscopy) the organic solvent was evaporated under reduced pressure. The crude product was dissolved in H_2O (80 mL) and extracted with *t*-BuOMe (3 × 50 mL). Combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to give crude product, which was purified by flash column chromatography (Hexane/*t*-BuOMe 1:1 to 3:1 gradient) resulting in pure product **4**.

***tert*-Butyl 3-(3,3-difluorooxetan-2-yl)piperidine-1-carboxylate (3d).** Yield 19.0 g, 68.5 mmol, 86% (from 28.4 g of **1d**). Yellow oil. Analytical samples of individual diatereomers were obtained by column chromatography (hexane – *t*-BuOMe, 4:1 as eluan) of small portion of the isolated product.

***(S*,R*)*-3d.** Colorless crystals, mp = 48 – 49 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 – 4.56 (m, 3H), 3.89 – 3.50 (m, 2H), 3.29 – 2.75 (m, 2H), 2.18 – 2.01 (m, 1H), 1.86 (s, 1H), 1.71 – 1.60 (m, 1H), 1.43 (s, 11H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 154.7, 118.1 (t, *J* = 278.3 Hz), 90.7, 79.7, 78.1 (t, *J* = 25.1 Hz), 35.7, 31.5, 31.4, 30.2, 30.1, 28.3, 24.5, 23.3. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –98.52 (d, *J* = 200.1 Hz), –116.48 (d, *J* = 205.6 Hz). HRMS (ESI/QTOF) m/z: $[M - t\text{Bu} + H]^+$ Calcd for $C_9H_{14}F_2NO_3^+$: 222.0933; Found: 222.0932.

***(S*,S*)*-3d.** Colorless crystals, mp = 59 – 60 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87 – 4.55 (m, 3H), 4.05 (d, *J* = 11.5 Hz, 1H), 3.88 (d, *J* = 13.2 Hz, 1H), 2.95 – 2.82 (m, 1H), 2.71 (t, *J* = 11.1 Hz, 1H), 2.17 – 2.00 (m, 1H), 1.87 – 1.76 (m, 1H), 1.66 (dt, *J* = 12.8, 3.8 Hz, 1H), 1.46 (s, 10H), 1.27 – 1.13 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.8, 118.2 (t, *J* = 278.3 Hz), 91.2 (t, *J* = 22.9 Hz), 79.6, 78.1 (t, *J* = 26.0 Hz), 44.6 (br), 36.4, 28.4, 25.3, 23.8. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –98.12 (d, *J* = 197.4 Hz), –116.32 (d, *J* = 201.1 Hz). HRMS (ESI/QTOF) m/z: $[M - t\text{Bu} + H]^+$ Calcd for $C_9H_{14}F_2NO_3^+$: 222.0933; Found: 222.0930.

The authors have cited additional works within the Supporting Information.[61–65]

Acknowledgements

This work was funded by Enamine Ltd. The authors thank Olga Kovalenko and Margaryta Bolgova for a part of pK_a measurements, Anastasia Bondaruk for help with kinetic experiments, Karina Turenko for her help with biological experiments, Prof. Dr. Svitlana Shyshkina for X-Ray diffraction studies, Prof. Andriy A. Tolmachov for his encouragement and support, and all the people of Ukraine for making this manuscript possible.

Conflict of Interest

Most of the authors are / have been employees, trainees, or consulting scientists of Enamine Ltd. that offers all the building blocks described in this paper in the company's catalog.

Keywords: Fluorine • Oxetane • Building Blocks • Bioisosteres • Functional Groups

[1] J. March, *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, Wiley, **1985**.

[2] P. Muller, *Pure Appl. Chem.* **1994**, *66*, 1077–1184.
[3] L. Schaeffer, *The Role of Functional Groups in Drug-Receptor Interactions*, Elsevier Ltd, **2008**.
[4] P. Ertl, E. Altmann, J. M. McKenna, *J. Med. Chem.* **2020**, *63*, 8408–8418.
[5] C. M. Marshall, J. G. Federice, C. N. Bell, P. B. Cox, J. T. Njardarson, *J. Med. Chem.* **2024**, DOI 10.1021/acs.jmedchem.4c01122.
[6] P. Shah, A. D. Westwell, *J. Enzyme Inhib. Med. Chem.* **2007**, *22*, 527–540.
[7] S. Holovach, K. P. Melnykov, A. Skreminskiy, M. Herasymchuk, O. Tavlui, D. Aloshyn, P. Borysko, A. B. Rozhenko, S. V Ryabukhin, D. M. Volochnyuk, O. O. Grygorenko, *Chem. – A Eur. J.* **2022**, *28*, e202200331.
[8] K. Müller, C. Faeh, F. F. F. Diederich, K. Müller, C. Faeh, F. F. F. Diederich, K. Müller, C. Faeh, F. F. F. Diederich, *Science* **2007**, *317*, 1881–1886.
[9] Q. A. Huchet, B. Kuhn, B. Wagner, N. A. Kratochwil, H. Fischer, M. Kansy, D. Zimmerli, E. M. Carreira, K. Müller, *J. Med. Chem.* **2015**, *58*, 9041–9060.
[10] T. T. Talele, *J. Med. Chem.* **2016**, *59*, 8712–8756.
[11] M. R. van der Kolk, M. A. C. H. Janssen, F. P. J. T. Rutjes, D. Blanco-Ania, *ChemMedChem* **2022**, *17*, e202200020.
[12] M. R. Bauer, P. Di Fruscia, S. C. C. Lucas, I. N. Michaelides, J. E. Nelson, R. I. Storer, B. C. Whitehurst, *RSC Med. Chem.* **2021**, *12*, 448–471.
[13] J. Shearer, J. L. Castro, A. D. G. Lawson, M. MacCoss, R. D. Taylor, *J. Med. Chem.* **2022**, *65*, 8699–8712.
[14] G. Wuitschik, M. Rogers-Evans, K. Müller, H. Fischer, B. Wagner, F. Schuler, L. Polonchuk, E. M. Carreira, *Angew. Chem. Int. Ed.* **2006**, *45*, 7736–7739.
[15] G. Wuitschik, E. M. Carreira, B. Wagner, H. Fischer, I. Parrilla, F. Schuler, M. Rogers-Evans, K. Müller, *J. Med. Chem.* **2010**, *53*, 3227–3246.
[16] J. A. Bull, R. A. Croft, O. A. Davis, R. Doran, K. F. Morgan, *Chem. Rev.* **2016**, *116*, 12150–12233.
[17] D. Tian, G. Chen, X. Wang, H.-J. Zhang, *J. Am. Chem. Soc.* **2024**, *146*, 18011–18018.
[18] J. J. Rojas, J. A. Bull, *J. Med. Chem.* **2023**, *66*, 12697–12709.
[19] G. Huang, D. Hucek, T. Cierpicki, J. Grembecka, *Eur. J. Med. Chem.* **2023**, *261*, 115802.
[20] M. A. J. Dubois, R. A. Croft, Y. Ding, C. Choi, D. R. Owen, J. A. Bull, J. J. Mousseau, *RSC Med. Chem.* **2021**, *12*, 2045–2052.
[21] P. Saejong, J. J. Rojas, C. Denis, A. J. P. White, A. S. Voisin-Chiret, C. Choi, J. A. Bull, *Org. Biomol. Chem.* **2023**, *21*, 5553–5559.
[22] B. Chalyk, A. Grynyova, K. Filimonova, T. V Rudenko, D. Dibchak, P. K. Mykhailiuk, *Org. Lett.* **2022**, *24*, 4722–4728.
[23] O. A. Davis, J. A. Bull, *Synlett* **2015**, *26*, 1283–1288.
[24] V. A. Petrov, F. Davidson, B. E. Smart, *J. Org. Chem.* **1995**, *60*, 3419–3422.
[26] M. A. Gomez Fernandez, C. Lefebvre, A. Sudau, P. Genix, J.-P. Vors, M. Abe, N. Hoffmann, *Chem. – A Eur. J.* **2021**, *27*, 15722–15729.
[26] E. R. Bissell, D. B. Fields, *J. Org. Chem.* **1964**, *29*, 249–252.
[27] Y. Ofuji, T. Kanbara, T. Yajima, *J. Fluor. Chem.* **2021**, *247*, 109805.
[28] X. X. Rong, H.-Q. Pan, W. R. J. Dolbier, B. E. Smart, *J. Am. Chem. Soc.* **1994**, *116*, 4521–4522.
[29] O. Jiménez, M. P. Bosch, A. Guerrero, *J. Org. Chem.* **2005**, *70*, 10883–10885.
[30] C.-P. Qian, T. Nakai, *Tetrahedron Lett.* **1988**, *29*, 4119–4122.
[31] O. V Fedorov, M. D. Kosobokov, V. V Levin, M. I. Struchkova, A. D. Dilman, *J. Org. Chem.* **2015**, *80*, 5870–5876.
[32] T. L. Andersen, M. W. Frederiksen, K. Domino, T. Skrydstrup, *Angew. Chem. Int. Ed.* **2016**, *55*, 10396–10400.
[33] R. D. Chambers, A. H. S. Gilani, A. F. Gilbert, J. Hutchinson, R. L. Powell, *J. Fluor. Chem.* **2000**, *106*, 53–67.
[34] A. Fedinchyk, M. Herasymchuk, V. O. Smirnov, K. P. Melnykov, D. V Yarmoliuk, A. A. Kyrylchuk, O. O. Grygorenko, *Eur. J. Org. Chem.* **2022**, *2022*, e202200274.
[35] V. M.-Y. Leung, M. H. Gieuw, Z. Ke, Y.-Y. Yeung, *Adv. Synth. Catal.* **2020**, *362*, 2039–2044.
[36] S. Bhagwanth, A. G. Waterson, G. M. Adjabeng, K. R. Hornberger, *J. Org. Chem.* **2009**, *74*, 4634–4637.
[37] L. P. Hammett, *J. Am. Chem. Soc.* **1937**, *59*, 96–103.
[38] P. Ertl, *Quant. Struct. Relationships* **1997**, *16*, 377–382.
[39] M. J. Sahre, G. F. von Rudorff, O. A. von Lilienfeld, *J. Am. Chem. Soc.* **2023**, *145*, 5899–5908.
[40] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–195.
[41] S. L. Keenan, K. P. K. Peterson, K. P. K. Peterson, K. Jacobson, *J. Chem. Educ.* **2008**, *85*, 558.
[42] C. M. Masimirembwa, U. Bredberg, T. B. Andersson, *Clin. Pharmacokinet.* **2003**, *42*, 515–528.
[43] P. Baranczewski, A. Stańczak, K. Sundberg, R. Svensson, A. Wallin, J. Jansson, P. Garberg, H. Postlind, *Pharmacol. Rep.* **2006**, *58*, 453–472.
[44] In *Side Reactions in Organic Synthesis*, **2004**, pp. 35–58.
[45] F. Pellerin, D. Baylocq, N. Chanon, *Rev. Anal. Chem.* **1992**, *11*, 171–194.
[46] S. Ahmad, M. Yousaf, A. Mansha, N. Rasool, A. F. Zahoor, F. Hafeez, S. M. A. Rizvi, *Synth. Commun.* **2016**, *46*, 1397–1416.
[47] L. Siqi, X. Jiaxi, *Prog. Chem.* **2016**, *28*, 1798–1810.
[48] J. X. Wenhao Yuan, *Chin. J. Org. Chem.* *41*, 947–958.
[49] D. G. Brown, J. Boström, *J. Med. Chem.* **2016**, *59*, 4443–4458.
[50] C. J. Briscoe, D. S. Hage, *Bioanalysis* **2009**, *1*, 205–220.
[51] B. Ringnér, S. Sunner, H. Watanabe, A. A. Lindberg, I. Lagerlund, L. Ehrenberg, *Acta Chem. Scand.* **1971**, *25*, 141–146.
[52] Deposition Number <url href="https://www.ccdc.cam.ac.uk/services/structures?id=doi:10.1002/chem.202403277">2377049 (for (*S**,*S**)-**3c**), </url> contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe <url href="http://www.ccdc.cam.ac.uk/structures">Access Structures service</url>
[53] A. F. Stepan, K. Karki, W. S. McDonald, P. H. Dorff, J. K. Dutra, K. J. DiRico, A. Won, C. Subramanyam, I. V Efremov, C. J. O'Donnell, C. E. Nolan, S. L. Becker, L. R. Pustilnik, B. Sneed, H. Sun, Y. Lu, A. E. Robshaw, D. Riddell, T. J. O'Sullivan, E. Sibley, S. Capetta, K. Atchison, A. J. Hallgren, E. Miller, A. Wood, R. S. Obach, *J. Med. Chem.* **2011**, *54*, 7772–7783.
[54] D. Hu, X. Jiang, *Green Chem.* **2022**, *24*, 124–129.
[55] P.-P. Lin, L.-L. Huang, S.-X. Feng, S. Yang, H. Wang, Z.-S. Huang, Q. Li, *Org. Lett.* **2021**, *23*, 3088–3093.
[56] A. E. Reed, R. B. Weinstock, F. Weinhold, *J. Chem. Phys.* **1985**, *83*, 735–746.
[57] P. R. Spackman, M. J. Turner, J. J. McKinnon, S. K. Wolff, D. J.

Grimwood, D. Jayatilaka, M. A. Spackman, *J. Appl. Crystallogr.* **2021**, *54*, 1006–1011.

[58] S. Lain, J. J. Hollick, J. Campbell, O. D. Staples, M. Higgins, M. Aoubala, A. McCarthy, V. Appleyard, K. E. Murray, L. Baker, A. Thompson, J. Mathers, S. J. Holland, M. J. R. Stark, G. Pass, J. Woods, D. P. Lane, N. J. Westwood, *Cancer Cell* **2008**, *13*, 454–463.

[59] L. Pirie, A. R. McCarthy, L. L. Major, V. Morkūnaitė, A. Zubrienė, D. Matulis, S. Lain, T. Lebl, N. J. Westwood, *Molecules* **2012**, *17*, 12206–12224.

[60] S. Hirai, S. Endo, R. Saito, M. Hirose, T. Ueno, H. Suzuki, K. Yamato, M. Abei, I. Hyodo, *PLoS One* **2014**, *9*, e102831.

[61] A. R. McCarthy, L. Pirrie, J. J. Hollick, S. Ronseaux, J. Campbell, M. Higgins, O. D. Staples, F. Tran, A. M. Z. Slawin, S. Lain, N. J. Westwood, *Bioorg. Med. Chem.* **2012**, *20*, 1779–1793.

[62] W. L. F. Armarego, C. Chai, *Purification of Laboratory Chemicals*, Elsevier: Oxford, **2003**.

[63] W. J. Hehre, R. Ditchfield, J. A. Pople, *J. Chem. Phys.* **1972**, *56*, 2257–2261.

[64] F. Neese, *WIREs Comput. Mol. Sci.* **2022**, *12*, e1606.

[65] F. Neese, *WIREs Comput. Mol. Sci.* **2012**, *2*, 73–78.

[66] F. Neese, *WIREs Comput. Mol. Sci.* **2018**, *8*, e1327.

[67] T. Y. Nikolaienko, L. A. Bulavin, D. M. Hovorun, *Comput. Theor. Chem.* **2014**, *1050*, 15–22.

[68] The JANPA project homepage, can be found under https://janpa.sourceforge.net/.

[69] M. D. Hanwell, D. E. Curtis, D. C. Lonie, T. Vandermeersch, E. Zurek, G. R. Hutchison, *J. Cheminform.* **2012**, *4*, 17.

[70] J. E. Phillips, A. Arena, *MultiScreen Caco-2 Assay System*, Danvers, MA.

[71] E. Sevin, L. Dehouck, A. Fabulas-da Costa, R. Cecchelli, M. P. Dehouck, S. Lundquist, M. Culot, *J. Pharmacol. Toxicol. Methods* **2013**, *68*, 334–339.

[72] B. Srinivasan, A. R. Kolli, M. B. Esch, H. E. Abaci, M. L. Shuler, J. J. Hickman, *SLAS Technol.* **2015**, *20*, 107–126.

[73] Z. S. Teksin, P. R. Seo, J. E. Polli, *AAPS J.* **2010**, *12*, 238–241.

[74] F. Halley, J. Reinshagen, B. Ellinger, M. Wolf, A. L. Niles, N. J. Evans, T. A. Kirkland, J. M. Wagner, M. Jung, P. Gribbon, S. Gul, *SLAS Discov.* **2011**, *16*, 1227–1235.

[75] A. Rahaman, A. Kumar Singh, A. Gupta, S. Bhadra, *Eur. J. Org. Chem.* **2021**, *2021*, 2198–2202.

[76] M. Budéšínský, V. Vaněk, M. Dračínský, R. Pohl, L. Poštová-Slavětínská, V. Sychrovský, J. Přcha, I. Císařová, *Tetrahedron* **2014**, *70*, 3871–3886.

[77] G. Chen, B. Xu, *Org. Lett.* **2023**, *25*, 6334–6339.

[78] M.-S. Dai, Z.-M. Zheng, S.-L. Zhang, *Org. Biomol. Chem.* **2023**, *21*, 935–939.

[79] M. Zhang, S. Zhang, G. Zhang, F. Chen, J. Cheng, *Tetrahedron Lett.* **2011**, *52*, 2480–2483.

[80] G. M. Sheldrick, *Acta Crystallogr. Sect. A* **2008**, *64*, 112–122.

[81] C. Adamo, M. Cossi, V. Barone, *J. Mol. Struct. THEOCHEM* **1999**, *493*, 145–157.

[82] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789.

[83] N. Mardirossian, M. Head-Gordon, *Phys. Chem. Chem. Phys.* **2014**, *16*, 9904–9924.

[84] Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215–241.

[85] F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297–3305.

WILEY-VCH

Physicochemical and Biological Evaluation of *gem*-Difluorinated Saturated Oxygen Heterocycles as Bioisosteres for Drug Discovery

Kostiantyn P. Melnykov,[a,b] Oleksandr S. Liashuk,[a,b] Serhii Holovach,[a,c] Valeriia Shatnia,[a,d] Artur Horbenko,[a,e] Dmytro Lesyk,[b,f] Varvara Melnyk,[f] Daniil Skrypnik,[f] Anna Beshtynarska,[f] Petro Borysko,[f] Oleksandr Viniichuk,[a,b] Oleksandr O. Grygorenko[a,b]*

Dedicated to the people of Ukraine

[a] Dr. K. P. Melnykov, Dr. O. S. Liashuk, Dr. S. Holovach, V. Shatnia, Dr. A. Horbenko, Dr. O. Viniichuk, Prof. Dr. O. O. Grygorenko
Enamine Ltd., Winston Churchill Street 78, 02094, Kyiv, Ukraine
Web page: www.enamine.net

[b] Dr. K. P. Melnykov, Dr. O. S. Liashuk, Dr. O. Viniichuk, Prof. Dr. O. O. Grygorenko
Taras Shevchenko National University of Kyiv, Volodymyrska Street 60, 01601, Kyiv, Ukraine
E-mail: gregor@univ.kiev.ua
Web page: www.grygorenko.com

[c] Dr. S. Holovach
Institute of Organic Chemistry, National Academy of Sciences of Ukraine
Akademik Kukhar Street 5, Kyiv 02660, Ukraine

[d] V. Shatnia
National Technical University of Ukraine "Igor Sikorsky Kyiv Polytechnic Institute"
Beresteiskyi Avenue 37, Kyiv 03056, Ukraine

[e] Dr. A. Horbenko
V. I. Vernadsky Institute of General and Inorganic Chemistry, National Academy of Sciences of Ukraine
Akademik Palladin Street 32/34, Kyiv 03142, Ukraine

[f] D. Lesyk, V. Melnyk, D. Skrypnik, A. Beshtynarska, Dr. P. Borysko
Bienta/Enamine Ltd., Winston Churchill Street 78, 02094, Kyiv, Ukraine
Web page: www.bienta.net

Supporting information for this article is given via a link at the end of the document.

Abstract: A comprehensive study on the physicochemical properties of *gem*-fluorinated *O*-heterocyclic substituents is reported. Systematic additive effects of introducing *O*- and *gem*-CF_2 group introduction on acidic properties (pK_a) of the corresponding carboxylic acids / protonated primary amines were demonstrated. The impact of the O/CF_2 moieties on lipophilicity (Log*P*) was found to be complex; significant mutual influence of the corresponding polar moieties governed the compound's overall properties in this case. Biological evaluation of MAPK kinase inhibitors incorporating the title substituents demonstrated their utility as promising fragments for bioisosteric replacements in drug discovery campaigns.

Introduction

Cyclic systems are fundamental structural motifs prevalent in a vast array of pharmacologically active compounds.[1–3] By introducing the fully saturated cyclic fragments into the potential drug molecule, one could modulate the most important drug substance properties, including but not limited to alterations in molecular conformations, physicochemical characteristics, or metabolic stability.[4]

Saturated cyclic ethers represent a broad subclass of cyclic motifs that have garnered significant attention in modern drug discovery. Widely distributed among natural products,[5,6] *O*-heterocyclic compounds rapidly became one of the key components in numerous synthetic drugs (Figure 1, *A*).[5,7,8] Often being used as mimetics of naturally occurring fragments,[9] saturated oxygen heterocycles can improve the compound's hydrophilicity,[10] enhance its metabolic stability[11] or biological activity[12] when introduced into a molecule of interest.

The incorporation of fluorine atoms into cyclic compounds has recently emerged as a cornerstone strategy in medicinal chemistry for enhancing therapeutic efficacy.[13,14] Fluorination offers unique opportunities to modulate the physicochemical characteristics of (hetero)cyclic structures, thereby influencing their interactions with biological targets and pharmacokinetic behavior.[15] Along with notable influence on the acidity/basicity of ionizable groups[16–18] and lipophilicity of the whole molecule,[19] fluorination-based strategy could offer the possibility of radio-labeling active therapeutics for *in vivo* probing purposes[20] or eliminate the unstable functionalities *via* the bioisosteric replacement approach.[14,21–23]

Despite the growing number of examples of late-stage fluorination of complex organic structures,[24,25] fluorinated

building blocks[15,26,27] are still keeping their dominating role as a source of fluorine in complex fluorinated compounds.[28–30] Extensive application of the fluorinated fragments raised a question of their rational exploitation, thus encouraging a series of systematic studies in this area. The groups of Müller,[31,32] O'Hagan,[33–43] Linclau,[44–47] and others revealed a number of valuable insights on the effects of the fluorination pattern on the compound's physicochemical properties (Figure 2). In our group, we continuously extended this knowledge by investigating fluorinated alicyclic,[15,18,26,48] aza-heterocyclic,[19,49] and (recently) oxetane-derived (3,3-*di*Fox)[50] building blocks.

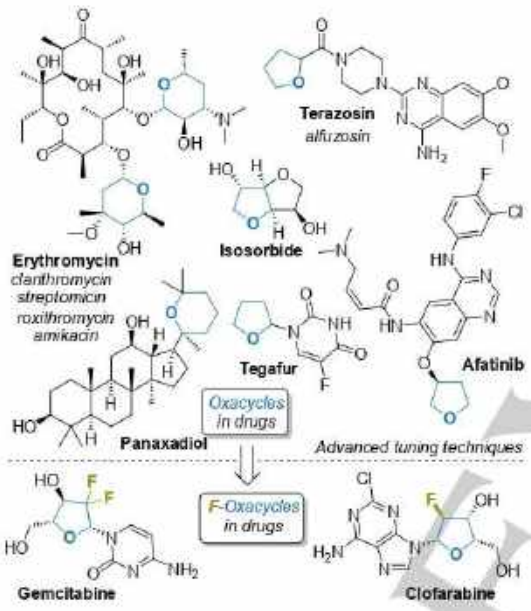


Figure 1. (A) Biologically active compounds with five- and six-membered saturated oxygen heterocycles. (B) Drugs with fluorinated saturated oxygen heterocycles.

As a part of this ongoing project, in this work, we performed a comprehensive characterization of *gem*-difluorinated five- and six-membered *O*-heterocycles. We studied the physicochemical parameters of their model derivatives (i.e., pK_a and Log*P*) with a focus on the *gem*-difluorination and *O*-substitution effects. Furthermore, we have performed the synthesis and biological evaluation of fluorinated analogs of p38α mitogen-activated protein kinase (MAPK) inhibitor R-1487[51] to illustrate the utility of the title fluorinated building blocks for the pharmacokinetic properties modulation.

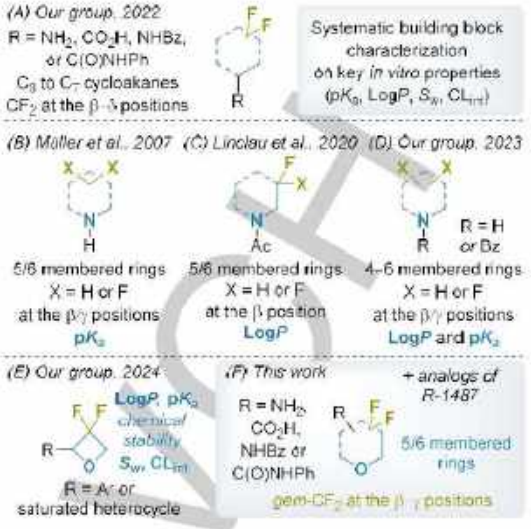


Figure 2. Series of comprehensively characterized *gem*-difluorinated saturated building blocks: (A) carbocyclic; (B–D) *N*-heterocyclic; (E) oxetane-derived; (F) *O*-heterocyclic compounds studied in this work.

Results and Discussion

We started our study by collecting commercially available fluorinated *O*-heterocyclic carboxylic acids **1**[2–4,β–δ] and **2**[2,γ], as well as primary amines **3**[3,β–γ] and **4**[3,β] (Figure 3). To this set, non-fluorinated *O*-heterocyclic compounds **1–4**[2–4,0], *gem*-difluorinated cyclohexane and cyclopentanes **1–4**[β–δ,0], as well as parent cycloalkane derivatives **1–4**[0,0] were added (the corresponding data for the alicyclic compounds was retrieved from our previous work[26]). The following compound numbering system was used: **n**[x,y], where **n** – general chemotype, x = 2–4 – the oxygen atom position relative to the functional group (x = 0 – no oxygen); y = β–δ – the CF_2 fragment position relatively to the functional group (y = 0 – no fluorine).

Physicochemical studies. The pK_a values for carboxylic acids **1**, **2** and protonated amines **3**, **4** were measured by standard acid-base titration[26] (Figure 3). As anticipated, the introduction of the oxygen atom into the ring led to a significant decrease in the pK_a value that correlated with its inductive effect (i.e., the through-bond distance to the functional group). In particular, the most significant decrease was observed for the **1**[1,0]/**1**[2,0] and **2**[0,0]/**2**[2,0] carboxylic acid pairs. For amines, this effect was even more pronounced, with ΔpK_a = 1.7–1.8 units for **3**[1,0]/**3**[3,0] and **4**[0,0]/**4**[3,0] pairs. *gem*-Difluorination of both alicyclic and *O*-heterocyclic carboxylic acids and amines also led to an expected pK_a decrease, with its absolute value following the trend: $\beta > \gamma > \delta$ position. Again, the acidity of protonated amines was more susceptible to the CF_2 group effects, with the largest ΔpK_a of 3.1 units observed for the **3**[0,0]/**3**[0,β] and **4**[3,0]/**4**[3,β] pairs.

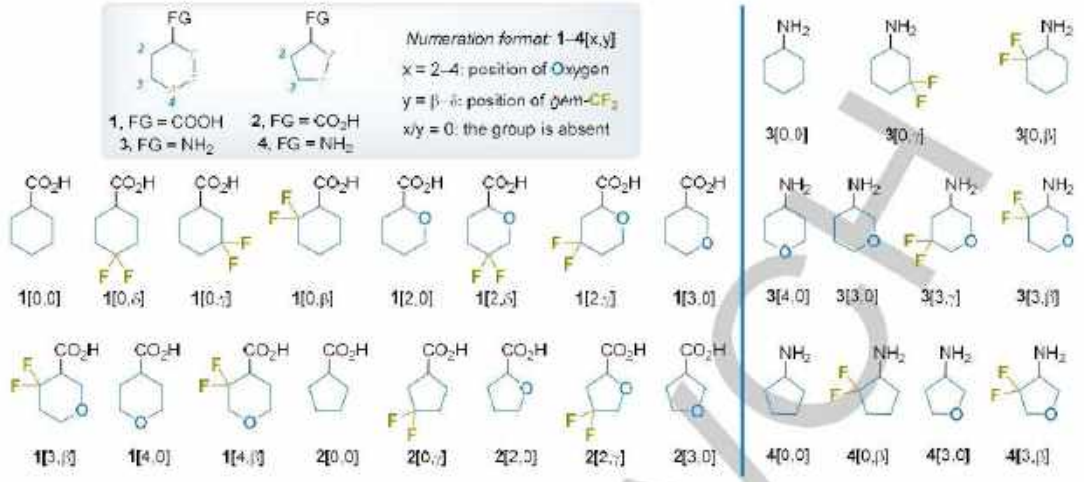


Figure 3. Building blocks **1–4** discussed in this work.

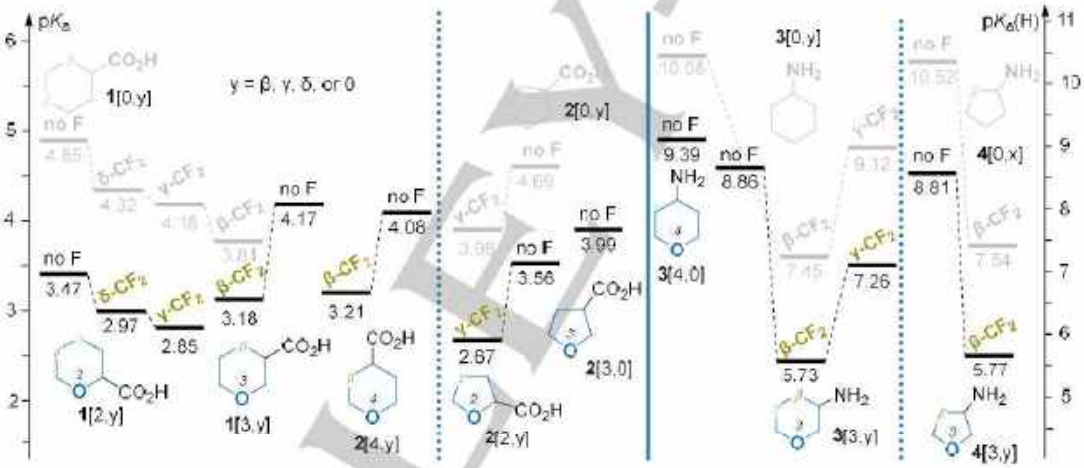


Figure 4. Acidity/basicity of compounds **1–4** studied in this work (21 °C).

WILEY-VCH

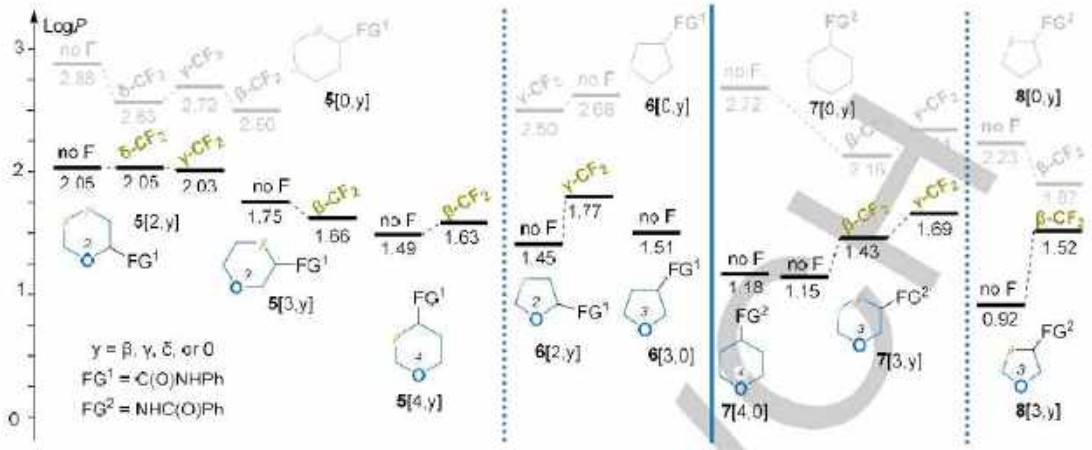


Figure 5. Lipophilicity of model amides **5**–**8** studied in this work (21 °C).

The Log*P* values were measured for anilides **5**, **6** and benzamides **7**, **8** (prepared by reaction of carboxylic acids **1**, **2** with aniline in the presence of EDC, DMAP, and Et_3N, or amines **3**, **4** with benzoyl chloride in the presence of Et_3N) using the classical shake-flask method combined with HPLC quantitative analysis[50] (Figure 4). It was found that introducing the oxygen atom resulted in lowered lipophilicity (by 0.83–1.57 Δ Log*P* units), with the largest difference (1.57) for the **7**[3,0]/**7**[0,0] pair. Notably, the effect of *gem*-difluorination of alicyclic and *O*-heterocyclic compounds on their lipophilicity was different. In particular, *gem*-difluorination of cycloalkane derivatives **5**–**8**[0,0] typically resulted in a lipophilicity decrease (by 0.16–0.56 Log*P* units). The highest Δ Log*P* values were observed for the β,β-difluorinated isomers (up to 0.56 for the **7**[0,0]/**7**[0,β] pair). For heterocyclic derivatives **5**–**8**[2–4,0], *gem*-difluorination either virtually did not change or increased lipophilicity (except anilide pair 5[3,0]/**5**[3,β] with Δ Log*P* = –0.09). The highest Log*P* increase was identified for benzamide pairs **7**[3,0]/**7**[3,γ] (0.54) and **8**[3,0]/**8**[3,β] (0.60).To gain a deeper insight into the nature of the O/CF_2 effects on the compound's lipophilicity in the studied series, we calculated average ΔpK_a and Δ Log*P* values for the corresponding amide pairs (i.e., with/without O or CF_2 group) for each position of the five- and six-membered rings (2, 3, or 4 for O, and β, γ, or δ for CF_2). For example, to evaluate the effect of introducing an oxygen atom at position 2 of the six-membered ring on the COOH group acidity, pK_a values of all available tetrahydropyran-3-carboxylic acids (**1**[2,0], **1**[2,γ], and **1**[2,δ]) were compared to those of cyclohexane counterparts (**1**[0,0], **1**[0,γ], and **1**[0,δ]), and average ΔpK_a was determined within this subset. The resulting ΔpK_a and Δ Log*P* increments are summarized in Figure 6, *A*.

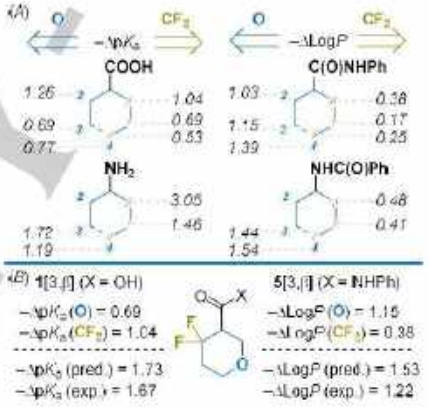


Figure 6. (*A*) Average ΔpK_a and Δ Log*P* increments of the O/CF_2 moieties for each position of the five- and six-membered rings. (*B*) Prediction of ΔpK_a for compound **1**[3,β] and Δ Log*P* for compound **5**[3,β] (relative to parent non-fluorinated cycloalkane derivatives **1**[0,0] and **5**[0,0]) using the above increments and comparison of the obtained values with experimental data. This deliberately selected example is given for illustration purposes; see Table 1 for the full dataset.

Furthermore, we have evaluated if the above increments are additive by prediction of ΔpK_a and Δ Log*P* of *gem*-difluorinated *O*-heterocyclic compounds **1**–**4**[2–4,β–δ] relatively to parent non-fluorinated cycloalkane derivatives **1**–**4**[0,0] (Figure 6, *B*; Table 1). For the ΔpK_a values, the additivity was confirmed: the corresponding prediction error ($\Delta\Delta pK_a$ = –0.08±0.56) was within the 3σ confidence interval, which correlated with the literature data.[52] For the Δ Log*P* values, the predictions had much larger errors (ΔΔLog*P*=0.56±0.79) and were systematically higher than the corresponding experimental values. In other words, the lipophilicity decrease from both O and CF_2 moieties acting simultaneously was lower than anticipated from the separate increments of these fragments.

Notably, higher prediction errors were observed for the amine and benzamide series.

Table 1. Predicted and experimental values of ΔpK_a and $\Delta LogP$ values of **1**–**4**[2–4,β–δ] relatively to **1**–**4**[0,0].

№	$-\Delta pK_a$			№	$-\Delta LogP$		
	Pred.[a]	Exp.	Error		Pred.[a]	Exp	Error
1[2,δ]	1.76	1.88	0.12	**5**[2,δ]	1.28	0.83	–0.45
1[2,γ]	1.96	2.00	0.04	**5**[2,γ]	1.20	0.85	–0.35
1[3,δ]	1.79	1.67	–0.12	**5**[3,δ]	1.53	1.22	–0.31
1[4,δ]	1.87	1.64	–0.23	**5**[4,δ]	1.77	1.25	–0.52
2[2,γ]	1.96	2.02	0.06	**6**[2,γ]	1.20	0.91	–0.29
3[3,δ]	4.52	4.85	0.33	**7**[3,δ]	1.92	1.29	–0.63
3[3,γ]	3.12	3.32	0.20	**7**[3,γ]	1.85	1.03	–0.82
4[3,δ]	4.52	4.75	0.23	**8**[3,δ]	1.92	0.71	–1.21

[a] Predicted values are obtained by adding the corresponding O/CF_2 group increments shown in Figure 6, *A*. See Figure 6, *B* for a deliberately selected example of such calculation.

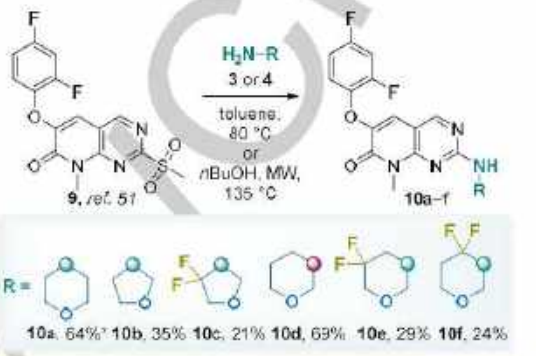
These results show that the mutual influence of both oxygen and *gem*-CF_2 fragments should be taken into account when discussing their effects on the compound's lipophilicity. Interestingly, the prediction error ($\Delta\Delta LogP$) of the simple additive model was higher for the compounds with higher ΔpK_a values (see the Supporting Information, Figure S3). Since ΔpK_a correlates with electronic distribution changes in the molecules of the corresponding building blocks (and hence in part – of their model derivatives), this result shows that the properties of the amide functional group attached to the saturated ring may also be important for the compound's lipophilicity. It should be noted that we have already observed similar trends for the *gem*-difluorinated cycloalkane series.[26]

Biological evaluation. To evaluate the utility of the discussed building blocks for bioisosteric replacements, we prepared five analogs of R-1487 (**10a**) – a known highly potent and selective p38α mitogen-activated protein kinase (MAPK) inhibitor developed by Roche scientists. R-1487 (**10a**) and its analogs **10b–f** were prepared by S_NAr reaction of known key intermediate **9** (synthesized in five steps from a commercially available pyrimidine derivative) and amines **3** or **4**.

As in the case of model amide derivatives **7** and **8**, replacing the tetrahydropyran moiety in the molecule of **10a** with gem-difluorinated analogs resulted in slightly increased lipophilicity. Notably, the changes in $LogD_{7.4}$ values of compounds **10a–f** correlated with Log*P* trends observed for benzamides **7** and **8** (with a single exception of compounds **10d**/**3**[3,0]). This result confirms the suitability of the model systems used by us in this work for the lipophilicity studies.

Kinetic aqueous solubility of compounds **10a–f** correlated with the $LogD_{7.4}$ data; more lipophilic *gem*-difluorinated representatives were by 30–100 μM less soluble in PBS as compared to non-fluorinated counterparts. Metabolic stability (measured as intrinsic clearance, CL_{int}) demonstrated 1.5-fold improvement for some representatives (**14** and **15** μL/min/mg for **10e** and **10f** vs 23 μL/min/mg for **10a**). Importantly, the potency of all the fluorinated derivatives against human recombinant full-length p38α MAPK remained in the nanomolar range, albeit a 5- to 8-fold decrease was observed. These results show that *gem*-difluorinated *O*-heterocyclic substituents discussed in this work can indeed be used for isosteric replacements in medicinal chemistry.

Table 2. Synthesis, physicochemical and biological properties of compounds **10a–f**



*R-1487, a highly potent p38α MAPK inhibitor

Compound	$LogD_{7.4}$	S_w, μM	IC_{50}, nM	CL_{int}, μl/min/mg
10a	2.7	175	1.6	23
10b	2.5	184	13.2	48
10c	2.9	101	11.1	30
10d	2.9	177	7.2	42
10e	3.2	73	12.9	14
10f	2.9	142	9.1	15

Conclusions

Fluorination of cyclic compounds represents a potent strategy in drug discovery, offering fine control over physicochemical properties and pharmacological profiles. In this work, we demonstrated this by a comprehensive study of *gem*-difluorinated saturated *O*-heterocyclic building blocks (carboxylic acids and primary amines) along with their non-fluorinated and carbocyclic counterparts. Increments of introducing an oxygen atom or a *gem*-CF_2 group to the compound's physicochemical properties were established for each position of the five- and six-membered saturated ring. It was found that whereas for acidity (pK_a), these increments demonstrated additivity and correlated with the substituent's inductive effects, for lipophilicity (Log*P*), a more complex behavior was characteristic. In particular, while *gem*-fluorination of cyclohexane- and cyclopentane-derived

amides typically led to a decrease in their lipophilicity, *gem*-difluorinated *O*-heterocyclic derivatives were typically more lipophilic than their non-fluorinated counterparts. Finally, we demonstrated the potential of *gem*-difluorinated *O*-heterocyclic substituents for bioisosteric replacements by the synthesis and evaluation of was demonstrated by the synthesis of p38α MAPK inhibitors – analogs of Roche's clinical candidate R-1487. The synthesized fluorinated mimetics retained nanomolar potency against their biological target and had somewhat higher lipophilicity and lower aqueous solubility but improved metabolic stability. We believe that these results will help the fluorinated five- and six-membered *O*-heterocyclic fragments to find their place in the medicinal chemists' toolbox and promote their wider applications in early drug discovery.

Experimental Section

The solvents were purified according to the standard procedures.[53] Compound **9** was synthesized according to the literature method.[51,54] Building blocks **1–4** were obtained from Enamine stock; all other starting materials were available commercially. Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. Reverse-phase HPLC purifications were performed using XBridge C18 (100 × 19mm, 5 μm) or Chromatorex 18 SMB100-5T (100 × 19mm, 5 μm) columns with H_2O/MeOH or H_2O/CH_3CN gradient elution. ^1H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^1H NMR, 126 MHz for ^{13}C NMR, and 470 MHz for ^{19}F NMR) and Varian Unity Plus 400 spectrometer (at 400 MHz for ^1H NMR, 101 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR). NMR chemical shifts are reported in pp (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^1H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^1H and ^{13}C in DMSO-d_6. Coupling constants (*J*) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and Agilent 5890 Series II 5972 MS instrument (electron impact ionization (EI)). High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer.

General procedure for the synthesis of anilides 5 and 6. To a solution of corresponding acid (1.00 mmol) and aniline (93 mg, 1.00 mmol) in CH_3CN (5 mL), 1-methylimidazole (246 mg, 3.00 mmol) and TCFH (308 mg, 1.10 mmol) were subsequently added. The resulting mixture was stirred at room temperature overnight and concentrated under reduced pressure to dryness. The residue was dissolved in EtOAc (15 mL) and washed with saturated aq $NaHCO_3$ (3 × 10 mL), 10% aq citric acid (3 × 10 mL), brine (3 × 10 mL), dried over Na_2SO_4, and evaporated under reduced pressure to give pure anilide.

General procedure for the synthesis of benzamides 7 and 8. To a solution of corresponding amine (1.00 mmol) and benzoic acid (122 mg, 1.00 mmol) in CH_3CN (5 mL), 1-methylimidazole (246 mg, 3.00 mmol) and TCFH (308 mg, 1.10 mmol) were subsequently added. The resulting mixture was stirred at room temperature overnight and concentrated under reduced pressure to dryness The residue was dissolved in EtOAc (15 mL) and washed with saturated aq $NaHCO_3$ (3 × 10 mL), 10% aq citric acid (3 × 10 mL), brine (3 × 10 mL), dried over Na_2SO_4, and evaporated under reduced pressure to give pure amide.

General procedures for the synthesis of R-1487 and its analogs (10a–h).

Compounds 10a,b,d. To a stirred solution of compound **9** (367 mg, 1.00 mmol) in toluene (10 mL), amine (1.50 mmol) and Na_2CO_3 (228 mg, 2.15 mmol) were subsequently added. The resulting mixture was heated to 80 °C in an oil bath, stirred at the same temperature overnight, and concentrated under reduced pressure to dryness. The residue was dissolved in EtOAc (15 mL) and washed with saturated aq $NaHCO_3$ (3 × 10 mL), 10% aq citric acid (3 × 10 mL), brine (3 × 10 mL), dried over Na_2SO_4, and evaporated under reduced pressure. Crude material was purified with reverse-phase HPLC to give pure product **10**.

Compounds 10c,e,f. To a stirred solution of compound **9** (367 mg, 1.00 mmol) in *n*-BuOH (10 mL), amine (2.00 mmol) and 4 M HCl in Dioxane (50 μL, 0.20 mmol) were subsequently added. The resulting mixture was stirred under microwave irradiation (heating to 130 °C) for 0.5 h and concentrated under reduced pressure to dryness. The residue was dissolved in EtOAc (15 mL) and washed with saturated aq $NaHCO_3$ (3 × 10 mL), 10% aq citric acid (3 × 10 mL), brine (3 × 10 mL), dried over Na_2SO_4, and evaporated under reduced pressure. Crude material was purified with reverse-phase HPLC to give pure product **10.**

Supporting Information

The authors have cited additional works within the Supporting Information.[51,55]

Acknowledgements

The work was funded by Enamine Ltd. The authors thank Olga Kovalenko and Margaryta Bolgova for the pK_a titrations, Vladyslav Stadnichenko, Anna Pashchenko, Nadiia Diyuk, and Yuliia Holota for their help with biological experiments, Prof. Andrii A. Tolmachov for his encouragement and support, and all the brave people of Ukraine for making finalizing this publication possible.

Conflict of Interests

The authors are employees, trainees, or consulting scientists of Enamine Ltd. that offers the building blocks described in this paper in the company's catalog.

Keywords: Building blocks • Fluorine • Oxygen heterocycles • Physicochemical parameters • Lipophilicity

[1] R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* **2014**, *57*, 5845–5859.

[2] J. Shearer, J. L. Castro, A. D. G. Lawson, M. MacCoss, R. D. Taylor, *J. Med. Chem.* **2022**, *65*, 8699–8712.

[3] C. M. Marson, in *Heterocyclic Chemistry in the 21st Century* (Eds.: E. Scriven, C. Ramsden), Academic Press, **2017**, pp. 13–33.

[4] J. Tsien, C. Hu, R. R. Merchant, T. Qin, *Nat. Rev. Chem.* **2024**, *8*, 605–627.

[5] Q. Lu, D. S. Harmalkar, Y. Choi, K. Lee, *Molecules* **2019**, *24*, DOI 10.3390/molecules24203778.

[6] J. Cossy, A. Guénnot, in *Heterocyclic Chemistry in the 21st Century* (Eds.: E.F. V Scriven, C.A.B.T.-A. in H.C. Ramsden), Academic Press, **2016**, pp. 107–142.

[7] M. D. Delost, D. T. Smith, B. J. Anderson, J. T. Njardarson, *J. Med. Chem.* **2018**, *61*, 10996–11020.

[8] G. Wuitschik, E. M. Carreira, B. Wagner, H. Fischer, I. Parrilla, F. Schuler, M. Rogers-Evans, K. Müller, *J. Med. Chem.* **2010**, *53*, 3227–3246.

[9] A. M. V Delos Reyes, C. S. Nieves Escobar, A. Muñoz, M. I. Huffman, D. S. Tan, *Chem. Sci.* **2023**, *14*, 10624–10631.

[10] M. A. J. Dubois, R. A. Croft, Y. Ding, C. Choi, D. R. Owen, J. A. Bull, J. J. Mousseau, *RSC Med. Chem.* **2021**, *12*, 2045–2052.

[11] A. Denisenko, P. Garbuz, N. M. Voloshchuk, Y. Holota, G. Al-Maali, P. Borysko, P. K. Mykhailiuk, *Nat. Chem.* **2023**, *15*, 1155–1163.

[12] V. V Levterov, Y. Panasiuk, K. Sahun, O. Stashkevych, V. Badlo, O. Shablykin, I. Sadkova, L. Bortnichuk, O. Klymenko-Ulianov, Y. Holota, L. Lachmann, P. Borysko, K. Horbatok, I. Bodenchuk, Y. Bas, D. Dudenko, P. K. Mykhailiuk, *Nat. Commun.* **2023**, *14*, 5608.

[13] E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315–8359.

[14] N. A. Meanwell, *J. Med. Chem.* **2018**, *61*, 5822–5880.

[15] O. O. Grygorenko, K. P. Melnykov, S. Holovach, O. Demchuk, *ChemMedChem* **2022**, *17*, e202200365.

[16] D. Marych, V. Bilenko, Y. V Ilchuk, S. Kinakh, V. Soloviov, A. Yatsymyrskiy, O. Liashuk, S. Shishkina, I. V Komarov, O. O. Grygorenko, *J. Fluor. Chem.* **2024**, *277*, 110307.

[17] O. Pidvyshennyi, K. P. Melnykov, O. Liashuk, D. Lesyk, Y. Holota, P. Borysko, O. O. Grygorenko, *J. Fluor. Chem.* **2024**, *278*, 110316.

[18] B. Moroz, K. P. Melnykov, S. Holovach, A. A. Filatov, O. Raievskyi, M. Platonov, O. Liashuk, D. M. Volochnyuk, O. O. Grygorenko, *J. Fluor. Chem.* **2023**, *272*, 110215.

[19] K. P. Melnykov, K. Nazar, O. Smyrnov, A. Skreminskyi, S. Pavlenko, O. Klymenko-Ulianov, S. Shishkina, D. M. Volochnyuk, O. O. Grygorenko, *Chem. Eur. J.* **2023**, *29*, e202301383.

[20] E. Henary, S. Casa, T. L. Dost, J. C. Sloop, M. Henary, *Pharmaceuticals* **2024**, *17*, DOI 10.3390/ph17030281.

[21] N. A. Meanwell, *J. Agric. Food Chem.* **2023**, *71*, 18087–18122.

[22] N. A. Meanwell, in *Burger's Medicinal Chemistry and Drug Discovery*, **2021**, pp. 1–81.

[23] S. Kumari, A. V. Carmona, A. K. Tiwari, P. C. Trippier, *J. Med. Chem.* **2020**, *63*, 12290–12358.

[24] C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2015**, *54*, 3216–3221.

[25] M. G. Campbell, T. Ritter, *Org. Process Res. Dev.* **2014**, *18*, 474–480.

[26] S. Holovach, K. P. Melnykov, A. Skreminskiy, M. Herasymchuk, O. Tavtui, D. Aloshyn, P. Borysko, A. B. Rozhenko, S. V Ryabukhin, D. M. Volochnyuk, O. O. Grygorenko, *Chem. Eur. J.* **2022**, *28*, e202200331.

[27] S. Holovach, I. Poroshyn, K. P. Melnykov, O. S. Liashuk, O. O. Pariiska, S. V Kolotilov, A. B. Rozhenko, D. M. Volochnyuk, O. O. Grygorenko, *ACS Org. Inorg. Au* **2024**, DOI 10.1021/acsorginorgau.4c00028.

[28] R. Britton, V. Gouverneur, J.-H. Lin, M. Meanwell, C. Ni, G. Pupo, J.-C. Xiao, J. Hu, *Nat. Rev. Methods Prim.* **2021**, *1*, 47.

[29] Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata, *iScience* **2020**, *23*, 101467.

[30] S. Caron, *Org. Process Res. Dev.* **2020**, *24*, 470–480.

[31] M. Morgenthaler, E. Schweizer, A. Hoffmann-Röder, F. Benini, R. E. Martin, G. Jaeschke, B. Wagner, H. Fischer, S. Bendels, D. Zimmerli, J. Schneider, F. Diederich, M. Kansy, K. Müller, *ChemMedChem* **2007**, *2*, 1100–1115.

[32] K. Müller, *Chim. Int. J. Chem.* **2014**, *68*, 356–362.

[33] Z. Fang, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan, *Chem. Commun.* **2019**, *55*, 10539–10542.

[34] C. J. Thomson, Q. Zhang, N. Al-Maharik, M. Bühl, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan, *Chem. Commun.* **2018**, *54*, 8415–8418.

[35] T. J. Poskin, B. A. Piscelli, K. Yoshida, D. B. Cordes, A. M. Z. Slawin, R. A. Cormanich, S. Yamada, D. O'Hagan, *Chem. Commun.* **2022**, *58*, 7968–7971.

[36] Z. Fang, D. B. Cordes, A. M. Z. Slawin, D. O'hagan, *Chem. Commun.* **2019**, *55*, 10539–10542.

[37] D. O'Hagan, *Chem. Eur. J.* **2020**, *26*, 7981–7997.

[38] J. L. Clark, R. M. Neyyappadath, C. Yu, A. M. Z. Slawin, D. B. Cordes, D. O'Hagan, *Chem. Eur. J.* **2021**, *27*, 16000–16005.

[39] A. Rodil, S. Bosisio, M. S. Ayoup, L. Quinn, D. B. Cordes, A. M. Z. Slawin, C. D. Murphy, J. Michel, D. O'Hagan, *Chem. Sci.* **2018**, *9*, 3023–3028.

[40] J. L. Clark, R. M. Neyyappadath, C. Yu, A. M. Z. Slawin, D. B. Cordes, D. O'Hagan, *Chem. Eur. J.* **2021**, *27*, 16000–16005.

[41] Z. Fang, N. Al-Maharik, A. M. Z. Slawin, M. Bühl, D. O'Hagan, *Chem. Commun.* **2016**, *52*, 5116–5119.

[42] J. L. Clark, A. Taylor, A. Geddis, R. M. Neyyappadath, B. A. Piscelli, C. Yu, D. B. Cordes, A. M. Z. Slawin, R. A. Cormanich, S. Guldin, D. O'Hagan, *Chem. Sci.* **2021**, *12*, 9712–9719.

[43] N. S. Keddie, A. M. Z. Slawin, T. Lebl, D. Philp, D. O'Hagan, *Nat. Chem.* **2015**, *7*, 483–488.

[44] B. Jeffries, Z. Wang, R. I. Troup, A. Goupille, J. Y. Le Questel, C. Fallan, J. S. Scott, E. Chiarparin, J. Graton, B. Linclau, *Beilstein J. Org. Chem.* **2020**, *16*, 2141–2150.

[45] B. Linclau, Z. Wang, G. Compain, V. Paumelle, C. Q. Fontenelle, N. Wells, A. Weymouth-Wilson, *Angew. Chem. Int. Ed.* **2016**, *55*, 674–678.

[46] B. Jeffries, Z. Wang, H. R. Felstead, J. Y. Le Questel, J. S. Scott, E. Chiarparin, J. Graton, B. Linclau, *J. Med. Chem.* **2020**, *63*, 1002–1031.

[47] J. Graton, Z. Wang, A.-M. Brossard, D. Gonçalves Monteiro, J.-Y. Le Questel, B. Linclau, *Angew. Chem. Int. Ed.* **2012**, *51*, 8176–8180.

[48] K. P. Melnykov, O. V Voloshyna, B. V Vashchenko, O. P. Demchuk, O. V Hryshchuk, O. O. Grygorenko, *Eur. J. Org. Chem.* **2022**, e202200863.

[49] S. Kinakh, K. P. K. P. Melnykov, V. Bilenko, S. Trofymchuk, O. S. O. S. Liashuk, O. O. O. O. Grygorenko, *Eur. J. Org. Chem.* **2024**, *27*,

WILEY-VCH

e202300937.

[50] O. S. Liashuk, A. Fedinchyk, K. P. Melnykov, M. Herasymchuk, D. Alieksieieva, D. Lesyk, Y. P. Bas, T. Y. Keda, A. V Yatsymyrskiy, Y. Holota, P. Borysko, V. S. Yarmolchuk, O. O. Grygorenko, *Chem. Eur. J.* **2024**, *n/a*, e202403277.

[51] D. M. Goldstein, M. Soth, T. Gabriel, N. Dewdney, A. Kuglstatter, H. Arzeno, J. Chen, W. Bingenheimer, S. A. Dalrymple, J. Dunn, R. Farrell, S. Frauchiger, J. La Fargue, M. Ghate, B. Graves, R. J. Hill, F. Li, R. Litman, B. Loe, J. McIntosh, D. McWeeney, E. Papp, J. Park, H. F. Reese, R. T. Roberts, D. Rotstein, B. San Pablo, K. Sarma, M. Stahl, M.-L. Sung, R. T. Suttman, E. B. Sjogren, Y. Tan, A. Trejo, M. Welch, P. Weller, B. R. Wong, H. Zecic, *J. Med. Chem.* **2011**, *54*, 2255–2265.

[52] Q. A. Huchet, B. Kuhn, B. Wagner, N. A. Kratochwil, H. Fischer, M. Kansy, D. Zimmerli, E. M. Carreira, K. Müller, *J. Med. Chem.* **2015**, *58*, 9041–9060.

[53] W. L. F. Armarego, C. Chai, *Purification of Laboratory Chemicals*, Elsevier: Oxford, **2003**.

[54] L. Simon-Szabó, M. Kokas, Z. Greff, S. Boros, P. Bánhegyi, L. Zsákai, C. Szántai-Kis, T. Vantus, J. Mandl, G. Bánhegyi, I. Vályi-Nagy, L. Őrfi, A. Ullrich, M. Csala, G. Kéri, *Bioorg. Med. Chem. Lett.* **2016**, *26*, 424–428.

[55] M. M. Madkour, H. S. Anbar, M. I. El-Gamal, *Eur. J. Med. Chem.* **2021**, *213*, 113216.

WILEY-VCH

ISSN 1814-9758. Ukr. Bioorg. Acta, 202X, Vol. XX, N X
UDC 547.51:547.7+546.16
DOI:

Ukrainica Bioorganica Acta
www.bioorganica.org.ua

UBA

RESEARCH ARTICLE

Multigram synthesis of β-fluorinated saturated heterocyclic methanamines

Volodymyr Semeno[1,2] and Kostiantyn P. Melnykov[1,2]*

[1] *Enamine Ltd. (www.enamine.net), Winston Churchill Street 78, Kyiv 02094, Ukraine*
[2] *Taras Shevchenko National University of Kyiv, Volodymyrska Street 60, Kyiv 01601, Ukraine*

Abstract: An efficient multigram synthesis of β-fluorinated saturated heterocyclic methanamines – promising building blocks for drug discovery–starting from the corresponding saturated heterocyclic ketones is described. The method includes Wittig olefination, bromofluorination, nucleophilic substitution with azide, and Staudinger reaction and works well for four- to seven-membered nitrogen- and oxygen-containing heterocyclic derivatives.

Keywords: organofluorine compounds; heterocycles; amines; building blocks.

Introduction

Over the recent years, saturated heterocyclic scaffolds have gained much attention in drug discovery due to three-dimensionality, improved aqueous solubility, and increased hydrophilicity of their derivatives [1–3]. On the other hand, fluorination can improve binding to the biological target, as well as pharmacokinetic and physicochemical properties of the compound, and it is, therefore, an important design approach in medicinal chemistry [4–8]. Fluorinated saturated heterocyclic building blocks are becoming increasingly popular in drug discovery projects [9,10]. In particular, derivatives of β-fluorinated saturated heterocyclic methanamines (general structure **1**) include potent and selective 5-hydroxytriptamine 1A (5-HT_{1A}) receptor agonists *Befiradol* and *F-15,599* [11], covalent Bruton tyrosine kinase (BTK) inhibitors [12], estrogen receptor (ER) antagonists [13], and retinoic acid receptor-related orphan receptor γ (RORγ) inverse agonists [14] (Figure 1).

Received: 00.00.202X
Revised: 00.00.202X
Accepted: 00.00.202X
Published online: 00.00.202X

* Corresponding author. Tel.: +380-44-239-3315;
e-mail: konstantyn.melnykov@gmail.com (K. P. Melnykov)
ORCID: 0009-0003-6522-681X

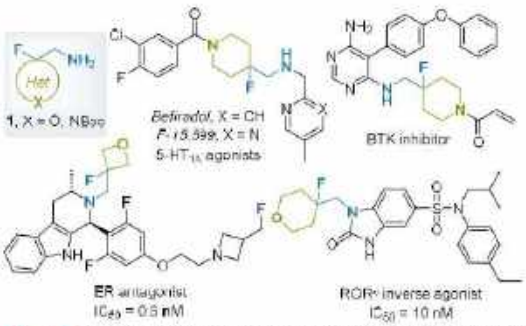


Figure 1. Biologically active derivatives of β-fluorinated saturated heterocyclic methanamines **1**

Some β-fluorinated saturated heterocyclic methanamine building blocks (e.g., compounds **1a** and **1f**) have been widely used in medicinal chemistry, which is confirmed by the number of patents referenced in *Reaxys*® database (Figure 2) [15]. Meanwhile, approaches to their synthesis are covered scarcely in the literature. Thus, De Kimpe and co-authors described preparation of compound **1a** and **1b** starting from exomethylene derivatives **2a** and **2b** via bromofluorination, S_N2 reaction with azide, and reduction reaction sequence (Scheme 1) [16]. Other methods relied on phthalimide alkylation [17] and [3+2] cycloaddition of α-fluoroacrylate [18].

© V. Semeno et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

ISSN 1814-9758. Ukr. Bioorg. Acta. 202X. Vol. XX. N.X
UDC 547.51:547.7+546.16
DOI

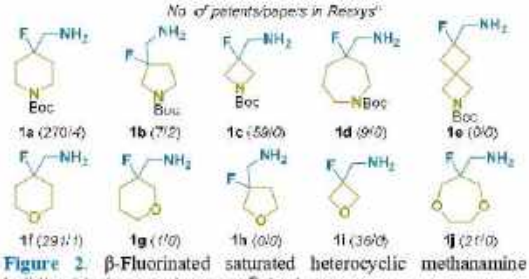
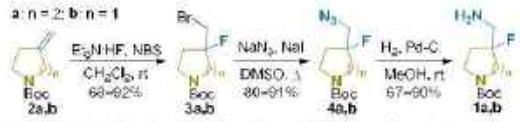


Figure 2. β-Fluorinated saturated heterocyclic methanamine building blocks **1a–k** in *Reaxys*® database

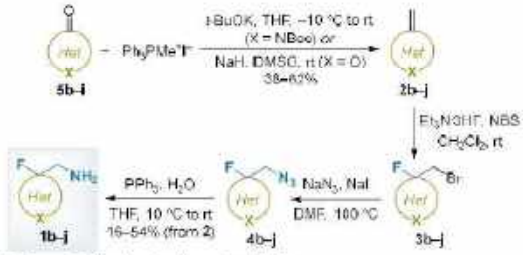


Scheme 1. Synthesis of amines **1a** and **1b** according to De Kimpe and co-authors

In this work, we describe application of a modified De Kimpe's approach for the synthesis of a series of fluorine-containing saturated heterocyclic building blocks **1b–j**. The title compounds have been prepared at multigram scale (up to 77 g in a single run).

Results and Discussion

Synthesis of the title compounds started with Wittig olefination of saturated heterocyclic ketones **5b–i**. For non-volatile *N*-Boc derivatives **5b–e**, the reaction was performed upon action of $Ph_3PCH_3I^-$–*t*-BuOK in THF according to the literature method [19,20] (Scheme 2). For volatile oxa-heterocyclic ketones **5f–i**, NaH was used as the base (to avoid formation of *tert*-butanol), and DMSO–as the high-boiling solvent; olefination products **2f–i** were distilled from the reaction mixture. Alkene **2j** is more commercially accessible than the corresponding ketone and was used directly.



Scheme 2. Synthesis of amines **1b–j**

Bromofluorination of alkenes **2b–j** was performed with $Et_3N{\cdot}3HF$–NBS in CH_2Cl_2 using the protocol reported previously by our group [19]. Notably, the reaction had limited regioselectivity with azeditine derivative **2c** (a detail that was not documented in the previous work). With tetrahydropyran derivative **2g**, the reaction was complicated by partial HF elimination. We used resulting crude products **3b** and **3g**, respectively (as well as all other products **3b–j**) in the next step without purification.

The nucleophilic substitution step was carried out in DMF at 100 °C in the presence of NaI to transform substrate **3b–j** into the corresponding iodide and hence facilitate the subsequent S_N2 reaction with NaN_3. Due to the potentially explosive nature of products **4b–j**, they were also used in the next step without purification.

For the final step of the synthesis–azide reduction, we initially tried the catalytic hydrogenation conditions reported by the previous authors for the synthesis of **1a,b** [16]. It was found that upon attempted scale-up, the conversion at 1 atm was very slow due to N_2 evolution (and hence H_2 partial pressure decrease). Even with periodic refilling the reaction system with H_2, the reaction was not complete after a week. Therefore, we turned our attention to the Staudinger reaction (PPh_3–H_2O) as the alternative method for the azide reduction. Although this approach had poorer atom economy, it worked well at multigram scale and allowed preparation of all target products **1b–j** in a reasonable time (overnight). Importantly, compounds **1b–j** could be purified by distillation and hence isolated as free bases or hydrochlorides in 21–54 % overall yield without the use of chromatographic purification (Table 2).

Table 1. Yields of alkenes **2b–j** and amines **1b–j** prepared according to Scheme 2.

#	Starting ketone	Alkene	Yield		Amine	Yield[a]	
			g	%		g	%
1	**5b**	**2b**	99	50	**1b**	63	54
2	**5c**	**2c**	72	49	**1c**	33	38
3	**5d**	**2d**	74	50	**1d**	34	25
4	**5e**	**2e**	55	58	**1e**	27	42
5	**5f**	**2f**	48	49	**1f**	31	48
6	**5g**	**2g**	61	62	**1g**	18	21
7	**5h**	**2h**	145	60	**1h**	77	38
8	**5i**	**2i**	37	38	**1i**	25	45
9	–	**2j**	–	–	**1j**	32	16

[a] Yield over three steps

Conclusions

An efficient multigram synthesis of β-fluorinated saturated heterocyclic methanamines is described. The proposed procotol is based on the literature method described for the simplest *N*-heterocyclic derivatives (i.e., Wittig olefination of the corresponding heterocyclic ketone, bromofluorination with $Et_3N{\cdot}3HF$–NBS, S_N2 reaction with NaN_3, and azide reduction) but included several important modifications required for the successful scale up. In particular, Wittig olefination of volatile oxygen-containing heterocyclic ketones was performed with NaH in DMSO to enable isolation of the corresponding alkenes by distillation. Furthermore, azide reduction was very efficient under the Staudinger reaction conditions (Ph_3P–H_2O) instead of

catalytic reduction. The optimized protocol was successfully applied for the synthesis of nine title saturated *N*- or *O*-containing 4- to 7-membered heterocyclic amines on up to 77 g scale. The obtained products are promising fluorinated sp^3-enriched building blocks for medicinal chemistry, and in our opinion, they have a great potential for drug discovery programs.

Experimental section

Alkene **2c** was prepared according to the literature method [19]. Alkenes **2b** [20], **2d** [21], and **2e** were synthesized in a similar manner; their spectral and physical data were in accordance with the literature. All other reagents were obtained from Enamine Ltd. or UkrOrgSyntez. Melting points were measured on MPA100 OptiMelt automated melting point system. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on an Agilent ProPulse 600 spectrometer (at 600 MHz for ^{1}H NMR, 151 MHz for ^{13}C NMR), Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR and 470 MHz for ^{19}F NMR) or Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6. Coupling constants (J) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and Agilent 5890 Series II 5972 MS instrument (electron impact ionization (EI)). High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer.

*General procedure for the preparation of alkenes **2f–i**.*

Sodium hydride (52 g, 1.30 mol, 60% in mineral oil) was added in portions to DMSO (500 mL) at rt, and the mixture was stirred at 70 °C for 2 h, then cooled to rt, and methyltriphenylphosphonium iodide (525 g, 1.30 mol) was added in portions. The mixture was stirred for 20 min, and a solution of ketone **2** (1 mol) in THF (100 mL) was added dropwise at rt upon stirring. The resulting mixture was stirred at rt for 14 h, then connected to a liquid nitrogen trap (–198 °C), in turn connected to vacuo. The crude product was distilled directly into the trap at 1 mmHg and then purified by fractional distillation.

*4-Methylenetetrahydro-2H-pyran (**2f**).*

Yield 31.0 g (48%); bp 39–41 °C (40 mmHg) (lit. [22] 104–107 °C). All spectral and physical data were in accordance to the literature [19].

*3-Methylenetetrahydro-2H-pyran (**2g**).*

Yield 18.1 g (21%); bp 40–41 °C (40 mmHg). All spectral and physical data were in accordance to the literature [23].

*3-Methylenetetrahydrofuran (**2h**).*

Yield 145.2 g (60%); bp = 91–93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (q, J = 2.2 Hz, 1H), 4.92 (q, J = 2.2 Hz, 1H), 4.23 (q, J = 2.0 Hz, 2H), 3.87 (td, J = 6.9, 1.5 Hz, 2H), 2.53 (ddd, J = 7.1, 5.0, 2.5 Hz, 2H). All other spectral data were in accordance to the literature.[24]

*3-Methyleneoxetane (**2i**).*

Yield 37.1 g (38%); bp 67–69 °C (lit. [25] 70 °C). All spectral and physical data were in accordance to the literature [20].

*General procedure for the preparation of amines **1b–j**.*

Alkene **2** (1 mol) was dissolved in CH_2Cl_2 (1.5 L), and $Et_3N{\cdot}3HF$ (483 g, 3 mol) was added at rt. The mixture was cooled to 5 °C, and NBS (196 g, 1.1 mol) was added in one portion at the same temperature. The resulting mixture was warmed to rt and stirred overnight. Then, the reaction mixture was washed with H_2O (1 L), 10% aq K_2CO_3 (1 L), and brine (1 L), dried over Na_2SO_4, and evaporated in vacuo below 45 °C. Crude bromide **3** (ca. 0.7 mol) thus obtained was dissolved in DMF (1 L), and sodium iodide (115 g, 0.77 mol) was added. The mixture was stirred at rt for 10 min, and sodium azide (136 g, 2.1 mol) was added in portions. The resulting mixture was stirred at 100 °C for 16–50 h (monitored by ^{1}H NMR spectroscopy), then cooled to 40 °C, poured into water (1 L), and extracted with ethyl acetate (3×1.5 L). The combined organic layers were washed with brine (5×0.5L), dried over Na_2SO_4, filtered, and concentrated in vacuo below 45 °C. Crude azide **4** (ca. 0.4 mol) was dissolved in THF (1 L), cooled to 10 °C, and PPh_3 (115 g, 0.44 mol) was added in portions at 10 °C. The mixture was stirred at rt for 2 h, and H_2O (216 mL, 12 mol) was added to the mixture in one portion. The resulting mixture was stirred at rt overnight, most of THF was evaporated in vacuo at 40 °C, and the residue was triturated with 20% aq $NaHSO_4$ (480 mL, ca. 0.8 mol). The aqueous solution was separated, washed with *t*-BuOMe (3×0.5 L), then K_2CO_3 (124 g, 0.9 mol) was added in portions. The resulting mixture extracted with CH_2Cl_2 (2×1.5 L). The combined organic layers were washed with brine (0.5 L), dried over Na_2SO_4, and evaporated in vacuo below 45 °C. Crude product **1** was purified by distillation in vacuo.

*tert-Butyl 3-(aminomethyl)-3-fluoropyrrolidine-1-carboxylate (**1b**).*

Yield 63.0 g (54%); bp 85–87 °C (1 mmHg). All spectral and physical data were in accordance to the literature [16].

*tert-Butyl 3-(aminomethyl)-3-fluoroazetidine-1-carboxylate (**1c**).*

Yield 33.4 g, 0.164 mol, 38%. Colourless oil, bp = 71–73 °C (1 mmHg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.04–3.90 (m, 2H), 3.86–3.74 (m, 2H), 2.81 (d, J = 21.1 Hz, 2H), 1.70 (s, 2H), 1.36 (s, 9H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.3, 91.8 (d, J = 207.0 Hz), 80.0, 57.9, 46.6 (d, J = 24.6 Hz), 28.3. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ -155.6. MS (APCI) m/z = 205 ([M+H]$^+$). HRMS (ESI/QTOF) m/z: [M + H]$^+$ Calcd for $C_9H_{18}FN_2O_2^+$: 205.1347; Found: 205.1347.

*tert-Butyl 4-(aminomethyl)-4-fluoroazepane-1-carboxylate (**1d**).*

Yield 34.2 g, 0.139 mol, 25%. Colourless oil, bp = 124–126 °C (1 mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80–3.45 (m, 2H), 3.34–3.10 (m, 2H), 2.96–2.60 (m, 2H), 2.16–1.86 (m, 3H), 1.79–1.53 (m, 2H), 1.44 (s, 12H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 155.1 and 155.0, 97.0 (d, J = 173.5 Hz), 78.9, 50.6 (d, J = 23.4 Hz) and 50.5 (d, J = 22.9 Hz), 46.1, 45.1, 39.5, 39.1, 36.4 (d, J = 23.1 Hz) and 36.0 (d, J = 23.1 Hz), 32.7 (d, J = 23.0 Hz) and 32.4 (d, J = 22.4 Hz), 28.0, 20.2 (d, J = 5.5 Hz) and 19.8 (d, J = 6.1 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -162.4, -163.1. MS (APCI) m/z = 247 ([M+H]$^+$). HRMS (ESI/QTOF) m/z: [M + H]$^+$ Calcd for $C_{12}H_{24}FN_2O_2^+$: 247.1816; Found: 247.1815.

*tert-Butyl 6-(aminomethyl)-6-fluoro-2-azaspiro[3.3]heptane-2-carboxylate (**1e**).*

Yield 27.3 g, 0.112 mol, 42%, bp = 110–112 °C (1 mmHg). Analytical sample was obtained by precipitation *via* trituration of the ethereal base solution with 1M HCl in Et_2O. Colourless powder, mp = 46–49 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (d, J = 41.5 Hz, 4H), 2.77 (d, J = 23.2 Hz, 2H), 2.52–2.29 (m, 4H), 1.45 (s, 2H), 1.41 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 155.5, 92.3 (d, J = 210.9 Hz), 79.00, 60.4 (br), 47.7 (d, J = 24.0 Hz), 41.9 (d, J = 22.4 Hz), 28.2 (d, J = 13.0 Hz), 27.8. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -145.7. MS (APCI) m/z = 245.2 ([M+H]$^+$). Anal. calcd. for $C_{12}H_{21}FN_2O_2$: C 59.00; H 8.66; N 11.47. Found: C 58.86; H 8.75; N 11.65.

*(4-Fluorotetrahydro-2H-pyran-4-yl)methanamine (**1f**).*

Yield 31.1 g, 0.183 mol, 48%, bp 38–40 °C (40 mmHg). Analytical sample was obtained by precipitation *via* trituration of the ethereal base solution with 1M HCl in Et_2O. Beige solid, mp = 138–140 °C. 1H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 3H), 3.75 (dt, J = 11.6, 3.9 Hz, 2H), 3.53 (ddd, J = 11.7, 8.7, 4.1 Hz, 2H), 3.17 – 2.96 (m, 2H), 1.92 – 1.51 (m, 4H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -162.4. MS (APCI) m/z = 134 ([M+H]$^+$). Anal. calcd. for $C_6H_{13}ClFNO$: C 42.49; H 7.73; N 8.26; Cl 20.90. Found: C 42.75; H 7.50; N 7.87; Cl 20.85.

*(3-Fluorotetrahydro-2H-pyran-3-yl)methanamine (**1g**).*

Yield 31.0 g, 0.183 mol, 48%, bp = 70–72 °C (20 mmHg). Analytical sample was obtained by precipitation *via* trituration of the ethereal base solution with 1M HCl in Et_2O. Beige solid, mp = 141–143 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.35 (s, 3H), 3.84–3.66 (m, 2H), 3.47 (dd, J = 29.0, 12.8 Hz, 1H), 3.37 (t, J = 10.5 Hz, 1H), 3.02 (d, J = 20.3 Hz, 2H), 1.98–1.87 (m, 1H), 1.83–1.65 (m, 2H), 1.59–1.48 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 90.4 (d, J = 177.9 Hz), 69.6 (d, J = 22.4 Hz), 66.4, 42.7 (d, J = 21.4 Hz), 29.2 (d, J = 21.5 Hz), 21.2. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ -165.5. MS (APCI) m/z = 134 ([M+H]$^+$). Anal. calcd. for $C_6H_{13}ClFNO$: C 42.49; H 7.73; N 8.26; Cl 20.90. Found: C 42.78; H 7.78; N 8.64; Cl 21.16.

*(3-Fluorotetrahydrofuran-3-yl)methanamine (**1h**).*

Yield 77.2 g, 0.496 mol, 38%, bp = 54–56 °C (20 mmHg). Analytical sample was obtained by precipitation *via* trituration of the ethereal base solution with 1M HCl in Et_2O. Beige powder, mp = 110–112 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (s, 3H), 4.00–3.79 (m, 3H), 3.73 (dd, J = 34.3, 11.2 Hz, 1H), 3.26 (d, J = 20.4 Hz, 2H), 2.24–2.06 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 103.3, 74.7 (d, J = 24.6 Hz), 67.2, 42.5 (d, J = 24.1 Hz), 36.2 (d, J = 21.9 Hz). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ -156.7. MS (APCI) m/z = 120 ([M+H]$^+$). Anal. calcd. for $C_5H_{11}ClFNO$: C 38.60; H 7.13; N 9.00; Cl 22.78. Found: C 38.88; H 7.30; N 8.80; Cl 22.95.

*(3-Fluorooxetan-3-yl)methanamine (**1i**).*

Yield 25.3 g, 0.179 mol, 45%, bp = 41–43 °C (20 mmHg). Analytical sample was obtained by precipitation *via* trituration of the ethereal base solution with 1M HCl in Et_2O. Yellowish crystals, mp = 164–165 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.47 (s, 3H), 4.70 (dd, J = 20.7, 8.9 Hz, 2H), 4.62 (dd, J = 21.3, 8.9 Hz, 2H), 3.42 (d, J = 20.0 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 93.1 (d, J = 209.4 Hz), 77.9 (d, J = 23.0 Hz), 41.3 (d, J = 23.8 Hz). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ -154.2. HRMS (ESI/QTOF) m/z: [M + H]$^+$ Calcd for $C_4H_9FNO^+$: 106.0663; Found: 106.0665.

*(6-Fluoro-1,4-dioxepan-6-yl)methanamine (**1j**).*

Yield 32.3 g, 0.174 mol, 16%, bp = 46–48 °C (20 mmHg). Analytical sample was obtained by precipitation *via* trituration of the ethereal base solution with 1M HCl in Et_2O. Colourless powder, mp = 127–130 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (s, 3H), 3.99–3.79 (m, 4H), 3.79–3.71 (m, 2H), 3.66 (dd, J = 13.2, 5.5 Hz, 2H), 3.22–2.96 (m, 12H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 97.8 (d, J = 179.6 Hz), 73.9, 73.6 (d, J = 28.7 Hz), 41.4 (d, J = 22.9 Hz). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ -160.3. HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_6H_{12}FNO_2Na^+$: 172.0744; Found: 172.0749.

Notes

Acknowledgments and finances. The work was supported by Enamine Ltd. and Ministry of Education and Science of Ukraine (Grants No. 0121U100387 (21BF037-01M) and 0122U001962 (22BF037-02)). The authors thank Prof. Dr. Oleksandr Grygorenko and Oleksandr Liashuk for their help with manuscript preparation, Prof. Andrey A. Tolmachev for his encouragement and support, and all the brave people of Ukraine for making this publication possible.

Conflict of interests. The authors are employees of Enamine Ltd. that offers the building blocks described in this paper in the company's catalog.

Supporting information

The Supporting Information contains copies of NMR spectra for the synthesized products.

References

1. Grygorenko, O. O.; Volochnyuk, D. M.; Ryabukhin, S. V.; Judd, D. B. *Chem. Eur. J.* **2020**, *26*, 1196–1237.
2. Aldeghi, M.; Malhotra, S.; Selwood, D. L.; Chan, A. W. E. *Chem. Biol. Drug Des.* **2014**, *83*, 450–461.
3. Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, *57*, 5845–5859.
4. Shah, P.; Westwell, A. D. *J. Enzyme Inhib. Med. Chem.* **2007**, *22*, 527–540.
5. Yerien, D. E.; Bonesi, S.; Postigo, A. *Org. Biomol. Chem.* **2016**, *14*, 8398–8427.
6. Han, J.; Remete, A. M.; Dobson, L. S.; Kiss, L.; Izawa, K.; Moriwaki, H.; Soloshonok, V. A.; O'Hagan, D. *J. Fluor. Chem.* **2020**, *239*, 109639.
7. Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422–518.
8. Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432–2506.
9. Grygorenko, O. O.; Volochnyuk, D. M.; Vashchenko, B. V. *Eur. J. Org. Chem.* **2021**, 6478–6510.
10. Grygorenko, O. O.; Melnykov, K. P.; Holovach, S.; Demchuk, O. *ChemMedChem* **2022**, *17*, e202200365.
11. Vacher, B.; Bonnaud, B.; Funes, P.; Jubault, N.; Koek, W.; Assié, M. B.; Cosi, C.; Kleven, M. *J. Med. Chem.* **1999**, *42*, 1648–1660.
12. Rothbaum, W. P. PCT Int. Pat. WO2021142257, 2021.
13. Liang, J.; Zbieg, J. R.; Blake, R. A.; Chang, J. H.; Daly, S.; Dipasquale, A. G.; Friedman, L. S.; Gelzleichter, T.; Gill, M.; Giltnane, J. M.; Goodacre, S.; Guan, J.; Hartman, S. J.; Ingalla, E. R.; Kategaya, L.; Kiefer, J. R.; Kleinheinz, T.; Labadie, S. S.; Lai, T., et al. *J. Med. Chem.* **2021**, *64*, 11841–11856.
14. Ouvry, G.; Arnux-Tallau, N.; Bihl, F.; Boudu, A.; Boux-Peter, C.; Carlavan, I.; Christin, O.; Cuadrado, M. J.; Defoin-Platel, C.; Deret, S.; Duvert, D.; Feret, C.; Forissier, M.; Fournet, J. F.; Froude, D.; Hacini-Rachinel, F.; Harris, C. S.; Hervouet, C.; Huguet, H., et al. *ChemMedChem* **2018**, *13*, 321–337.
15. Reaxys Database www.reaxys.com (accessed Nov 27, 2023).
16. Verniest, G.; Piron, K.; Van Hende, E.; Thuring, J. W.; MacDonald, G.; Deroose, F.; De Kimpe, N. *Org. Biomol. Chem.* **2010**, *8*, 2509–2512.
17. Shipe, W. D.; Barrow, J. C.; Yang, Z. Q.; Lindsley, C. W.; Yang, F. V.; Schlegel, K. A. S.; Shu, Y.; Rittle, K. E.; Bock, M. G.; Hartman, G. D.; Tang, C.; Ballard, J. E.; Kuo, Y.; Adarayan, E. D.; Prueksaritanont, T.; Zrada, M. M.; Uebele, V. N.; Nuss, C. E.; Cormolly, T. M.; et al. *J. Med. Chem.* **2008**, *51*, 3692–3695.
18. Yarmolchuk, V. S.; Mykhalchuk, V. L.; Mykhailiuk, P. K. *Tetrahedron* **2014**, *70*, 3011–3017.
19. Gurbanov, R.; Sokolov, A.; Golovach, S.; Melnykov, K.; Dobrydnev, A. V.; Grygorenko, O. O. *Synthesis* **2020**, *53*, 1771–1784.
20. Green, S. A.; Vásquez-Céspedes, S.; Shenvi, R. A. *J. Am. Chem. Soc.* **2018**, *140*, 11317–11324.
21. Law, J. A.; Bartfield, N. M.; Frederich, J. H. *Angew. Chem. Int. Ed.* **2021**, *60*, 14360–14364.
22. Margot, C.; Rizzolio, M.; Schlosser, M. *Tetrahedron* **1990**, *46*, 2411–2424.
23. Kimse, W.; Rode, K. *Chem. Ber.* **1987**, *120*, 847–848.
24. Senda, Y.; Ohno, A.; Ishiyama, J.; Imaizumi, S.; Kamiyama, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 613–616.
25. Applequist, D. E.; Roberts, J. D. *J. Am. Chem. Soc.* **1956**, *78*, 4012–4022.

Багатограмовий синтез β-флуорованих насичених гетероциклічних метанамінів

В.В. Семено[1,2], К. П. Мельников[1,2]*

[1]*ТОВ «НВП «Єнамін», вул. Вінстона Черчилля 78, Київ 02094, Україна.*
[2]*Київський національний університет імені Тараса Шевченка, вул. Володимирська 60, Київ 01601, Україна.*

Резюме. У роботі описано ефективний багатограмовий синтез β-флуорованих насичених гетероциклічних метанамінів–перспективних будівельних блоків для створення лікарських засобів–виходачи з відповідних насичених гетероциклічних кетонів. Метод передбачає використання олефінування за Вітгігом, нуклеофільного заміщення азид-іоном та реакції Штаудінгера та добре працює для нітрогено- та оксигеновмісних гетероциклічних сполук із розміром циклу від чотирьох до семи.

Ключові слова: фторорганічні сполуки, гетероцикли, аміни, будівельні блоки.



Journal of Fluorine Chemistry

journal homepage: www.elsevier.com



Acidity of Saturated (Hetero)cyclic α-Fluoro Carboxylic Acids and Lipophilicity of Their Amide Derivatives

Oleksii Pidvyshennyi,[a,b] Kostiantyn P. Melnykov,[a,b] Oleksandr Liashuk,[a,b] Dmytro Lesyk,[b,c] Yuliia Holota,[c] Petro Borysko,[c] Oleksandr O. Grygorenko[a,b]*

[a] *Enamine Ltd. (www.enamine.net), Winston Churchill Street 78, Kyiv 02094, Ukraine*

[b] *Taras Shevchenko National University of Kyiv, Volodymyrska Street 60, Kyiv 01601, Ukraine*

[c] *Bienta/Enamine Ltd. (www.bienta.net), Winston Churchill Street 78, Kyiv 02094, Ukraine*

ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Available online

Keywords:

Acidity

Building blocks

Lipophilicity

α-Fluorination

Saturated rings

ABSTRACT

Analysis of the physicochemical parameters of saturated (hetero)cyclic carboxylic acids and their α-fluorinated analogues is described. Measured pK_a values revealed a significant influence of the single fluorine substituent on the compound's acidity (pK_a decreased by 1.3–2.4 units). This effect did not demonstrate additivity with electronic effects of other heteroatom (i.e., cyclic ether moiety). On the contrary, lipophilicity (Log*P*) of the corresponding anilides was almost unaffected upon α-substitution with a fluorine atom and mainly governed by the nature of the (hetera)cycloalkyl substituent. The obtained results suggest that polarization of the C–F bonds themselves does not define the fluorine effect on the compound's lipophilicity.

2024 Elsevier Ltd. All rights reserved.

Corresponding author. Tel.: +38-044-239-33-15; fax: +38-044-537-32-53; e-mail: gregon@univ.kiev.ua

Dedicated to the memory of Ukrainian scientists who perished because of russian aggression

1. Introduction

Over the last decades, organofluorine derivatives have been firmly rooted in drug discovery, being a part of more than 300 marketed drugs [1–4]. The relatively small size (comparable to a hydrogen atom) and high electronegativity of fluorine, as well as the ability to establish weak intermolecular interactions, cause a significant impact of the fluorinated fragments on the key parameters of the studied molecule [5–12]. The diversity of fluorination patterns in modern drug discovery contrasts with the comparative scarcity of naturally occurring organofluorine compounds [2]. Among only five identified natural fluorine-containing compounds [13], fluoroacetic acid **1** holds a special position. As a part of defensive mechanisms, it can be found in more than 40 different plant species worldwide; moreover, several bacteria are also capable of fluoroacetate biosynthesis and accumulation [13,14]. High toxicity of **1** (almost 200 times higher than commonly used trifluoroacetic acid, Figure 1, *A*) is connected with his enzymatic transformations in the citric acid cycle [15–17]. The reaction of fluoroacetyl-CoA (derived from **1**) with oxaloacetate produces (2*R*,3*R*)-fluorocitrate **2**, an effective inhibitor of aconitase and the main reason for the toxicity of **1**. At the same time, α-mono- and α,α-disubstituted derivatives of fluoroacetic acid do not have such safety concerns and can be found in several marketed and investigational drugs (Figure 1, *B*).

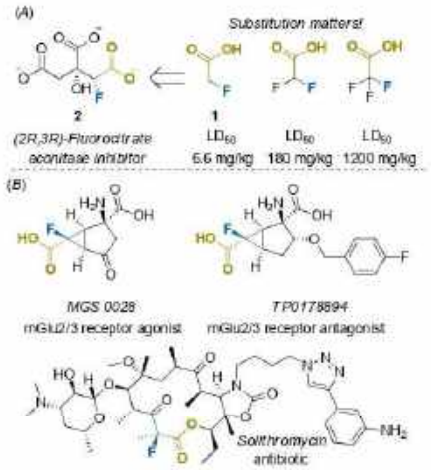


Figure 1. (*A*) Fluoroacetic acid **1**, toxic metabolite **2**, and toxicity of other fluorinated acetic acid derivatives; (*B*) Marketed and investigational drugs with α-fluorocarboxylate fragment.

In the recent decade, a number of works describing a thorough examination of fluorine's impact on the physicochemical properties of organic molecules was performed. As a result, a number of general trends for the Fluorine influence was established,[5] including polarity enhancement in fluorinated saturated cyclic systems (especially pronounced for all-*cis* derivatives, also known as "Janus face" cycloalkanes) [18–21] (Figure 2, *A*), distance-dependent effects on the acid-base properties of carboxylic acids and amines [6,7,22–28] (*B*), or conformational effects [29–37] (*C*). It is worth noting that there is a clear differentiation of the observed effects depending on the nature of fluorine-containing fragment – *gem*-CF_2 [38,39], single fluorine atom [22,40], fluoroalkyl groups (CF_3,

CHF_2, CH_2F) [41], or other fluorination patterns [42]. In particular, it was demonstrated that substitution with a single fluorine atom resulted in a considerable Log*P* decrease in acyclic compound series, while adding further fluorine atoms had non-linear effects (*D*) [27,43]. For cyclic systems, this effect was even more complex [6,44].

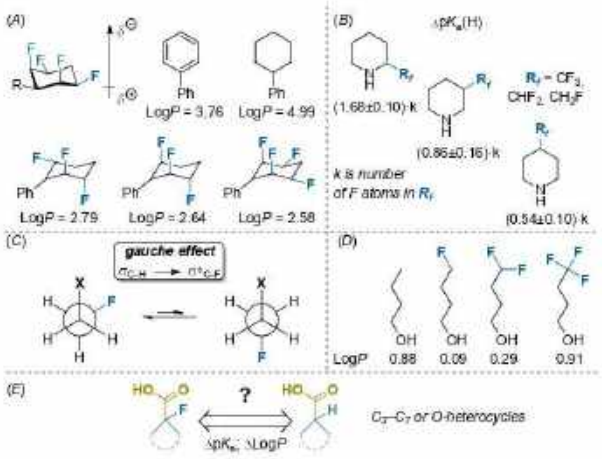


Figure 2 (*A–D*) Previous studies on physico-chemical properties of saturated fluorinated compounds. (*E*) General representation of the aims of this work.

In a series of previous works, we have demonstrated the effect of fluorine-containing substituents on the key physicochemical parameters (*i.e.*, acidity, pK_a, and lipophilicity, Log*P*) of a variety of cycloalkyl building blocks or their model derivatives [10,18–24]. Herein, we evaluate the impact of a single fluorine atom as an α-substituent on the acidity and lipophilicity of saturated (hetero)cyclic carboxylic acids (Figure 2, *E*).

2. Results and discussion

First, we selected a set of α,α-disubstituted derivatives of α-fluorinated carboxylic acids **3** and their non-fluorinated counterparts (Figure 3). This set was initialized with isobutyric acid **4a** and its fluorinated counterpart **3a**. Considering the high value of saturated (hetero)cyclic scaffolds for drug discovery [45,46], five cycloalkane carboxylic acids **4b–f** (C_3 to C_7) and their α-fluorinated analogues **3b–f** were included into the set. Since the expected lipophilicity of their model derivatives tends to lean towards higher values, heterocyclic substrates **3/4g–i** bearing hydrophilic cyclic ether fragment were also added.

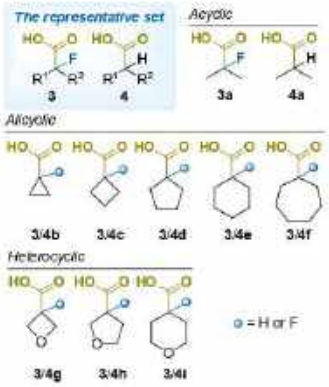


Figure 3. (Hetera)cycloalkyl carboxylic acids **3** and **4**, studied in this work.

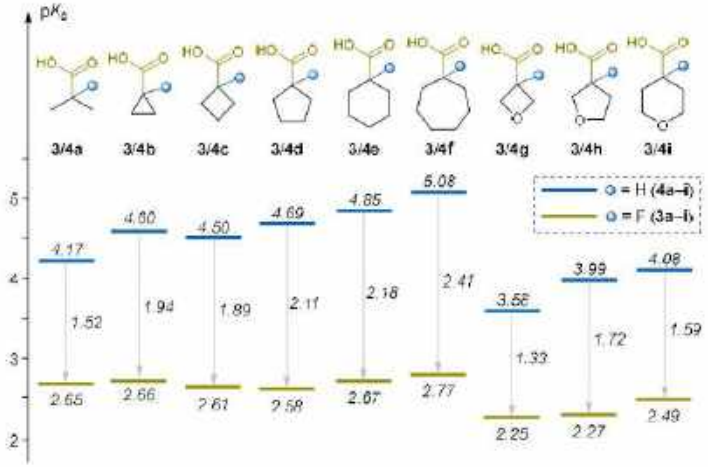
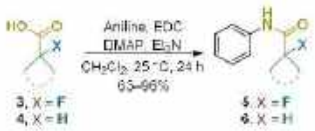


Figure 4. pK_a values measured for compounds **3** and **4** (21 °C).

The pK_a values for α-fluorinated carboxylic acids **3a**,**g**–**k** and their non-fluorinated analogs **4a**–**j** were measured by standard acid-base titration; for the cycloalkane carboxylic acids **4b**–**f**, the corresponding data was retrieved from our previous work [23] (Figure 4). Expectedly, α-substitution with fluorine atom led to a considerable decrease in the pK_a values for all studied compounds **3a**–**i** (ΔpK_a = 1.33…2.41 units). Notably, the acidity of fluorine-substituted carboxylic acids **3a**–**i** was in a narrower range as compared to the non-fluorinated compounds **4a**–**i** – the differences between the highest and lowest pK_a values within each series were 0.52 and 1.50 units, respectively. In particular, a general trend of pK_a increase in homologous series clearly observable for the non-fluorinated compounds (i.e. carboxylic acids **4c**–**f**) was less prominent after the α-substitution with a fluorine atom (note ΔpK_a = 0.58 and 0.16 units for the **3c**/**3f** and **4c**/**4f** pairs, respectively). Finally, introducing oxygen atom into the carbocyclic ring had more negligible effect on the pK_a values as compared to that of the fluorine atom, and it was more pronounced for the non-fluorinated series (ΔpK_a for the **4c**/**4g**, **4d**/**4h**,

and **4e/4i** pairs were 0.92, 0.70, and 0.77 units, whereas for **3c/3g**, **3d/3h**, and **3e/3i** – 0.36, 0.31, and 0.18 units, respectively). These results show that pK_a increments of fluorine and oxygen atoms are not additive in the series studied.

The Log*P* values were measured for anilides **5a–i**, **6a**, and **6g–i** (prepared by reaction of carboxylic acids **3** and **4** with aniline in the presence of EDC, DMAP, and Et_3N) using the classical shake-flask method combined with HPLC quantitative analysis (Figure 3). The corresponding Log*P* values for anilides **6b–f** were retrieved from the literature [23].



Scheme 1. Synthesis of model anilides **5** and **6** used for the Log*P* measurements.

Contrary to the case of pK_a discussed previously, the effect of α-substitution with fluorine atom on the compounds' lipophilicity was far less notable (Figure 5). Indeed, the difference between Log*P* values for anilides **5** and **6** (–0.04…0.12, ca. 0.08 units on average) clearly demonstrates that the fluorine atom has a minor effect on their lipophilicity. This is contrary to the case of other monofluorinated derivatives with the fluorine atom attached to a primary/secondary carbon atom [22,43,47] that are significantly more hydrophilic than the corresponding non-fluorinated counterparts. The results obtained for the **5**/**6** compound pairs can be explained by the absence of a neighboring C–H bond. Apparently, the effects of substitution with a fluorine atom(s) on the Log*P* values observed in the previous works are strongly dependent on the adjacent C–H bond polarization caused by the fluorine atom, while the polarization of the C–F bond itself is less influential (Figure 6). If the hydrogen atom is replaced with an electron-withdrawing carbonyl group, the Log*P* decrease becomes neglectable. In some cases (*i. e.*, **5e–h**), the substitution with fluorine atom even resulted in a slight increase of the compounds' lipophilicity.

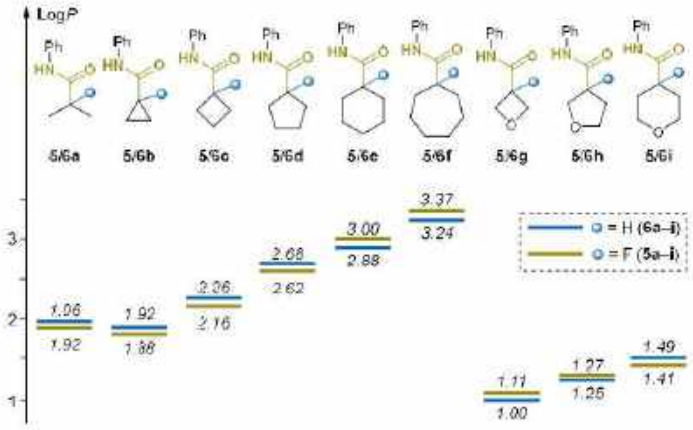


Figure 5. Log*P* values measured for compounds **5** and **6** (21 °C).



Figure 6. Possible rationalization of the substitution with fluorine atom effects on the Log*P* values.

On the contrary, introducing oxygen atom into the carbocyclic ring resulted in an expected decrease in the compound's lipophilicity, and this effect was not particularly dependent on the presence of fluorine atom (ΔLog*P* for the **6c**/**6g**, **6d**/**6h**, and **6e**/**6i** pairs were 1.26, 1.43, and 1.39 units, whereas for **5c**/**5g**, **5d**/**5h**, and **5e**/**5i** – 1.15, 1.35, and 1.59, respectively).

3. Conclusions

Since fluorination is an increasingly influential design approach in medicinal chemistry, it is important to understand its impact on the compound's physicochemical properties (*e. g.*, acidity/basicity and lipophilicity). In this study, we have shown that for the series of α-branched (mostly alicyclic and saturated heterocyclic) saturated carboxylic acids, α-fluorination results in an expected decrease of the pK_a values (by 1.33–2.41 units) due to the inductive electronic effect of the fluorine atom. Introducing an ether moiety into the carbocyclic ring also resulted in increased compounds' acidities, although to a lesser extent. Notably, the latter effect was different for the fluorinated and non-fluorinated series (ΔpK_a = 0.70–0.92 and 0.18–0.35, respectively). In other words, the pK_a increments of fluorine and oxygen atoms were not additive for the series studied.

Notably, α-fluorination had only a minor impact on the lipophilicity of model anilides obtained from the title carboxylic acids (ΔLog*P* = 0.08 on average). This is contrary to the previous data where the fluorine atom was introduced at the primary/secondary position: in those cases, a considerable decrease in the compound's Log*P* was observed. Apparently, this observation can be related to the lack of C–H bonds at the adjacent position in the fluorinated series studied in this work. These results suggest that polarization of the C–F bonds themselves is not defining the fluorine effect on the compound's lipophilicity.

We hope that the results obtained in this work will drive more rational application of α-fluorinated saturated (hetero)cyclic building blocks in early drug discovery programs and also provide the basis for a deeper understanding of the effects of substitution with fluorine atom(s) on the key physicochemical properties.

4. Experimental

4.1. General

The solvents were purified according to the standard procedures.[48] All starting materials were obtained from Enamine Ltd. Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase ^{1}H, $^{13}C\{^{1}H\}$ and $^{19}F\{^{1}H\}$ NMR spectra were recorded on an Agilent ProPulse 600 spectrometer (at 600 MHz for ^{1}H NMR and 151 MHz for $^{13}C\{^{1}H\}$ NMR), a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H, 126 MHz for ^{13}C, and 470 MHz for ^{19}F), or a Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H, 101 MHz for ^{13}C, and 376 MHz for ^{19}F). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6. Coupling constants (J) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and Agilent 5890 Series II 5972 MS instrument (electron impact ionization (EI)). High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer. pK_a values were measured using the reported protocol [23].

*4.2. Synthesis of amides **5** and **6**.*

To a solution of the corresponding carboxylic acid (1.00 mmol) and aniline (0.10 mL, 1.10 mmol) in CH_2Cl_2 (5 mL), DMAP (0.012 g, 0.10 mmol) and TEA (0.14 mL, 1.00 mmol) were added in one portion, followed by addition of EDC·HCl (0.19 g, 1.00 mmol). The resulting mixture was stirred at rt ovemight, then diluted with CH_2Cl_2 (10 mL) and water (20 mL). The organic layer was washed with saturated aq $NaHCO_3$ (3×10 mL), 10% aq citric acid (3×10 mL), brine (3×10 mL), dried over Na_2SO_4, and evaporated under reduced pressure to give pure product after flash column chromatography.

*4.2.1. 2-Fluoro-2-methyl-N-phenylpropanamide (**5a**).*

Yield 0.154 g, 0.85 mmol, 85%. Beige powder, mp = 95 – 98 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.58 (d, J = 1.3 Hz, 2H), 7.41 – 7.33 (m, 2H), 7.20 – 7.07 (m, 1H), 1.67 (d, J = 22.4 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.5, 128.6, 124.2, 119.4, 96.0 (d, J = 182.5 Hz), 24.5 (d, J = 23.9 Hz). $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ –145.6. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{13}FNO^+$: 182.0976; Found: 182.0972. Other spectral data are in accordance with those reported in the literature.[49]

*4.2.2. 1-Fluoro-N-phenylcyclopropane-1-carboxamide (**5b**).*

Yield 0.143 g, 0.80 mmol, 80%. Colourless solid, mp = 108 – 110 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.64 – 7.52 (m, 2H), 7.45 – 7.30 (m, 2H), 7.20 – 7.07 (m, 1H), 1.54 – 1.45 (m, 2H), 1.43 – 1.30 (m, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 167.3 (d, J = 18.6 Hz), 136.6, 128.6, 124.3, 119.4, 78.2 (d, J = 234.1 Hz), 13.4 (d, J = 10.3 Hz). $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ –196.4. MS (APCI) m/z = 180 ($[M+H]^+$). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{10}H_{10}FNONa^+$: 202.0639; Found: 202.0637.

*4.2.3. 1-Fluoro-N-phenylcyclobutane-1-carboxamide (**5c**).*

Yield 0.139 g, 0.72 mmol, 72%. Yellowish powder, mp = 117 – 119 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.70 – 7.51 (m, 2H), 7.34 (t, J = 8.0 Hz, 2H), 7.18 – 7.08 (m, 1H), 2.75 (ttd, J = 13.8, 6.6, 3.1 Hz, 2H), 2.58 – 2.33 (m, 2H), 2.08 – 1.88 (m, 2H).

$^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 169.7 (d, J = 21.9 Hz), 137.0, 129.1, 124.7, 119.9, 96.5 (d, J = 225.6 Hz), 32.9 (d, J = 21.0 Hz), 13.0 (d, J = 9.9 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –144.0. MS (APCI) m/z = 194 ($[M+H]^+$). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{13}FNO^+$: 194.0976; Found: 194.0975.

*4.2.4. 1-Fluoro-N-phenylcyclopentane-1-carboxamide (**5d**).*

Yield 0.145 g, 0.70 mmol, 70%. Colourless crystals, mp = 132 – 134 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.59 (d, J = 7.9 Hz, 2H), 7.35 (t, J = 7.8 Hz, 2H), 7.15 (d, J = 7.4 Hz, 1H), 2.51 – 2.23 (m, 2H), 2.18 – 1.99 (m, 2H), 1.89 (dq, J = 8.6, 4.1 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1 (d, J = 21.7 Hz), 136.6, 128.5, 124.2, 119.3, 105.5 (d, J = 191.0 Hz), 37.2 (d, J = 22.9 Hz), 24.3. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –147.8. MS (APCI) m/z = 208 ($[M+H]^+$). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{15}FNO^+$: 208.1132; Found: 208.1131. Other spectral data are in accordance with those reported in the literature. [49]

*4.2.5. 1-Fluoro-N-phenylcyclohexane-1-carboxamide (**5e**).*

Yield 0.161 g, 0.73 mmol, 73%. Colourless crystals, mp = 140 – 142 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.31 – 8.07 (m, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.34 (t, J = 7.7 Hz, 2H), 7.13 (t, J = 7.4 Hz, 1H), 2.06 (td, J = 13.9, 4.6 Hz, 1H), 2.01 – 1.88 (m, 3H), 1.73 (dt, J = 9.5, 4.1 Hz, 3H), 1.68 – 1.55 (m, 2H), 1.36 (dd, J = 17.4, 7.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 171.1 (d, J = 19.3 Hz), 137.1, 129.0, 124.6, 119.8, 97.6 (d, J = 186.9 Hz), 32.3 (d, J = 22.1 Hz), 24.4, 21.0. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –163.6. MS (APCI) m/z = 222 ($[M+H]^+$). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{17}FNO^+$: 222.1289; Found: 222.1286.

*4.2.6. 1-Fluoro-N-phenylcycloheptane-1-carboxamide (**5f**).*

Yield 0.186 g, 0.79 mmol, 79%. Colourless crystals, mp = 129 – 131 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 9.1 Hz, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.34 (t, J = 7.9 Hz, 2H), 7.13 (t, J = 7.4 Hz, 1H), 2.37 – 2.13 (m, 2H), 2.02 (tdd, J = 15.2, 6.8, 3.2 Hz, 2H), 1.76 – 1.60 (m, 8H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 171.8 (d, J = 20.2 Hz), 136.6, 128.5, 124.1, 119.3, 100.1 (d, J = 185.7 Hz), 36.5 (d, J = 23.4 Hz), 28.9, 21.9 (d, J = 4.2 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –146.4. MS (APCI) m/z = 236 ($[M+H]^+$). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{19}FNO^+$: 236.1445; Found: 236.1445.

*4.2.7. 3-Fluoro-N-phenyloxetane-3-carboxamide (**5g**).*

Yield 0.169 g, 0.87 mmol, 87%. Yellowish powder, mp = 113 – 115 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.96 (s, 1H), 7.58 (d, J = 7.9 Hz, 2H), 7.58 (d, J = 7.9 Hz, 2H), 7.36 (t, J = 7.8 Hz, 2H), 7.36 (t, J = 7.8 Hz, 2H), 7.18 (t, J = 7.4 Hz, 1H), 7.18 (t, J = 7.4 Hz, 1H), 5.40 – 5.06 (m, 2H), 5.31 – 5.03 (m, 2H), 4.98 – 4.77 (m, 2H), 4.93 – 4.73 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 164.5 (d, J = 22.7 Hz), 135.8, 128.7, 124.8, 119.5, 94.7 (d, J = 223.9 Hz), 78.1 (d, J = 23.3 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –161.4. MS (APCI) m/z = 196 ($[M+H]^+$). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{11}FNO_2^+$: 196.0768; Found: 196.0765.

*4.2.8. 3-Fluoro-N-phenyloxolane-3-carboxamide (**5h**).*

Yield 0.134 g, 0.64 mmol, 64%. Yellowish powder, mp = 100 – 102 °C. ^1H NMR (500 MHz, DMSO-d_6) δ 10.31 – 9.64 (m, 1H), 7.70 (d, J = 7.9 Hz, 2H), 7.31 (t, J = 7.7 Hz, 2H), 7.10 (t, J = 7.4 Hz, 1H), 4.23 – 3.78 (m, 4H), 2.72 – 2.49 (m, 1H), 2.36 – 2.20 (m, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 167.2 (d, J = 24.1 Hz), 137.8, 128.5, 124.3, 120.6, 102.9 (d, J = 196.1 Hz), 75.9 (d, J

= 25.4 Hz), 67.6, 37.7 (d, J = 22.3 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ −152.5. MS (APCI) m/z = 210 ($[M+H]^+$). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{11}H_{12}FNO_2Na^+$: 232.0744; Found: 232.0742.

4.2.9. 4-Fluoro-N-phenyloxane-4-carboxamide (5i).

Yield 0.214 g, 0.96 mmol, 96%. Colourless powder, mp = 165 – 166 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.20 – 8.03 (m, 1H), 7.57 (d, J = 7.9 Hz, 2H), 7.35 (t, J = 7.9 Hz, 2H), 7.15 (t, J = 7.4 Hz, 1H), 3.96 (ddd, J = 11.5, 5.2, 2.0 Hz, 2H), 3.75 (td, J = 12.0, 2.3 Hz, 2H), 2.56 – 2.19 (m, 2H), 1.81 (ddd, J = 14.2, 11.4, 2.3 Hz, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 169.4 (d, J = 19.5 Hz), 136.8, 129.1, 124.9, 119.9, 94.8 (d, J = 188.4 Hz), 62.9, 32.5 (d, J = 21.1 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −165.1. MS (APCI) m/z = 224 ($[M+H]^+$). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{15}FNO_2^+$: 224.1081; Found: 224.1080.

4.2.10. 2-Methyl-N-phenylpropanamide (6a).

Yield 0.142 g, 0.87 mmol, 87%. Beige powder, mp = 102 – 104 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 7.9 Hz, 2H), 7.43 (s, 1H), 7.30 (t, J = 7.9 Hz, 2H), 7.09 (t, J = 7.4 Hz, 1H), 2.52 (p, J = 6.9 Hz, 1H), 1.24 (d, J = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 138.1, 128.9, 124.1, 119.8, 36.6, 19.6. MS (APCI) m/z = 164 ($[M+H]^+$). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{10}H_{13}NONa^+$: 186.0889; Found: 186.0888. Other spectral data are in accordance with those reported in the literature [50].

4.2.11. N-Phenyloxetane-3-carboxamide (6g).

Yield 0.163 g, 0.92 mmol, 92%. Beige powder, mp = 122 – 124 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.53 (d, J = 7.9 Hz, 2H), 7.31 (t, J = 7.8 Hz, 2H), 7.12 (t, J = 7.4 Hz, 1H), 4.95 (t, J = 6.3 Hz, 2H), 4.83 (dd, J = 8.3, 6.0 Hz, 2H), 3.87 (p, J = 7.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 169.7, 137.5, 129.1, 124.8, 120.2, 73.3, 41.1. MS (APCI) m/z = 178 ($[M+H]^+$). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{12}NO_2^+$: 178.0863; Found: 178.0862.

4.2.12. N-Phenyloxolane-3-carboxamide (6h).

Yield 0.151 g, 0.79 mol, 79%. Beige powder, mp = 98 – 100 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.64 (m, 1H), 7.51 (d, J = 7.9 Hz, 2H), 7.31 (t, J = 7.7 Hz, 2H), 7.10 (t, J = 7.4 Hz, 1H), 4.17 – 3.98 (m, 2H), 3.94 (dd, J = 9.0, 7.2 Hz, 1H), 3.88 – 3.75 (m, 1H), 3.22 – 2.98 (m, 1H), 2.65 – 2.11 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 171.6, 137.3, 128.5, 123.9, 119.5, 70.5, 67.7, 46.0, 30.1. MS (APCI) m/z = 192 ($[M+H]^+$). Anal. calcd. for $C_{12}H_{13}NO_2$: C 69.09; H 6.85; N 7.32. Found: C 69.12; H 6.45; N 7.32.

4.2.13. N-Phenyloxane-4-carboxamide (6i).

Yield 0.143 g, 0.70 mmol, 70%. Beige crystals, mp = 146 – 148 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 7.9 Hz, 2H), 7.40 (s, 1H), 7.31 (t, J = 7.7 Hz, 2H), 7.10 (t, J = 7.4 Hz, 1H), 4.05 (ddd, J = 11.5, 4.3, 2.1 Hz, 2H), 3.62 – 3.32 (m, 2H), 2.49 (ddd, J = 11.5, 7.4, 4.1 Hz, 1H), 2.12 – 1.73 (m, 4H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 172.1, 158.5, 137.3, 128.5, 123.9, 119.4, 66.7, 42.7, 28.7. MS (APCI) m/z = 206 ($[M+H]^+$). Anal. calcd. for $C_{12}H_{15}NO_2$: C 70.22; H 7.37; N 6.82. Found: C 70.42; H 7.44; N 6.53. All spectral data are in accordance with those reported in the literature [51].

4.3. pKa measurements.

Compound **5** ($\nu \sim 0.500$ mmol) was dissolved in distilled H_2O ($V_0 = 50.0$ mL), and the resulting solution was titrated with standard 0.1 M (c_{tit}) aq NaOH (for **1** and **2**·HCl) or HCl (for **2**). The pH values were collected with $\Delta V_{tit} = 0.5$ mL step. For the pK_a calculations, the first part of the titration curve before the equivalence point was used where $\Delta pH/\Delta V_{tit} < 1$ (in some cases, the first and the last one or two data points were discarded if the corresponding $\Delta pH/\Delta V_{tit}$ was considerably larger than for the rest of the series). The pK_a value for each data point was determined from the following equations (all volumes are in mL); then, the final value was obtained as an average:

$$[HA] = (\nu - V_{tit} \cdot c_{tit}/1000) \cdot 1000/(V_0 + V_{tit})$$

$$[A^-] = \nu \cdot 1000/(V_0 + V_{tit}) - [HA]$$

$$pK_a = pH + \mathrm{Log}([HA]/[A^-])$$

4.4. LogP measurements.

The experiments were carried out in Eppendorf-type polypropylene microtubes in triplicates. A 2.5-μL aliquot of 20 mM DMSO stock solution of a test compound was added into a preliminarily mutually saturated mixture containing 500 μL of H_2O and 500 μL of 1-octanol. The solution was allowed to mix in a rotator at 30 rpm for 1 h. Phase separation was assured by centrifugation for 2 min at 6000 rpm. The octanol phase was diluted 100-fold with 40% aqueous acetonitrile, and the aqueous phase was diluted 10-fold with the same solvent. The samples of both phases were analyzed using an HPLC system coupled with a tandem mass spectrometer. Mebendazole was used as a reference compound.

Partition coefficient P was calculated using the following equation:

$$P = (p_o \cdot S_o) / (p_w \cdot S_w) \quad (1)$$

where S_o – peak area of the analyte in the octanol phase;

S_w – peak area of the analyte in the aqueous phase;

p_o – dilution coefficient for the octanol phase ($p_o = 100$);

p_w – dilution coefficient for the aqueous phase ($p_w = 10$).

Acknowledgements

The work was funded by Enamine Ldt. Additional funding from Ministry of Education and Science of Ukraine, Grants No. 21BF037-01M (O.O.G., O.S.L., K.P.M.) and 22BF037-02 (O.O.G.) is also acknowledged. The authors thanks Olga Kovalenko and Margaryta Bolgova for pK_a titrations, Prof. Andrey A. Tolmachev for his encouragement and support, and all the brave defenders of Ukraine who made this publication possible.

References and notes

[1] G. Shabir, A. Saeed, W. Zahid, F. Naseer, Z. Riaz, N. Khalil, Muneeba, F. Albericio, Chemistry and Pharmacology of Fluorinated Drugs Approved by the FDA (2016–2022), Pharmaceuticals. 16 (2023). https://doi.org/10.3390/ph16081162.

[2] M. Inoue, Y. Sumii, N. Shibata, Contribution of Organofluorine Compounds to Pharmaceuticals, ACS Omega. 5 (2020) 10633–10640. https://doi.org/10.1021/acsomega.0c00830.

[3] J. Han, L. Kiss, H. Mei, A.M. Remete, M. Ponikvar-Svet, D.M. Sedgwick, R. Roman, S. Fustero, H. Moriwaki, V.A. Soloshonok, Chemical Aspects of Human and Environmental Overload with Fluorine, Chem. Rev. 121 (2021) 4678–4742. https://doi.org/10.1021/acs.chemrev.0c01263.

[4] E. Henary, S. Casa, T.L. Dost, J.C. Sloop, M. Henary, The Role of Small Molecules Containing Fluorine Atoms in Medicine and Imaging Applications, Pharmaceuticals. 17 (2024). https://doi.org/10.3390/ph17030281.

[5] K. Müller, C. Faeh, F.F.F. Diederich, K. Müller, C. Faeh, F.F.F. Diederich, K. Müller, C. Faeh, F.F.F. Diederich, Fluorine in Pharmaceuticals: Looking Beyond Intuition, Science. 317 (2007) 1881–1886. https://doi.org/10.1126/science.1131943.

[6] K. Müller, Fluorination patterns in small alkyl groups: their impact on properties relevant to drug discovery, Academic Press, 2019. https://doi.org/10.1016/B978-0-12-812733-9.00002-7.

[7] N.A. Meanwell, Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design, J. Med. Chem. 61 (2018) 5822–5880. https://doi.org/10.1021/acs.jmedchem.7b01788.

[8] G. Xu, J. Guo, Y. Wu, Chemokine Receptor CCR5 Antagonist Maraviroc: Medicinal Chemistry and Clinical Applications, Curr. Top. Med. Chem. 14 (2014) 1504–1514. https://doi.org/10.2174/1568026614666140827143745.

[9] J. Popovici-Muller, R.M. Lemieux, E. Artin, J.O. Saunders, F.G. Salituro, J. Travins, G. Cianchetta, Z. Cai, D. Zhou, D. Cui, P. Chen, K. Straley, E. Tobin, F. Wang, M.D. David, V. Penard-Lacronique, C. Quivoron, V. Saada, S. de Botton, S. Gross, L. Dang, H. Yang, L. Utley, Y. Chen, H. Kim, S. Jin, Z. Gu, G. Yao, Z. Luo, X. Lv, C. Fang, L. Yan, A. Olaharski, L. Silverman, S. Biller, S.-S.M. Su, K. Yen, Discovery of AG-120 (Ivosidenib): A First-in-Class Mutant IDH1 Inhibitor for the Treatment of IDH1 Mutant Cancers, ACS Med. Chem. Lett. 9 (2018) 300–305. https://doi.org/10.1021/acsmedchemlett.7b00421.

[10] R. Xu, K. Wang, J.P. Rizzi, H. Huang, J.A. Grina, S.T. Schlachter, B. Wang, P.M. Wehn, H. Yang, D.D. Dixon, R.M. Czerwinski, X. Du, E.L. Ged, G. Han, H. Tan, T. Wong, S. Xie, J.A. Josey, E.M. Wallace, 3-[(1 S,2 S,3 R)-2,3-Difluoro-1-hydroxy-7-methylsulfonylindan-4-yl]oxy-5-fluorobenzonitrile (PT2977), a Hypoxia-Inducible Factor 2α (HIF-2α) Inhibitor for the Treatment of Clear Cell Renal Cell Carcinoma, J. Med. Chem. 62 (2019) 6876–6893. https://doi.org/10.1021/acs.jmedchem.9b00719.

[11] V. Gouverneur, K. Seppelt, Introduction: Fluorine Chemistry, Chem. Rev. 115 (2015) 563–565. https://doi.org/10.1021/cr500686k.

[12] O.O. Grygorenko, K.P. Melnykov, S. Holovach, O. Demchuk, Fluorinated Cycloalkyl Building Blocks for Drug

Discovery, ChemMedChem. 17 (2022) e202200365. https://doi.org/10.1002/cmdc.202200365.

[13] K.K.J. Chan, D. O'Hagan, Chapter Eleven - The Rare Fluorinated Natural Products and Biotechnological Prospects for Fluorine Enzymology, in: D. Hopwood (Ed.), Nat. Prod. Biosynth. by Microorg. Plants, Part B, Academic Press, 2012: pp. 219–235. https://doi.org/10.1016/B978-0-12-394291-3.00003-4.

[14] L.E.X. Leong, S. Khan, C.K. Davis, S.E. Denman, C.S. McSweeney, Fluoroacetate in plants - a review of its distribution, toxicity to livestock and microbial detoxification., J. Anim. Sci. Biotechnol. 8 (2017) 55. https://doi.org/10.1186/s40104-017-0180-6.

[15] R. Peters, R.W. Wakelin, Biochemistry of fluoroacetate poisoning; the isolation and some properties of the fluorotricarboxylic acid inhibitor of citrate metabolism., Proc. R. Soc. London. Ser. B, Contain. Pap. a Biol. Character. 140 (1953) 497–507. https://doi.org/10.1098/rspb.1953.0004.

[16] C.M. Timperley, Chapter 29 - Highly-toxic fluorine compounds, in: R. Banks (Ed.), Elsevier Science Ltd, Oxford, 2000: pp. 499–538. https://doi.org/10.1016/B978-008043405-6/50040-2.

[17] M.W. van der Kamp, J.D. McGeagh, A.J. Mulholland, "Lethal Synthesis" of Fluorocitrate by Citrate Synthase Explained through QM/MM Modeling, Angew. Chem. Int. Ed. 50 (2011) 10349–10351. https://doi.org/https://doi.org/10.1002/anie.201103260.

[18] Y. Wang, W. Lee, Y.-C. Chen, Y. Zhou, E. Plise, M. Migliozzi, J.J. Crawford, Turning the Other Cheek: Influence of the cis-Tetrafluorocyclohexyl Motif on Physicochemical and Metabolic Properties, ACS Med. Chem. Lett. 13 (2022) 1517–1523. https://doi.org/10.1021/acsmedchemlett.2c00312.

[19] D. O'Hagan, Polar Organofluorine Substituents: Multivicinal Fluorines on Alkyl Chains and Alicyclic Rings, Chem. Eur. J. 26 (2020) 7981–7997. https://doi.org/10.1002/chem.202000178.

[20] Z. Fang, D.B. Cordes, A.M.Z.Z. Slawin, D. O'hagan, Fluorine containing cyclopropanes: synthesis of aryl substituted all- cis 1,2,3-trifluorocyclopropanes, a facially polar motif, Chem. Commun. 55 (2019) 10539–10542. https://doi.org/10.1039/C9CC05749H.

[21] B. Jeffries, Z. Wang, R.I. Troup, A. Goupille, J.Y. Le Questel, C. Fallan, J.S. Scott, E. Chiarparin, J. Graton, B. Linclau, Lipophilicity trends upon fluorination of isopropyl, cyclopropyl and 3-oxetanyl groups, Beilstein J. Org. Chem. 16 (2020) 2141–2150. https://doi.org/10.3762/bjoc.16.182.

[22] K.P. Melnykov, K. Nazar, O. Smyrnov, A. Skreminskyi, S. Pavlenko, O. Klymenko-Ulianov, S. Shishkina, D.M. Volochnyuk, O.O. Grygorenko, Mono- and Difluorinated Saturated Heterocyclic Amines for Drug Discovery: Systematic Study of Their Physicochemical Properties, Chem. Eur. J. 29 (2023) e202301383. https://doi.org/10.1002/chem.202301383.

[23] S. Holovach, K.P. Melnykov, A. Skreminskiy, M. Herasymchuk, O. Tavlui, D. Aloshyn, P. Borysko, A.B. Rozhenko, S. V Ryabukhin, D.M. Volochnyuk, O.O. Grygorenko, Effect of gem-Difluorination on the Key Physicochemical Properties Relevant to Medicinal Chemistry: The Case of Functionalized Cycloalkanes, Chem. Eur. J. 28 (2022) e202200331. https://doi.org/10.1002/chem.202200331.

[24] K.P. Melnykov, O. Tavlui, A. Skreminskiy, Y.O. Kuchkovska, O.O. Grygorenko, Impact of Fluoroalkyl Substituents on the Physicochemical Properties of Saturated Heterocyclic Amines, Chem. Eur. J. 28 (2022) e202201601. https://doi.org/10.1002/chem.202201601.

[25] M. Morgenthaler, E. Schweizer, A. Hoffmann-Röder, F. Benini, R.E. Martin, G. Jaeschke, B. Wagner, H. Fischer, S. Bendels, D. Zimmerli, J. Schneider, F. Diederich, M. Kansy, K. Müller, Predicting and Tuning Physicochemical Properties in Lead Optimization: Amine Basicities, ChemMedChem. 2 (2007) 1100–1115. https://doi.org/10.1002/cmdc.200700059.

[26] P. Shah, A.D. Westwell, The role of fluorine in medicinal chemistry, J. Enzyme Inhib. Med. Chem. 22 (2007) 527–540. https://doi.org/10.1080/14756360701425014.

[27] B. Jeffries, Z. Wang, H.R. Felstead, J.Y. Le Questel, J.S. Scott, E. Chiarparin, J. Graton, B. Linclau, Systematic Investigation of Lipophilicity Modulation by Aliphatic Fluorination Motifs, J. Med. Chem. 63 (2020) 1002–1031. https://doi.org/10.1021/acs.jmedchem.9b01172.

[28] E.P. Gillis, K.J. Eastman, M.D. Hill, D.J. Donnelly, N.A. Meanwell, Applications of Fluorine in Medicinal Chemistry, J. Med. Chem. 58 (2015) 8315–8359. https://doi.org/10.1021/acs.jmedchem.5b00258.

[29] J. St-Gelais, É. Côté, D. Lainé, P.A. Johnson, D. Giguère, Addressing the Structural Complexity of Fluorinated Glucose Analogues: Insight into Lipophilicities and Solvation Effects, Chem. Eur. J. 26 (2020) 13499–13506. https://doi.org/10.1002/chem.202002825.

[30] D. Lainé, O. Lessard, J. St-Gelais, D. Giguère, From Carbohydrates to Complex Organofluorines: Synthesis, Conformation, and Lipophilicity of Multivicinal-Fluorine-Containing Hexitol Analogues, Chem. Eur. J. 27 (2021) 3799–3805. https://doi.org/10.1002/chem.202004646.

[31] R. Mondal, M. Agbaria, Z. Nairoukh, Fluorinated Rings: Conformation and Application, Chem. Eur. J. 27 (2021) 7193–7213. https://doi.org/10.1002/chem.202005425.

[32] D. Marych, V. Bilenko, Y. V Ilchuk, S. Kinakh, V. Soloviov, A. Yatsymyrskiy, O. Liashuk, S. Shishkina, I. V Komarov, O.O. Grygorenko, Synthesis and physicochemical evaluation of tetrafluorinated GABA analogue, J. Fluor. Chem. 277 (2024) 110307. https://doi.org/https://doi.org/10.1016/j.jfluchem.2024.110307.

[33] B.A. Piscelli, W. Sanders, C. Yu, N. Al Maharik, T. Lebl, R.A. Cormanich, D. O'Hagan, Fluorine-Induced Pseudo-

Anomeric Effects in Methoxycyclohexanes through Electrostatic 1,3-Diaxial Interactions, Chem. Eur. J. 26 (2020) 11989–11994. https://doi.org/10.1002/CHEM.202003058.

[34] T. Bykova, N. Al-Maharik, A.M.Z. Slawin, M. Bühl, T. Lebl, D. O'Hagan, Benzylic Functionalisation of Phenyl all-cis-2,3,5,6-Tetrafluorocyclohexane Provides Access to New Organofluorine Building Blocks, Chem. Eur. J. 24 (2018) 13290–13296. https://doi.org/10.1002/CHEM.201802166.

[35] C.J. Thomson, Q. Zhang, N. Al-Maharik, M. Bühl, D.B. Cordes, A.M.Z. Slawin, D. O'Hagan, Fluorinated cyclopropanes: synthesis and chemistry of the aryl α,β,β-trifluorocyclopropane motif, Chem. Commun. 54 (2018) 8415–8418. https://doi.org/10.1039/C8CC04964E.

[36] J.C.R. Thacker, P.L.A. Popelier, Fluorine Gauche Effect Explained by Electrostatic Polarization Instead of Hyperconjugation: An Interacting Quantum Atoms (IQA) and Relative Energy Gradient (REG) Study, J. Phys. Chem. A. 122 (2018) 1439–1450. https://doi.org/10.1021/acs.jpca.7b11881.

[37] C. Thiehoff, Y.P. Rey, R. Gilmour, The Fluorine Gauche Effect: A Brief History, Isr. J. Chem. 57 (2017) 92–100. https://doi.org/https://doi.org/10.1002/ijch.201600038.

[38] Y. Zafrani, G. Parvari, D. Amir, L. Ghindes-Azaria, S. Elias, A. Pevzner, G. Fridkin, A. Berliner, E. Gershonov, Y. Eichen, S. Saphier, S. Katalan, Modulation of the H-Bond Basicity of Functional Groups by α-Fluorine-Containing Functions and its Implications for Lipophilicity and Bioisosterism, J. Med. Chem. 64 (2021) 4516–4531. https://doi.org/10.1021/acs.jmedchem.0c01868.

[39] S. Saphier, S. Katalan, G. Yacov, A. Berliner, O. Redy-Keisar, G. Fridkin, L. Ghindes-Azaria, I. Columbus, A. Pevzner, E. Drug, H. Prihed, E. Gershonov, Y. Eichen, S. Elias, G. Parvari, Y. Zafrani, Placing CF2 in the Center: Major Physicochemical Changes Upon a Minor Structural Alteration in Gem-Difunctional Compounds, Chem. Eur. J. 29 (2023) e202202939. https://doi.org/10.1002/chem.202202939.

[40] R.J. Glyn, G. Pattison, Effects of Replacing Oxygenated Functionality with Fluorine on Lipophilicity, J. Med. Chem. 64 (2021) 10246–10259. https://doi.org/10.1021/acs.jmedchem.1c00668.

[41] T. Alle, S. Joyasawal, K. Oukoloff, K. Long, Z. Owyang, K.R. Francisco, D. Cahard, D.M. Huryn, C. Ballatore, Structure-property relationships of fluorinated carboxylic acid bioisosteres, Bioorg. Med. Chem. Lett. 91 (2023) 129363. https://doi.org/10.1016/j.bmcl.2023.129363.

[42] R.I. Troup, B. Jeffries, R.E.-B. Saudain, E. Georgiou, J. Fish, J.S. Scott, E. Chiarparin, C. Fallan, B. Linclau, Skipped Fluorination Motifs: Synthesis of Building Blocks and Comparison of Lipophilicity Trends with Vicinal and Isolated Fluorination Motifs, J. Org. Chem. 86 (2021) 1882–1900. https://doi.org/10.1021/acs.joc.0c02810.

[43] A. V Chernykh, O.S. Olifir, Y.O. Kuchkovska, D.M. Volochnyuk, V.S. Yarmolchuk, O.O. Grygorenko, Fluoroalkyl-

Substituted Cyclopropane Derivatives: Synthesis and Physicochemical Properties, J. Org. Chem. 85 (2020) 12692–12702. https://doi.org/10.1021/acs.joc.0c01848.

[44] B. Linclau, Z. Wang, B. Jeffries, J. Graton, R.J. Carbajo, D. Sinnaeve, J.-Y. Le Questel, J.S. Scott, E. Chiarparin, Relating Conformational Equilibria to Conformer-Specific Lipophilicities: New Opportunities in Drug Discovery, Angew. Chem. Int. Ed. 61 (2022) e202114862. https://doi.org/10.1002/anie.202114862.

[45] R.D. Taylor, M. MacCoss, A.D.G. Lawson, Rings in Drugs, J. Med. Chem. 57 (2014) 5845–5859. https://doi.org/10.1021/jm4017625.

[46] J. Shearer, J.L. Castro, A.D.G. Lawson, M. MacCoss, R.D. Taylor, Rings in Clinical Trials and Drugs: Present and Future, J. Med. Chem. 65 (2022) 8699–8712. https://doi.org/10.1021/acs.jmedchem.2c00473.

[47] A. Rodil, S. Bosisio, M.S. Ayoup, L. Quinn, D.B. Cordes, A.M.Z. Slawin, C.D. Murphy, J. Michel, D. O'Hagan, Metabolism and hydrophilicity of the polarised 'Janus face' all-cis tetrafluorocyclohexyl ring, a candidate motif for drug discovery, Chem. Sci. 9 (2018) 3023–3028. https://doi.org/10.1039/C8SC00299A.

[48] W.L.F. Armarego, C. Chai, Purification of laboratory chemicals, 5th ed., Elsevier: Oxford, 2003.

[49] T. Nishikata, S. Ishida, R. Fujimoto, Site-Selective Tertiary Alkyl–Fluorine Bond Formation from α-Bromoamides Using a Copper/CsF Catalyst System, Angew. Chem. Int. Ed. 55 (2016) 10008–10012. https://doi.org/10.1002/anie.201603426.

[50] Y. Lu, A. Kasahara, T. Hyodo, K. Ohara, K. Yamaguchi, Y. Otani, T. Ohwada, Isolation and Reactions of Imidoyl Fluorides Generated from Oxime Using the Diethylaminosulfur Trifluoride/Tetrahydrofuran (DAST–THF) System, Org. Lett. 25 (2023) 3482–3486. https://doi.org/10.1021/acs.orglett.3c01063.

[51] Q. Lian, J. Chen, K. Huang, K. Hou, J. Fang, W. Wei, J. Zhou, Alkali-Driven Photoinduced N-Dealkylation of Aryl Tertiary Amines and Amides, Org. Lett. 25 (2023) 8387–8392. https://doi.org/10.1021/acs.orglett.3c03519.



Journal of Fluorine Chemistry

journal homepage: www.elsevier.com



Lipophilicity Effects of Monofluorination at the Tertiary Aliphatic Carbon as a Function of α-Substituent

Kostiantyn P. Melnykov,[a,b] Oleksandr S. Liashuk,[a,b] Oleh Smyrnov,[a,b] Dmytro Lesyk,[b,c] Yuliia Holota,[c] Petro Borysko,[c] Viktor Yakubovskyi,[a,b] Oleksandr O. Grygorenko[a,b]*

[a] *Enamine Ltd. (www.enamine.net), Winston Churchill Street 78, Kyiv 02094, Ukraine*

[b] *Taras Shevchenko National University of Kyiv, Volodymyrska Street 60, Kyiv 01601, Ukraine*

[c] *Bienta/Enamine Ltd. (www.bienta.net), Winston Churchill Street 78, Kyiv 02094, Ukraine*

ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Available online

Keywords:

Saturated rings

Lipophilicity

Log*P*

α-Fluorination

Piperidine

ABSTRACT

Effects of monofluorination at the tertiary aliphatic carbon on the compound's lipophilicity were measured for a series of model 4-substituted piperidine-derived benzamides. It was found that the observed Δlog*P* values strongly depend on the nature of α-substituent present at the C-4 position. In particular, Δlog*P* increased with increasing the substituent's electronegativity (as described by field effect). Using qualitative molecular electrostatic potential surface (MEPS) analysis, we suggested that the fluorine effect on the compound's lipophilicity in the studied systems is defined by electronic distribution modulation at the neighboring atoms (especially Hydrogens).

© 2024 Elsevier Ltd. All rights reserved.

Corresponding author. Tel.: +38-044-239-33-15; fax: +38-044-537-32-53; e-mail: grygon@univ.kiev.ua

Dedicated to the memory of Ukrainian scientists who perished because of russian aggression

1. Introduction

It is widely recognized that fluorination has become a mainstream design approach in discovery of medicines, agrochemicals, and other biologically active compounds [1–10]. Fluorinated motifs can modulate the compound's potency, physicochemical parameters, and metabolic stability. Among other properties affected by Fluorine, lipophilicity (typically measured through 1-octanol – water partition coefficient logarithm, Log*P*) is one of the most complex phenomena, and despite numerous studies in this area [11–21], we are still far from its comprehensive understanding. It is generally accepted that monofluorination of aromatic compounds results in a slight increase of their lipophilicity (Hansch–Leo lipophilicity parameter $\pi = 0.14$ [22]) (Figure 1, *A*), albeit there are exceptions to this rule [9]. In the case of aliphatic counterparts, both decrease and increase of the Log*P* values upon the fluorination are common [15,23,24].

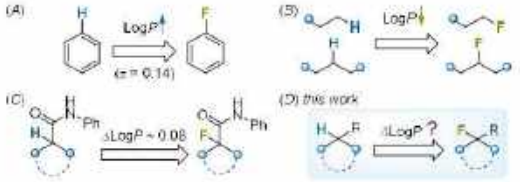


Figure 1. Effect of monofluorination at aromatic Carbon atoms (*A*), primary/secondary aliphatic Carbon atoms (*B*), α-branched carboxamides (*C*, ref. [25]), and tertiary aliphatic Carbon atoms (*D*) on the lipophilicity.

In numerous studies, it was shown that monofluorination results in lowering of the compound's lipophilicity (Figure 1, *B*) [15,18,21,26,27]. It should be noted, however, that in nearly all the above-referenced works, the Fluorine atom was introduced at the primary or secondary position. Recently, we have evaluated lipophilicity a series of α-branched carboxamides and were intrigued to find that the Log*P* values were only slightly affected upon α-fluorination at the tertiary Carbon atom adjacent to the C=O group (Figure 1, *C*) [25]. We have hypothesized that polarization of the adjacent C–H bonds may be the main factor responsible for the decreased lipophilicity of aliphatic monofluorinated compounds. When this factor is eliminated (due to the lack of the corresponding C–H bonds), the fluorination effect should be minimized. In this work, we have aimed at the verification of this hypothesis by studying a series of compounds fluorinated at the tertiary position and comparing them to the corresponding non-fluorinated counterparts. We have performed variation of the substituents at the α position to the fluorination site in order to assess the impact of their electronic properties on the compound's Δ Log*P*. It should be noted that a similar study was performed recently for fluorinated arenes; F/OH or F/OMe (and not F/H) replacements were evaluated in that case [28]. The authors found that the substituent electronic effects had a major impact on the observed Log*P* changes in these series. Nevertheless, this effect was mostly addressed to the modulation of properties of the corresponding phenols/anisoles and not their fluorinated counterparts.

A preliminary version of this work was published as a ChemRXiv preprint [29].

2. Results and discussion

Considering commercial availability of the corresponding monofluorinated representatives and their non-fluorinated counterparts, as well as the limitations of the Log*P* shake-flask measurement method combined with HPLC, were have chosen *N*-benzoylated 4-substituted piperidines **1** and **2** as the model substrates of this study (Scheme 1). These derivatives were prepared by the reaction of the corresponding amines **3** or **4** with benzoyl chloride. The following eight substituents R varying in electronic properties were evaluated at the C-4 position: CN **(a)**, F **(b)**, CF_3 **(c)**, Ph **(d)**, H **(e)**, CH_2F **(f)**, CH_2OMe **(g)**, and Me **(h)**. The corresponding Log*P* values for anilides **1b,c,e,f** and **2b** were retrieved from the literature [13,21,30].



3a–h, X = H
4a–h, X = F

1a–h, X = H
2a–h, X = F

R = CN (**a**), F (**b**), CF_3 (**c**), Ph (**d**), H (**e**), CH_2F (**f**), CH_2OMe (**g**), Me (**h**)

Scheme 1. Synthesis of amides **1** and **2**.

The results of the Log*P* measurements are summarized in Table 1. It is apparent that in the case of strong electron-withdrawing substituents, α-fluorination resulted in increased lipophilicity, whereas for weak acceptors and donors, decrease of the Log*P* value was observed. We checked correlation of the Δ Log*P* values with Hammett and other similar constants and found that modified Swain – Lupton field inductive effect parameter *F* [31] gave reasonable results ($R^2 = 0.78$) (Figure 2). We have also noticed that the substituents having α-Hydrogen atoms (CH_2F, CH_2OMe, and especially CH_3) demonstrated lowered negative Δ Log*P* values. If the CH_3 group was excluded as an outlier, even better correlation was observed ($R^2 = 0.83$). Notably, average Δ Log*P* for a series of α-fluorinated anilides studied in our previous work [25] fitted this correlation very well (the *F* value for the $C(O)NH_2$ group [31] was used).

Table 1. Results of the Log*P* measurements for compounds **1a–h** and **2a–h** (21 °C)

#	R	Amide **1**	Log*P*(**1**)	Amide **2**	Log*P*(**2**)	Δ Log*P*^{m}	*F*
1	CN	**1a**	0.75	**2a**	1.20	0.45	0.51
2	F	**1b**	1.26 [21]	**2b**	1.51 [21]	0.25	0.45
3	CF_3	**1c**	2.17 [13]	**2c**	2.30	0.13	0.38
4	Ph	**1d**	3.34	**2d**	3.39	0.05	0.12
5	H	**1e**	1.39 [21]	**1b**	1.26 [21]	–0.13	0.03
6	CH_2F	**1f**	1.51 [13]	**2f**	1.38	–0.13	0.15

7	CH_2OMe	**1g**	1.46	**2g**	1.32	–0.14	0.13
8	Me	**1h**	2.25	**2h**	1.69	–0.56	0.01

[a] $\Delta Log P = Log P(\mathbf{2}) - Log P(\mathbf{1})$

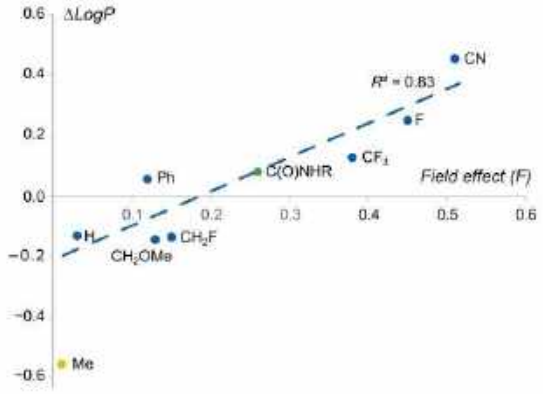


Figure 2. Lipophilicity effect of monofluorination at the tertiary position ($\Delta Log P$) as a function of α-substituent field effect (F). Data points coloring: yellow – CH_3 as the α-substituent, blue – all other derivatives, green – average value for α-fluorinated anilides from our previous work [25]

These results demonstrate that although our initial hypothesis about importance of the C–H bond polarization caused by the Fluorine atoms is confirmed to some extent (including *C*–H bonds at the vicinal position), some additional factors should be also taken into account. To get better insight into the observed phenomenon, we decided to compare molecular electrostatic potential surfaces (MEPS) [32] for amides **1a–h** and **2a–h** (Figure 3). In this model, the solvation can be described through the solvent-solute interactions at specific parts of the molecule. Previously, Hunter and co-workers demonstrated that maxima and minima distributions on the calculated gas-phase MEPS correlated with free energies of interphase transfer (which in our case is directly related to Log*P*) [33,34].

Figure 3 shows that that the fluorination typically caused either expansion of the negative MEPS area (for **1c**/**2c**, **1d**/**2d**, **1e**/**2e**, and **1h**/**2h**) or its redistribution around the fluorination site (for **1a**/**2a**, **1b**/**2b**, **1f**/**2f**, and **1g**/**2g**). Increased negative MEPS area correlated with better solvation with H_2O and hence lowered lipophilicity (which was observed for **1e**/**2e** (R = H), **1f**/**2f** (R = CH_2F), **1g**/**2g** (R = CH_2OMe), and **1h**/**2h** (R = Me)), and vice versa (**1b**/**2b**, R = F). In case of **1a**/**2a** (R = CN), fluorination caused lowered polarization of the highly polar C≡N bond, which might explain increased lipophilicity. For compounds **1c**/**2c** and **1d**/**2d** (R = CF_3 and Ph, respectively) the reasons behind the observed slightly positive $\Delta Log P$ values were not fully clear. It is possible that the polarization effects of the Fluorine atom are insignificant compared to these lipophilic groups, which results in small effect on the Log*P*. As mentioned above, the most significant effect of fluorination was detected for derivatives **1h**/**2h** (R = CH_3); in this case, highly negative MEPS area was generated at the Hydrogen atoms of methyl group.

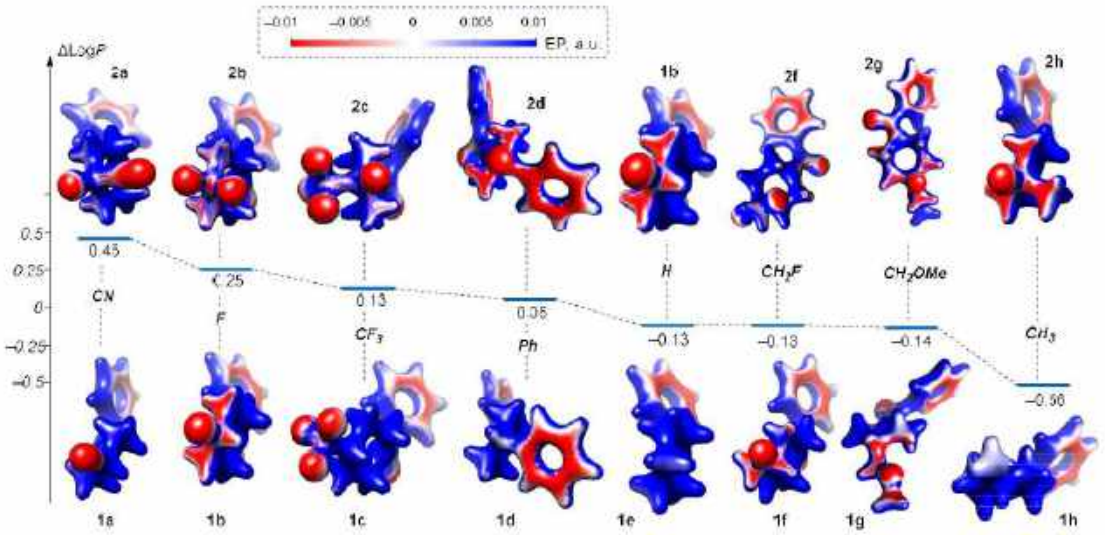


Figure 3. Molecular electrostatic potential (MEP) of compounds **1a–h** and **2a–h** mapped on 0.01 au electron density surface. Red regions indicate electron-rich negative MEPS, while the blue region corresponds to electron-deficient positive MEPS.

Based on these results, we believe that the solvation of Fluorine atom itself is not defining for the compound's lipophilicity; instead, the fluorination effect is expressed through modulating electronic distribution at the neighboring atoms (mostly Hydrogen). Indeed, the most significant lipophilicity decrease ($\Delta LogP = -0.56$) was observed for the **1h/2h** pair (eight Hydrogen atoms at the vicinal position to the fluorination site). For other derivatives having closely located Hydrogen atoms in the substituent (**1e/2e**, **1f/2f**, **1g/2g**), this effect was less pronounced ($\Delta LogP = -0.13 \ldots -0.14$). Electronegative substituents (CN, CF_3, F, or Ph) diminished the effect of Hydrogen atom polarization caused by fluorination; on the other hand, their own polarization was also decreased, which resulted in increased lipophilicity.

3. Conclusions

With increasing importance of fluorination as the design strategy in drug discovery, it is important to understand its impact on the compound's properties such as lipophilicity (Log*P*). Effects of the Fluorine atoms in saturated carbo- and heterocyclic systems are especially interesting, considering their complexity and growing popularity of such scaffolds in medicinal chemistry. In a series of model 4-substituted piperidine-derived benzamides, monofluorination at a tertiary Carbon atom either increased or decreased the compounds' lipophilicity depending on the α-substituent. The observed Δ Log*P* value showed reasonable correlation ($R^2 = 0.78$) with modified Swain – Lupton field inductive effect parameter *F* of the α-substituent, being positive for more electron-withdrawing and negative – for electron-donating or less electron-withdrawing groups. Qualitative analysis of molecular electrostatic potential surface (MEPS) showed that lowered Log*P* correlated with extended negative MEPS area caused by the Fluorine atom introduction, and vice versa. Changes in electronic distribution at the α-substituent itself were also found to be significant. These results suggest that that the

fluorination effect on the compound's lipophilicity in the series studied might be related to electronic distribution alterations at the neighboring atoms (mostly Hydrogen) and not by polarization of the Fluorine atom itself.

4. Experimental

4.1. General

The solvents were purified according to the standard procedures [35]. All starting materials were obtained from Enamine Ltd. Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase ^{1}H, $^{13}C\{^{1}H\}$ and $^{19}F\{^{1}H\}$ NMR spectra were recorded on an Agilent ProPulse 600 spectrometer (at 600 MHz for ^{1}H NMR and 151 MHz for $^{13}C\{^{1}H\}$ NMR), a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H, 126 MHz for ^{13}C, and 470 MHz for ^{19}F), or a Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H, 101 MHz for ^{13}C, and 376 MHz for ^{19}F). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6. Coupling constants (J) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and Agilent 5890 Series II 5972 MS instrument (electron impact ionization (EI)). High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer.

*4.2. Synthesis of amides **1** and **2**.*

To a pre-cooled to 0 °C solution of the corresponding piperidine (1.00 mmol) and NEt_3 (1.20 mmol for bases or 2.20 mmol for hydrochlorides) in CH_2Cl_2 (5 mL) pure benzoyl chloride (0.11 mL, 0.95 mmol) was added in a dropwise manner. Resulted mixture was stirred at rt overnight, then diluted with sat aq $NaHCO_3$ (15 mL) and CH_2Cl_2 (10mL). The layers were separated, organic solution was washed with sat aq $NaHCO_3$ (3 × 10 mL), 10% aq $NaHSO_4$ (3 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford crude product, which was triturated with minimum amounts of hexanes to afford analytically pure amide.

*4.2.1. 1-Benzoylpiperidine-4-carbonitrile (**1a**).*

Yield 182 mg, 0.850 mmol, 85%. Colorless powder, mp = 85 – 88 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.43 (d, J = 4.7 Hz, 3H), 7.40 – 7.30 (m, 2H), 3.89 (s, 1H), 3.29 (d, J = 12.1 Hz, 3H), 3.12 (dt, J = 8.5, 4.4 Hz, 1H), 1.88 (s, 2H), 1.71 (s, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6) δ 169.5, 136.3, 129.9, 128.9, 127.2, 122.3, 28.3, 25.9 (one of the signals is not resolved with the solvent peak). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{15}N_2O^+$: 215.1179; Found: 215.1182. All spectral data are in accordance with those reported in the literature [36].

*4.2.2. 1-Benzoyl-4-fluoropiperidine-4-carbonitrile (**2a**).*

Yield 193 mg, 0.831 mmol, 83%. Colorless crystals, mp = 80 – 82 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.43 (s, 5H), 3.87 (s, 1H), 3.44 (s, 3H), 2.37 – 1.99 (m, 4H). $^{13}C\{^{1}H\}$ NMR (151 MHz, DMSO-d_6) δ 169.6, 135.9, 130.1, 128.9, 127.3, 118.2 (d, J = 34.3 Hz), 87.6 (d,

J = 181.5 Hz), 42.8, 37.4, 34.1. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ −153.2. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{14}FN_2O^+$: 233.1085; Found: 233.1081.

*4.2.3. 1-Benzoyl-4-fluoro-4-(trifluoromethyl)piperidine (**2c**).*

Yield 236 mg, 0.866 mmol, 86%. Colorless powder, mp = 101 – 103 °C. ^1H NMR (500 MHz, DMSO-d_6) δ 7.44 (s, 5H), 4.54 (s, 1H), 3.62 (s, 1H), 3.24 (s, 1H), 2.98 (s, 1H), 2.21 – 1.80 (m, 4H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 169.7, 136.0, 130.1, 128.9, 127.4, 123.8 (qd, J = 283.0, 28.2 Hz), 92.3 (dq, J = 184.2, 31.3 Hz), 42.1, 36.5, 28.1. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ −83.3 (d, J = 6.3 Hz), -178.3 (q, J = 6.2 Hz). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{14}F_4NO^+$: 276.1006; Found: 276.1006.

*4.2.4. 1-Benzoyl-4-phenylpiperidine (**1d**).*

Yield 247 mg, 0.928 mmol, 93%. Yellowish solid, mp = 81 – 83 °C. ^1H NMR (500 MHz, DMSO-d_6) δ 7.43 (d, J = 6.5 Hz, 5H), 7.33 – 7.22 (m, 4H), 7.22 – 7.08 (m, 1H), 4.62 (s, 1H), 3.64 (s, 1H), 3.12 (s, 1H), 2.78 (dd, J = 16.3, 7.7 Hz, 2H), 1.95 – 1.49 (m, 4H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 168.9, 145.5, 136.4, 129.2, 128.3, 126.7, 126.6, 126.2, 47.7, 41.8, 33.0. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{20}NO^+$: 266.1539; Found: 266.1532. All spectral data are in accordance with those reported in the literature.[37]

*4.2.5. 1-Benzoyl-4-fluoro-4-phenylpiperidine (**2d**).*

Yield 249 mg, 0.880 mmol, 88%. Yellowish crystals, mp = 105 – 107 °C. ^1H NMR (500 MHz, DMSO-d_6) δ 7.55 – 7.25 (m, 10H), 4.54 (s, 1H), 3.57 (s, 1H), 3.36 (s, 1H), 3.08 (s, 1H), 2.25 – 1.73 (m, 4H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 169.5, 144.0 (d, J = 21.3 Hz), 136.6, 129.9, 128.8, 128.2, 127.3, 95.2 (d, J = 173.5 Hz), 43.7, 38.1, 36.5. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ −159.9. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{19}FNO^+$: 284.1445; Found: 284.1444.

*4.2.6. 1-Benzoyl-4-fluoro-4-(fluoromethyl)piperidine (**2f**).*

Yield 205 mg, 0.858 mmol, 86%. Colorless powder, mp = 104 – 106 °C. ^1H NMR (500 MHz, DMSO-d_6) δ 7.55 – 7.06 (m, 5H), 4.48 (dd, J = 47.5, 22.7 Hz, 2H), 4.31 (s, 1H), 3.47 (s, 1H), 3.25 (s, 1H), 3.07 (s, 1H), 1.97 – 1.49 (m, 4H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 169.0, 136.0, 129.4, 128.4, 126.6, 93.2 (dd, J = 174.7, 17.8 Hz), 86.0 (dd, J = 173.2, 22.5 Hz), 42.5, 36.9, 30.0. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ −166.8 (d, J = 14.5 Hz), -233.5 (d, J = 13.6 Hz). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{16}F_2NO^+$: 240.1194; Found: 240.1197.

*4.2.7. 1-Benzoyl-4-(methoxymethyl)piperidine (**1g**).*

Yield 212 mg, 0.909 mmol, 91%. Colorless oil. ^1H NMR (500 MHz, DMSO-d_6) δ 7.49 – 7.37 (m, 3H), 7.33 (dd, J = 6.5, 2.9 Hz, 2H), 4.45 (s, 1H), 3.69 – 3.33 (m, 2H), 3.21 (s, 3H), 2.99 (s, 1H), 2.72 (s, 1H), 1.98 – 1.43 (m, 4H), 1.09 (s, 2H). $^{12}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 169.3, 136.9, 129.7, 128.8, 127.0, 77.0, 58.6, 47.4, 41.7, 36.2, 29.6, 28.8. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{20}NO_2^+$: 234.1489; Found: 234.1485.

*4.2.8. 1-Benzoyl-4-fluoro-4-(methoxymethyl)piperidine (**2g**).*

Yield 199 mg, 0.792 mmol, 79%. Yellow viscous oil. ^1H NMR (500 MHz, DMSO-d_6) δ 7.49 – 7.31 (m, 5H), 4.27 (s, 1H), 3.41 (d, J = 21.6 Hz, 3H), 3.29 (s, 3H), 3.26 – 3.13 (m, 1H), 3.05 (s, 1H), 1.72 (t, J = 52.1 Hz, 4H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ

169.5, 136.5, 129.9, 128.9, 127.1, 94.6 (d, J = 173.4 Hz), 76.9 (d, J = 22.4 Hz), 59.4, 43.2, 37.5, 31.9, 31.1. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ –163.6. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{19}FNO_2^+$: 252.1394; Found: 252.1388.

*4.2.9. 1-Benzoyl-4-methylpiperidine (**1h**).*

Yield 193 mg, 0.951 mmol, 95%. Yellowish viscous oil. ^1H NMR (500 MHz, DMSO-d_6) δ 7.56 – 7.38 (m, 3H), 7.38 – 7.25 (m, 2H), 4.42 (s, 1H), 3.50 (s, 1H), 2.97 (s, 1H), 2.72 (s, 1H), 1.59 (s, 3H), 1.03 (s, 2H), 0.96 – 0.78 (m, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 169.3, 137.0, 129.7, 128.8, 127.0, 47.7, 42.2, 34.5, 33.9, 30.9, 22.0. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{18}NO^+$: 204.1383; Found: 204.1384.

*4.2.10. 1-Benzoyl-4-fluoro-4-methylpiperidine (**2h**).*

Yield 194 mg, 0.880 mmol, 88%. Beige powder, mp = 78 – 79 °C. ^1H NMR (500 MHz, DMSO-d_6) δ 7.51 – 7.28 (m, 5H), 4.22 (s, 1H), 3.39 (s, 1H), 3.22 (s, 1H), 3.07 (s, 1H), 1.75 (d, J = 54.5 Hz, 4H), 1.34 (d, J = 21.7 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 169.4, 136.6, 129.9, 128.8, 127.1, 93.3 (d, J = 167.9 Hz), 43.7, 38.2, 36.4, 35.9, 26.9 (d, J = 23.6 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ –150.1. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{17}FNO^+$: 222.1289; Found: 222.1284. All spectral data are in accordance with those reported in the literature.[38]

4.3. LogP measurements [39].

The experiments were carried out in Eppendorf-type polypropylene microtubes in triplicates. A 2.5-μL aliquot of 20 mM DMSO stock solution of a test compound was added into a preliminarily mutually saturated mixture containing 500 μL of H_2O and 500 μL of 1-octanol. The solution was allowed to mix in a rotator at 30 rpm for 1 h. Phase separation was assured by centrifugation for 2 min at 6000 rpm. The octanol phase was diluted 100-fold with 40% aqueous acetonitrile, and the aqueous phase was diluted 10-fold with the same solvent. The samples of both phases were analyzed using an HPLC system coupled with a tandem mass spectrometer. Mebendazole was used as a reference compound.

Partition coefficient P was calculated using the following equation:

$$P = (p_o \cdot S_o) / (p_w \cdot S_w) \quad (1)$$

where S_o – peak area of the analyte in the octanol phase;

S_w – peak area of the analyte in the aqueous phase;

p_o – dilution coefficient for the octanol phase (p_o = 100);

p_w – dilution coefficient for the aqueous phase (p_w = 10).

4.4. DFT calculations

The structures of the benzamides **1a–h** and **2a–h** conformers were optimized at the DFT level using PBE0 functional [40] and def2-TZVP [41] basis set. DFT calculations were performed using ORCA 5.0.4 software package [42–44] and Chimera software [45] for visualization. Atomic coordinates and detailed MEPS are given in the Supporting Information.

Acknowledgements

The work was funded by Enamine Ltd. The authors thank Prof. Dr. Andriy A. Tolmachov for his encouragement and support, and all the brave defenders of Ukraine who made this publication possible.

References and notes

[1] N.A. Meanwell, Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design, J. Med. Chem. 61 (2018) 5822–5880. https://doi.org/10.1021/acs.jmedchem.7b01788.

[2] P. Shah, A.D. Westwell, The role of fluorine in medicinal chemistry, J. Enzyme Inhib. Med. Chem. 22 (2007) 527–540. https://doi.org/10.1080/14756360701425014.

[3] D.E. Yerien, S. Bonesi, A. Postigo, Fluorination methods in drug discovery, Org. Biomol. Chem. 14 (2016) 8398–8427. https://doi.org/10.1039/C6OB00764C.

[4] J. Han, L. Kiss, H. Mei, A.M. Remete, M. Ponikvar-Svet, D.M. Sedgwick, R. Roman, S. Fustero, H. Moriwaki, V.A. Soloshonok, Chemical Aspects of Human and Environmental Overload with Fluorine, Chem. Rev. (2021) acs.chemrev.0c01263. https://doi.org/10.1021/acs.chemrev.0c01263.

[5] M. Inoue, Y. Sumii, N. Shibata, Contribution of organofluorine compounds to pharmaceuticals, ACS Omega 5 (2020) 10633–10640. https://doi.org/10.1021/acsomega.0c00830.

[6] J. Han, A.M. Remete, L.S. Dobson, L. Kiss, K. Izawa, H. Moriwaki, V.A. Soloshonok, D. O'Hagan, Next generation organofluorine containing blockbuster drugs, J. Fluor. Chem. 239 (2020) 109639. https://doi.org/10.1016/j.jfluchem.2020.109639.

[7] D. O'Hagan, R.J. Young, Future challenges and opportunities with fluorine in drugs?, Med. Chem. Res. 32 (2023) 1231–1234. https://doi.org/10.1007/S00044-023-03094-Y/FIGURES/3.

[8] D. O'Hagan, Fluorine in health care: Organofluorine containing blockbuster drugs, J. Fluor. Chem. 131 (2010) 1071–1081. https://doi.org/10.1016/j.jfluchem.2010.03.003.

[9] H.J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, Fluorine in Medicinal Chemistry, ChemBioChem 5 (2004) 637–643. https://doi.org/10.1002/CBIC.200301023.

[10] E.P. Gillis, K.J. Eastman, M.D. Hill, D.J. Donnelly, N.A. Meanwell, Applications of Fluorine in Medicinal Chemistry, J. Med. Chem. 58 (2015) 8315–8359. https://doi.org/10.1021/acs.jmedchem.5b00258.

[11] L. Xing, C. Keefer, M.F. Brown, Fluorine multipolar interaction: Toward elucidating its energetics in binding recognition, J. Fluor. Chem. 198 (2017) 47–53. https://doi.org/10.1016/j.jfluchem.2016.12.013.

[12] O.O. Grygorenko, K.P. Melnykov, S. Holovach, O. Demchuk, Fluorinated cycloalkyl building blocks for drug discovery, ChemMedChem 17 (2022) e202200365. https://doi.org/10.1002/cmdc.202200365.

[13] K.P. Melnykov, O. Tavlui, A. Skreminskiy, Y.O. Kuchkovska, O.O. Grygorenko, Impact of Fluoroalkyl Substituents on the Physicochemical Properties of Saturated Heterocyclic Amines, Chem. – A Eur. J. 28 (2022) e202201601. https://doi.org/10.1002/CHEM.202201601.

[14] K. Müller, Simple Vector Considerations to Assess the Polarity of Partially Fluorinated Alkyl and Alkoxy Groups, Chim. Int. J. Chem. 68 (2014) 356–362. https://doi.org/10.2533/chimia.2014.356.

[15] K. Müller, Fluorination patterns in small alkyl groups: their impact on properties relevant to drug discovery, in: Fluor. Life Sci. Pharm. Med. Diagnostics, Agrochem. Prog. Fluor. Sci. Ser., Academic Press, 2019: pp. 91–139. https://doi.org/10.1016/B978-0-12-812733-9.00002-7.

[16] K. Müller, C. Faeh, F. Diederich, Fluorine in Pharmaceuticals: Looking Beyond Intuition, Science 317 (2007) 1881–1886. https://doi.org/10.1126/science.1131943.

[17] B. Jeffries, Z. Wang, H.R. Felstead, J.Y. Le Questel, J.S. Scott, E. Chiarparin, J. Graton, B. Linclau, Systematic Investigation of Lipophilicity Modulation by Aliphatic Fluorination Motifs, J. Med. Chem. 63 (2020) 1002–1031. https://doi.org/10.1021/acs.jmedchem.9b01172.

[18] R.I. Troup, B. Jeffries, R.E.B. Saudain, E. Georgiou, J. Fish, J.S. Scott, E. Chiarparin, C. Fallan, B. Linclau, Skipped fluorination motifs: synthesis of building blocks and comparison of lipophilicity trends with vicinal and isolated fluorination motifs, J. Org. Chem. 86 (2021) 1882–1900. https://doi.org/10.1021/acs.joc.0c02810.

[19] D. O'Hagan, Polar Organofluorine Substituents: Multivicinal Fluorines on Alkyl Chains and Alicyclic Rings, Chem. – A Eur. J. 26 (2020) 7981–7997. https://doi.org/10.1002/CHEM.202000178.

[20] D. O'Hagan, The emergence and properties of selectively fluorinated 'Janus' cyclohexanes, Chem. Rec. 23 (2023) e202300027. https://doi.org/10.1002/tcr.202300027.

[21] K.P. Melnykov, K. Nazar, O. Smyrnov, A. Skreminskyi, S. Pavlenko, O. Klymenko-Ulianov, S. Shishkina, D.M. Volochnyuk, O.O. Grygorenko, Mono- and Difluorinated Saturated Heterocyclic Amines for Drug Discovery: Systematic Study of Their Physicochemical Properties, Chem. – A Eur. J. 29 (2023) e202301383. https://doi.org/10.1002/CHEM.202301383.

[22] B.E. Smart, Fluorine substituent effects (on bioactivity), J. Fluor. Chem. 109 (2001) 3–11. https://doi.org/10.1016/S0022-1139(01)00375-X.

[23] K. Müller, Fluorination patterns in small alkyl groups, in: Fluor. Life Sci. Pharm. Med. Diagnostics, Agrochem.,

Elsevier, 2019: pp. 91–139. https://doi.org/10.1016/B978-0-12-812733-9.00002-7.

[24] Q.A. Huchet, B. Kuhn, B. Wagner, H. Fischer, M. Kansy, D. Zimmerli, E.M. Carreira, K. Müller, On the polarity of partially fluorinated methyl groups, J. Fluor. Chem. 152 (2013) 119–128. https://doi.org/10.1016/j.jfluchem.2013.02.023.

[25] O. Pidvyshennyi, K.P. Melnykov, O. Liashuk, D. Lesyk, Y. Holota, P. Borysko, O.O. Grygorenko, Acidity of saturated (hetero)cyclic α-fluoro carboxylic acids and lipophilicity of their amide derivatives, J. Fluor. Chem. 278 (2024) 110316. https://doi.org/10.1016/J.JFLUCHEM.2024.110316.

[26] N.S. Keddie, A.M.Z. Slawin, T. Lebl, D. Philp, D. O'Hagan, All-cis 1,2,3,4,5,6-hexafluorocyclohexane is a facially polarized cyclohexane, Nat. Chem. 7 (2015) 483–488. https://doi.org/10.1038/nchem.2232.

[27] Q.A. Huchet, B. Kuhn, B. Wagner, N.A. Kratochwil, H. Fischer, M. Kansy, D. Zimmerli, E.M. Carreira, K. Müller, Fluorination Patterning: A Study of Structural Motifs That Impact Physicochemical Properties of Relevance to Drug Discovery, J. Med. Chem. 58 (2015) 9041–9060. https://doi.org/10.1021/acs.jmedchem.5b01455.

[28] R.J. Glyn, G. Pattison, Effects of Replacing Oxygenated Functionality with Fluorine on Lipophilicity, J. Med. Chem. 64 (2021) 10246–10259. https://doi.org/10.1021/acs.jmedchem.1c00668.

[29] K. Melnykov, O. Liashuk, O. Smyrnov, D. Lesyk, Y. Holota, P. Borysko, V. Yakubovskyi, O. Grygorenko, Lipophilicity Effects of Monofluorination at the Tertiary Aliphatic Carbon as a Function of alpha-Substituent, ChemRxiv (2024). https://doi.org/10.26434/chemrxiv-2024-ndxxb.

[30] S. Holovach, K.P. Melnykov, A. Skreminskiy, M. Herasymchuk, O. Tavlui, D. Aloshyn, P. Borysko, A.B. Rozhenko, S. V. Ryabukhin, D.M. Volochnyuk, O.O. Grygorenko, Effect of gem-Difluorination on the Key Physicochemical Properties Relevant to Medicinal Chemistry: The Case of Functionalized Cycloalkanes, Chem. – A Eur. J. 28 (2022) e202200331. https://doi.org/10.1002/CHEM.202200331.

[31] C. Hansch, A. Leo, R.W. Taft, A survey of Hammett substituent constants and resonance and field parameters, Chem. Rev. 91 (1991) 165–195. https://doi.org/10.1021/cr00002a004.

[32] J. Tomasi, B. Mennucci, R. Cammi, MEP: a tool for interpretation and prediction. From molecular structure to solvation effects, in: J.S. Murray, K.B.T.-T. and C.C. Sen (Eds.), Mol. Electrost. Potentials, Elsevier, 1996: pp. 1–103. https://doi.org/https://doi.org/10.1016/S1380-7323(96)80041-0.

[33] C.S. Calero, J. Farwer, E.J. Gardiner, C.A. Hunter, M. Mackey, S. Scuderi, S. Thompson, J.G. Vinter, Footprinting molecular electrostatic potential surfaces for calculation of solvation energies, Phys. Chem. Chem. Phys. 15 (2013) 18262–18273. https://doi.org/10.1039/C3CP53158A.

[34] D.P. Reynolds, M.C. Storer, C.A. Hunter, An empirical model for solvation based on surface site interaction points,

Chem. Sci. 12 (2021) 13193–13208. https://doi.org/10.1039/D1SC03392A.

[35] W.L.F. Armarego, C. Chai, Purification of laboratory chemicals, 5th ed., Elsevier: Oxford, 2003.

[36] V. Kumar, S.J. Connon, Direct, efficient NHC-catalysed aldehyde oxidative amidation: in situ formed benzils as unconventional acylating agents, Chem. Commun. 53 (2017) 10212–10215. https://doi.org/10.1039/C7CC05561G.

[37] A. Rahaman, A. Kumar Singh, A. Gupta, S. Bhadra, Catalytic N-Acylation of Cyclic Amines by Arylglyoxylic Acids via Radical-Radical Cross-Coupling, European J. Org. Chem. 2021 (2021) 2198–2202. https://doi.org/https://doi.org/10.1002/ejoc.202100381.

[38] H. Liang, Q. Liu, X. Zhao, T. He, J. Luo, S. Huang, Amidation of β-Keto Sulfonyl Fluorides via C−C Bond Cleavage, European J. Org. Chem. 27 (2024) e202400391. https://doi.org/https://doi.org/10.1002/ejoc.202400391.

[39] O.S. Liashuk, A. Fedinchyk, K.P. Melnykov, M. Herasymchuk, D. Alieksieieva, D. Lesyk, Y.P. Bas, T.Y. Keda, A. V. Yatsymyrskiy, Y. Holota, P. Borysko, V.S. Yarmolchuk, O.O. Grygorenko, 3,3-Difluorooxetane – A Versatile Functional Group for Bioisosteric Replacements in Drug Discovery, Chem. – A Eur. J. (2024) e202403277. https://doi.org/10.1002/CHEM.202403277.

[40] C. Adamo, M. Cossi, V. Barone, An accurate density functional method for the study of magnetic properties: the PBE0 model, J. Mol. Struct. THEOCHEM 493 (1999) 145–157. https://doi.org/https://doi.org/10.1016/S0166-1280(99)00235-3.

[41] F. Weigend, R. Ahlrichs, Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: Design and assessment of accuracy, Phys. Chem. Chem. Phys. 7 (2005) 3297–3305. https://doi.org/10.1039/B508541A.

[42] F. Neese, The ORCA program system, WIREs Comput. Mol. Sci. 2 (2012) 73–78. https://doi.org/https://doi.org/10.1002/wcms.81.

[43] F. Neese, Software update: the ORCA program system, version 4.0, WIREs Comput. Mol. Sci. 8 (2018) e1327. https://doi.org/10.1002/wcms.1327.

[44] F. Neese, Software update: The ORCA program system—Version 5.0, WIREs Comput. Mol. Sci. 12 (2022) e1606. https://doi.org/10.1002/wcms.1606.

[45] E.F. Pettersen, T.D. Goddard, C.C. Huang, G.S. Couch, D.M. Greenblatt, E.C. Meng, T.E. Ferrin, UCSF Chimera—A visualization system for exploratory research and analysis, J. Comput. Chem. 25 (2004) 1605–1612. https://doi.org/10.1002/jcc.20084.

4,4-Difluorospiro[2.2]pentan-1-yl – A Fluorinated Substituent to Expand the Synthetic and Medicinal Chemists' Toolbox

Dr. Kostiantyn P. Melnykov,[a,b] Olena V. Voloshyna,[a,b] Bohdan V. Vashchenko,[a,b] Oleksandr P. Demchuk,[a,c] Dr. Oleksandr V. Hryshchuk,[a,b] Prof. Dr. Oleksandr O. Grygorenko*[a,c]

Dedicated to the people of Ukraine

[a] Dr. K. P. Melnykov, O. V. Voloshyna, B. V. Vashchenko, O. P. Demchuk, Dr. O. V. Hryshchuk, Prof. Dr. O. O. Grygorenko
Enamine Ltd. (www.enamine.net),
Chervonotkatska Street 78, Kyiv 02094, Ukraine
[b] Dr. K. P. Melnykov, O. V. Voloshyna, B. V. Vashchenko, Dr. O. V. Hryshchuk, Prof. Dr. O. O. Grygorenko
Taras Shevchenko National University of Kyiv
Volodymyrska Street 60, Kyiv 01601, Ukraine
E-mail: gregor@univ.kiev.ua
[c] O. P. Demchuk,
Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanska Street 5, Kyiv 02660, Ukraine

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

Abstract: Functionalized 4,4-difluorospiro[2.2]pentan-1-yl derivatives are proposed as promising building blocks for synthetic and medicinal chemistry. Scalable, efficient, and diastereoselective approach to their preparation via the difluorocyclopropanation of (2-methylenecyclopropyl)methanol is developed. Stability of the title scaffolds towards common reaction conditions is confirmed by a series of typical functional group transformations. Physicochemical characteristics (pK_a, log*P*, and aqueous solubility) and structural features of the key 4,4-difluorospiro[2.2]pentan-2-yl derivatives are established and compared with those of non-fluorinated analog, 2,2-difluorinated isomer, as well as monocyclic *gem*-difluorinated counterparts.

Introduction

Modern organic and medicinal chemistry put great efforts toward conformationally restricted spirocycles.[1,2] Spiro-linkage of two saturated rings is widely represented among both natural products and synthetic compounds used in drug discovery.[3] The combination of three-dimensionality and conformational restriction provides privileged chemotypes with a well-defined spatial structure, which can improve the binding efficiency to the biological target.[4] For example, spiro[2.2]pentane (also known as [2]triangulane), the smallest and ultimately rigid spirocyclic system providing unusual spatial arrangement of substituents,[5] has two perfectly orthogonal cyclopropane rings and is therefore strongly relevant to the sp^3-enrichment design concept popular in medicinal chemistry in the last decades.[6,7] Examples of biologically active spiro[2.2]pentanes include nucleoside mimics (e.g., **1**),[8] lysine-specific demethylase 5A inhibitor **2** (IC_{50} = 0.078 nM),[9] or leucine-rich repeat kinase 2 (LRRK2) inhibitor **3** (IC_{50} = 0.6 nM) (Figure 1, *A*).

Another widely recognized possibility to improve the compound's physicochemical and pharmacokinetic parameters relies on the

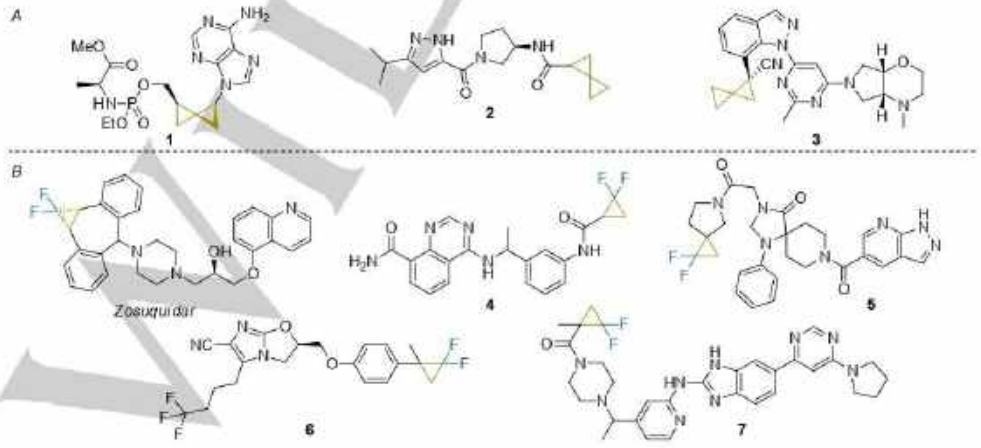
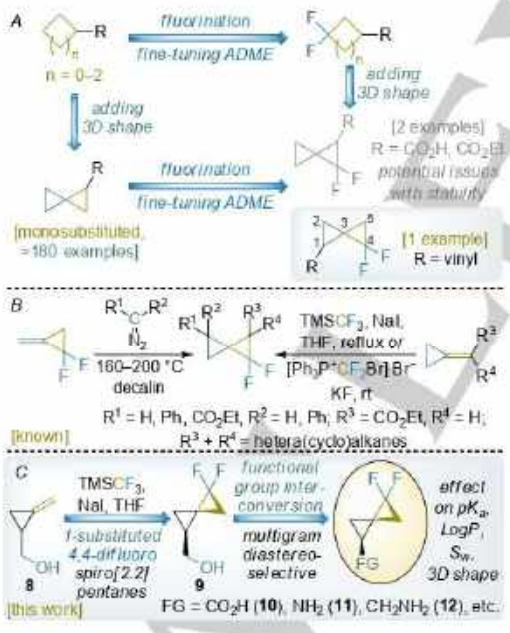


Figure 1. Pharmaceutically relevant spiro[2.2]pentanes (*A*) and *gem*-difluorocyclopropanes (*B*)

introduction of fluorine atoms.[10–13] Thus, *gem*-difluorinated cyclopropanes have attracted the attention of chemical community since the introduction of fluorine atoms causes significant changes in the geometry of the molecule and increases the ring strain energy.[14] *gem*-Difluorocyclopropanes have been also widely used in medicinal chemistry; their notable biologically active representatives include antineoplastic drug Zosuquidar,[15,16] Aurora kinase A inhibitor **4** (IC_{50} = 0.18 nM),[17] discoidin domain receptor 1 (DDR1) inhibitor **5**,[18] metabotropic glutamate receptor type 2 (mGluR2) modulator **6** (EC_{50} = 6.2 nM),[19] or TANK binding kinase 1 (TBK1) inhibitor **7** (IC_{50} = 0.86 nM)[20] (Figure 1, *B*).

In this context, *gem*-difluorospiro[2.2]pentane derivatives[21,22] can be considered very promising scaffolds for further implementations in drug discovery (Scheme 1, *A*). They can be considered as fluorinated analogs of spiro[2.2]pentanes, which in turn can be envisaged as a replacement for C_3–C_5 (cyclo)alkyl groups. On the other hand, the title substituent can be considered as a substitute for *gem*-difluorinated cycloalkanes that also have a very good track record in medicinal chemistry. Of the two theoretically possible monosubstituted *gem*-difluorospiro[2.2]pentane scaffolds, the 2,2-difluorinated isomer can have potential problems with unwanted reactivity due to the proximity of the fluorine atoms and the substituent. Meanwhile, its 4,4-difluorinated counterpart is more structurally attractive due to efficient use of both cyclopropane rings to provide the defined relative spatial orientation of the functional groups.



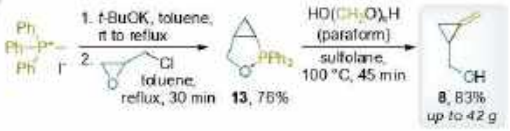
Scheme 1. (*A*) Design of 4,4-difluorospiro[2.2]pentan-1-yl scaffold; (*B*) known approaches to *gem*-difluorinated spiro[2.2]pentanes; (*C*) target building blocks of this study (relative configurations are shown)

Only a few representatives of mono- and polysubstituted *gem*-difluorinated spiro[2.2]pentanes were reported in the literature to date (Scheme 1, *B*). They were prepared by thermal cyclopropanation of 2,2-difluoromethylenecyclopropane with diazoalkanes[23] or by *gem*-difluorocyclopropanation of the corresponding alkenes using the $TMSCF_3$ – NaI system[24–27] or other reagents.[28–30] Allenes represent another interesting starting material type that have been used for the preparation of 1,1,4,4-tetrafluorospiro[2.2]pentanes.[31,32]

In this work, we have aimed at the development of a preparative and scalable method for the preparation of the title compounds via the *gem*-difluorocyclopropanation of (2-methylenecyclopropyl)methanol (**8**) (Scheme 1, *C*). Through further transformations of resulting key intermediate **9** to prepare the target building blocks (i.e., carboxylic acid **10**, amines **11** and **12**, organosulfur derivatives, etc.), tolerance of the *gem*-difluorospiro[2.2]pentane moiety to the common reaction conditions will be also assessed. To date, limited examples of such studies are available demonstrating thermal rearrangement into the fluorinated methylenecyclobutanes[22,32,33] and stability towards *N*-Boc-deprotection conditions.[24] In addition to that, we have aimed at evaluating structural and physicochemical properties of the title compounds (i.e., pK_a, Log*P*, aqueous solubility, and molecular geometry) in the context of their possible applications for isosteric replacements shown in Scheme 1, *A*.

Results and Discussion

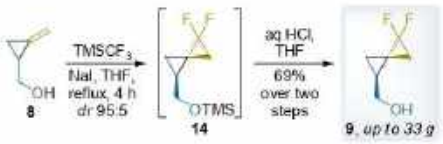
The synthesis of (2-methylenecyclopropyl)methanol (**8**) relied on the known Wittig-type reaction of oxaphospholane **13** with paraform in sulfolane at 100 °C (Scheme 2). The known preparation of oxaphospholane **13** included NaH-mediated recyclization of epichlorohydrin with methyltriphenylphosphonium iodide.[34–36] Using *t*-BuOK as a base at this step appeared to be more beneficial upon the scale-up, and we successfully obtained up to 42 g of product **8** (63% yield over two steps) in a single run using this slightly modified protocol.



Scheme 2. Synthesis of (2-methylenecyclopropyl)methanol (**8**)

The next step included optimization of the methylenecyclopropane double bond *gem*-difluorocyclopropanation for the preparation of (4,4-difluoro-spiro[2.2]pentan-1-yl)methanol (**9**) as the key intermediate to obtain all other functionalized derivatives (Scheme 3). We used the $TMSCF_3$ – NaI system in THF at reflux – a method initially introduced by Prakash and Hu.[27] As shown previously, the decomposition of the Rupert-Prakash reagent can occur faster than the difluorocyclopropanation reaction in the case of less reactive alkenes, resulting in low conversion thereof.[25,26] In this case, the "slow addition" protocol should be applied. With substrate **8**, the reaction appeared to be especially capricious. While the initial alcohol *O*-silylation occurred without problems, often, initiation of the *gem*-difluorocyclopropanation step did not happen even after addition of a substantial part of the reagent, which could become dangerous upon scale-up due

to further uncontrolled proceeding. We have found empirically that if the reaction initiation did not occur after the addition of the first 1.1–1.2 eq of $TMSCF_3$, filtering out the precipitate formed, evaporating the reaction mixture to nearly half of its volume, re-initiation by adding new portions of THF and NaI, and then continuing the slow addition of $TMSCF_3$ was beneficial. This observation is in agreement with the complex (and still fully not understood) initiation mechanism of the process.[37]

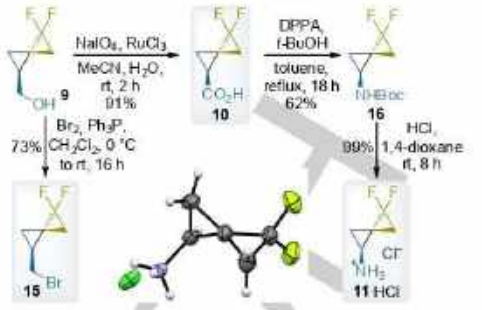


Scheme 3. Synthesis of (4,4-difluorospiro[2.2]pentan-1-yl)methanol (**9**) (relative configurations are shown)

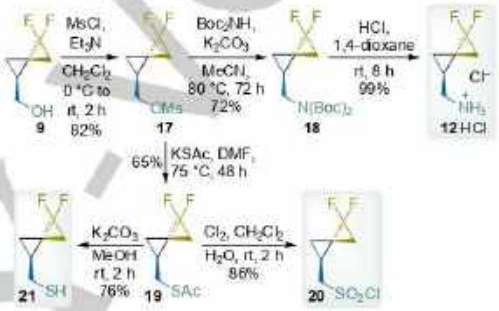
With all the above precautions, target product **9** could be obtained on up to 33 g scale in 69% yield after *O*-desilylation of intermediate **14** and further distillation. Notably, the reaction proceeded in a diastereoselective manner (*dr* ≥95:5), which is in accordance with the literature precedents for similar systems.[24] Compound **9** was used to obtain all other 4,4-difluorospiro[2.2]pentan-1-yl building blocks described in this work. Thus, alcohol **9** was introduced into the Appel reaction with Br_2 and PPh_3, which provided bromide **15** in 73% yield (Scheme 4). Oxidation of compound **9** with $NaIO_4$ – $RuCl_3$ in the MeCN – H_2O gave carboxylic acid **10** as a single diastereomer in 91% yield. Then, compound **10** was subjected to the Curtius reaction using diphenylphosphoryl azide (DPPA) in toluene – *tert*-butanol at 100 °C, which allowed for the preparation of *N*-Boc-protected amine **16** (62% yield). The carbamate protecting group was cleaved by treatment of *N*-Boc-protected amine **16** with HCl – 1,4-dioxane, which led to hydrochloride **11**·HCl. The structure of this product was confirmed by X-Ray diffraction studies, which also enabled the establishment of (±)-(1*S*,3*R*) relative configuration in all the compounds obtained.

Mesylate **17** (obtained from alcohol **9** by sulfonylation with MsCl in the presence of Et_3N) was used for the preparation of homologous primary amine **12** as a single diastereomer (Scheme 5). To achieve this, derivative **17** was involved into the nucleophilic substitution with Boc_2NH and K_2CO_3 in MeCN at 80 °C, which provided di-*N*-Boc-substituted amine **18** in 72% yield. Compound **18** was then involved into the acid-mediated cleavage of the protective groups to give (4,4-difluorospiro[2.2]pentan-1-yl)methanaminium chloride (**12**·HCl). Alternatively, mesylate **17** was introduced into a nucleophilic substitution reaction with KSAc in DMF at 75 °C to obtain thioacetate **19** in 65% yield. The subsequent oxidative chlorination of compound **19** with Cl_2 in CH_2Cl – H_2O proceeded smoothly and gave sulfonyl chloride **20** (86% yield). Also, we have performed the hydrolysis of thioacetate with K_2CO_3 in MeOH, which afforded thiol **21** in 76% yield.

Notably, in all of the above (and further) transformations, the 4,4-difluorospiro[2.2]pentan-1-yl moiety remained intact, which is a demonstration of its considerable stability.



Scheme 4. Preparation of bromide **15**, carboxylic acid **10**, and amine **11**·HCl (relative configurations and ORTEP diagram of **11**·HCl of are shown)



Scheme 5. Synthesis of amine **11**, sulfonyl chloride **20**, and thiol **21** (relative configurations are shown)

To reveal the potential of the synthesized building blocks for early drug discovery, we have measured physicochemical and structural characteristics for their model derivatives and compared them to those of possible isosteric replacement targets. In particular, the dissociation constant (pK_a) values were measured for carboxylic acids **10**, **22a**, and **23a**, as well as protonated amines **11** and **22b** (for isomeric derivative **23b**, the pK_a value could not be determined due to instability of the compound as a free base) and compared to those of monocyclic compounds **24a**–**31b**[38,39] (Table 1). Also, model anilides and *N*-benzoyl derivatives were obtained from the above compounds (see the Experimental Section for more details). Log*P* and aqueous solubility (S_w) were measured for these derivatives and compared with those for monocyclic counterparts **24c**–**31d**.[38,39] The obtained results are in line with the previous observations on the *gem*-difluorination of cycloalkane derivatives.[39,40] In particular, compounds **10** and **11** have pK_a values by 0.78 and 1.97 units lower than parent spiro[2.2]pentane derivatives **22a** and **22b**, respectively, which is similar to the monocyclic compounds bearing the CF_2 unit at the γ position to the functional group ($-\Delta pK_a$ = 0.7±0.2 and 1.4±0.3, respectively). The effect of the *gem*-difluorination on the lipophilicity is less obvious: while anilide **24** is by 0.31 Log*P* units more lipophilic than non-fluorinated analog **22c**, *N*-benzoyl derivative **25** has slightly lower Log*P* value as compared to **22d** (by 0.04 units). The dependance of ΔLog*P* upon *gem*-difluorination on the substituent present in the cyclic system, especially for the cyclo-

Table 1. pK_a values for carboxylic acids RCO_2H and protonates amines RNH_2 (H_2O, 21 °C), as well as Log*P* and S_w values for their model derivatives (21 °C)

R	R–CO_2H	pK_a[a]	R–NH_2	pK_a[a,c]	R–C(O)NHPh[d]	Log*P*[a]	S_w, g/L[a]	R–NHBz	Log*P*[a]	S_w, g/L[a]
	24a	4.60±0.02	**24b**	8.76±0.06	**24c**	1.92±0.01	0.97±0.01	**24d**	1.29±0.01	3.91±0.03
	25a	3.25±0.03	**25b**	–[b]	**25c**	2.07±0.01	0.99±0.03	**25d**	1.51±0.01	0.78±0.02
	26a	4.50±0.05	**26b**	9.86±0.08	**26c**	2.26±0.03	0.359±0.004	**26d**	1.95±0.01	0.82±0.02
	27a	3.62±0.05	**27b**	7.20±0.02	**27c**	2.03±0.01	0.73±0.01	**27d**	1.70±0.01	0.451±0.002
	28a	4.02±0.02	**28b**	8.37±0.03	**28c**	2.26±0.01	0.066±0.002	**28d**	1.94±0.01	0.231±0.002
	29a	4.69±0.06	**29b**	10.52±0.07	**29c**	2.68±0.01	0.046±0.001	**29d**	2.23±0.01	0.276±0.02
	30a	3.76±0.04	**30b**	7.54±0.01	**30c**	2.25±0.01	0.48±0.01	**30d**	1.87±0.02	0.218±0.006
	31a	3.98±0.09	**31b**	8.83±0.03	**31c**	2.50±0.02	0.121±0.001	**31d**	2.02±0.01	0.348±0.002
	22a	4.61±0.05	**22b**	9.41±0.04	**22c**[e]	2.35±0.07	0.048±0.001	**22d**[e]	2.08±0.01	0.77±0.03
	23a	3.51±0.04	**23b**	–[b]	**23c**[e]	2.42±0.01	0.050±0.001	**23d**[e]	2.14±0.01	0.060±0.001
	10	3.85±0.06	**11**	7.44±0.05	**24**[e]	2.66±0.01	0.094±0.007	**25**[e]	2.04±0.01	0.326±0.002

[a] Data for compounds **25a–32d** are taken from refs.[38,39] [b] For the conjugated acid [c] RC(O)NHPh [d] Could not be determined due to instability of the free base [e] The method for the preparation and the synthetic scheme are provided in the Experimental Part and the Supporting Information file, respectively.

propane derivatives, has been already outlined previously by us.[39,40] Similar (but opposite) effects were observed for aqueous solubility (S_w): while **24** was nearly twice more soluble than **22c**, **25** – nearly twice less than **22d**.

Depiction of the obtained results in the Log*P* – pK_a coordinates reveals that the 4,4-difluorospiro[2.2]pentyl substituent tends towards the upper right corner of the plot (i.e., less basic and less hydrophilic compounds, Figure 2). The closest data points correspond to 2,2-difluorocyclobutyl and 2,2-difluorocyclopentyl derivatives. Unlike the latter compounds, however, 4,4-difluorospiro[2.2]pentanes are not prone to HF elimination and can be therefore considered as a more stable alternative.

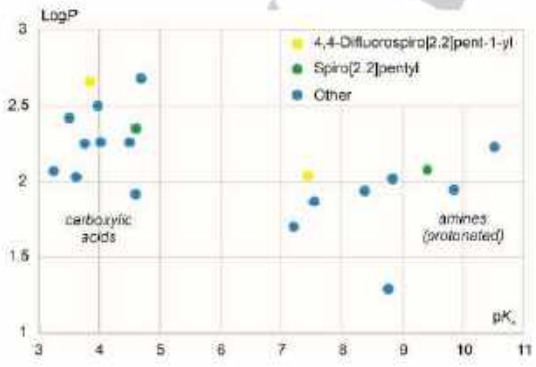


Figure 2. The compounds of this study depicted in the Log*P* – pK_a plot

On the other hand, there are data points that differ from the 4,4-difluorospiro[2.2]pentyl derivatives by only one of the parameters. For example, cyclopentyl derivatives have close Log*P* but very different pK_a values. These results can provide a background for rational isosteric replacements with controlled physicochemical parameters.

To discuss molecular geometry of the title compounds and their monocyclic counterparts, exit vector plot (EVP) tool can be applied.[41,42] In this approach, the functional group (R) attached to the scaffold and the CF_2 moiety can be simulated by two "exit" vectors $\boldsymbol{n}_1$ and $\boldsymbol{n}_2$ (defined by the C–R bond and a bisector of the F–C–F angle, respectively, Figure 3, *A*). The relative orientation of these vectors can be explicitly defined by four geometric parameters *r*, φ_1, φ_2, and θ, defined as shown in Figure 3, *B*. Higher values of angular parameters φ_1, φ_2, as well as absolute values of θ being far from 0° and 180° are characteristic for more three-dimensional structures.

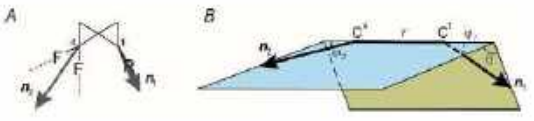


Figure 3. (A) Definition of exit vectors $\boldsymbol{n}_1$ and $\boldsymbol{n}_2$; (B) definition of geometric parameters *r*, φ_1, φ_2, and θ

The parameters *r*, φ_1, φ_2, and θ for the 4,4-difluorospiro[2.2]-pentane derivatives can be extracted from the experimentally

obtained molecular structure of compound **11**·HCl. The obtained results demonstrate high three-dimensionality (and, obviously, somewhat larger size) of the title scaffold as compared to the previously published data for cyclobutane derivatives **27b**·HCl and **28b**·HCl (Figure 4).[36]



Figure 4. Geometric parameters *r*, φ_1, φ_2, and θ for compounds **11**·HCl, **27b**·HCl, and **28b**·HCl according to X-ray diffraction studies (absolute values of θ are given; for **27b**·HCl, the values are average from two conformers)

Conclusions

gem-Difluorocyclopropanation of (2-methylenecyclopropyl)methanol provides an efficient, scalable, and diastereoselective entry into 4,4-difluorospiro[2.2]pentan-1-yl derivatives. Using the optimized protocols, the product of this reaction, (±)-(1*S*,3*R*)-(4,4-difluorospiro[2.2]pentan-1-yl)methanol, can be prepared on up to 33 g scale in a single run; higher loading under the batch conditions is not recommended due to the safety reasons. Further functional group transformations demonstrated stability of the title scaffolds towards common reaction conditions and allowed for the preparation of several building blocks useful for synthetic and medicinal chemistry (i.e. carboxylic acid, primary amines, bromide, thiol, and sulfonyl chloride). All these compounds were obtained in good yields (62–95% per step) on a gram scale. Provided that the first step can be applied to readily available (*R*)- or (*S*)-epichlorohydrin with retention of the compound's optical activity,[34] the proposed method is also potentially extendable for the preparation of enantiopure 4,4-difluorospiro[2.2]pentan-1-yl derivatives.

Physicochemical characteristics (i.e., pK_a, Log*P*, and aqueous solubility) of 4,4-difluorospiro[2.2]pentan-1-yl derivatives along with parameters of non-fluorinated and monocyclic counterparts provide a rationale for further isosteric replacements using the title scaffold. In particular, similarity to 2,2-difluorocyclobutyl, 2,2-difluorocyclopentyl, and the parent cyclopentyl moieties can be envisaged. Exit vector plot (EVP) analysis of 4,4-difluorospiro[2.2]pentane confirms its remarkable three-dimensionality and uncommon molecular geometry. Taking into account the substantially increased accessibility of the title building blocks, we believe that they will find an extensive application in early drug discovery projects in the nearest future, just as their monocyclic *gem*-difluorinated counterparts.

Experimental Section

The solvents were purified according to the standard procedures.[43] All starting materials were available from Enamine Ltd. or purchased from other commercial sources. Melting points were measured on MPA100 OptiMelt automated melting point system. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR and 470 MHz for ^{19}F NMR) and Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6. Coupling constants (*J*) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)). Physicochemical characteristics were measured as described elsewhere.[38] CCDC 2190852 contain (**11**·HCl) the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

2,2,2-Triphenyl-3-oxa-2λ^6-phosphabicyclo[3.1.0]hexane (13).[34-36] *t*-BuOK (167 g, 1.48 mol) was added in portions to the suspension of triphenylmethylphosphonium iodide (600 g, 1.48 mol) in dry toluene (2500 mL) at rt. The resulting mixture was heated to reflux, then epichlorohydrin (68.7 g, 0.747 mol) in toluene (150 mL) was added upon vigorous stirring (a mechanical stirrer is preferable). After 30 min, the resulting suspension was cooled and filtered, and solvents were evaporated *in vacuo*. The crude product was purified by recrystallization from dry MeCN (300 mL). Yield 188 g (76%); colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.30 (m, 6H), 7.33 – 6.98 (m, 9H), 3.61 (dd, *J* = 14.2, 8.8 Hz, 1H), 3.04 (dd, *J* = 8.8, 3.1 Hz, 1H), 1.87 – 1.72 (m, 1H), 1.54 – 1.45 (m, 1H), 1.47 – 1.31 (m, 1H), 1.22 (dtd, *J* = 12.3, 8.2, 3.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 130.5 (d, *J* = 8.4 Hz), 127.1, 127.0, 126.9, 57.4, 14.2, 11.3 (d, *J* = 140 Hz), 6.6 (d, *J* = 5.2 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ –57.1. LC/MS (ES-API): *m/z* = 333 $[M+H]^+$. Anal. Calcd. for $C_{22}H_{21}OP$: C 79.50; H 6.37. Found: C 79.31; H 6.38.

(2-Methylenecyclopropyl)methanol (8). A mixture of **13** (200 g, 0.602 mol) and paraformaldehyde (36.2 g, 1.20 mol) in sulfolane (100 mL) was heated to 100 °C for 45 min. Alcohol **8** was distilled out *in vacuo*; a fraction with bp 45–65 °C / 2 mmHg was collected. The second distillation *in vacuo* afforded pure **8**. Yield 42.0 g (83%); colorless oil, bp 42–43 °C / 1 mbar. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 – 5.32 (m, 2H), 3.57 (dd, *J* = 11.2, 6.2 Hz, 1H), 3.39 (dd, *J* = 11.2, 7.7 Hz, 1H), 3.03 (s, 1H), 1.84 – 1.59 (m, 1H), 1.26 (tt, *J* = 8.8, 2.2 Hz, 1H), 1.03 – 0.81 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.5, 103.6, 64.7, 17.4, 7.6. GC/MS (EI): *m/z* = 83 $[M]^+$. Anal. Calcd. for C_5H_8O: C 71.39; H 9.59. Found: C 71.76; H 9.51.

(±)-(1*S*,3*R*)-(4,4-Difluorospiro[2.2]pentan-1-yl)methanol (9). $TMSCF_3$ (101 g, 0.713 mol) was added very slowly dropwise to the refluxed mixture of **8** (30.0 g, 0.357 mol) and NaI (18.7 g, 0.125 mol) in THF (450 mL). CAUTION! $TMSCF_3$ should be added very slowly and carefully over 1.5 h since the reaction can occur vigorously after addition of 1.1–1.2 eq of reagent. At the first step, silylation of the hydroxyl group of **2** occurred according to ^{1}H NMR spectra. If the difluorocyclopropanation did not start then after adding 1.1–1.2 eq of the reagent, and the formation of precipitate was observed, the reaction mixture was cooled to rt, the precipitate was filtered off, and the filtrate evaporated *in vacuo* by 50–75% of initial volume (the temperature of a water bath was kept below 30 °C). THF (200–300 mL) and fresh NaI (18.7 g, 0.125 mol) were added, the resulting mixture was heated to reflux once again, and slow addition of $TMSCF_3$ was continued to ensure the reaction initiation. When all the amount of $TMSCF_3$ was added, the reaction mixture was refluxed for 1 h. Then, an additional portion of $TMSCF_3$ (101 g, 0.713 mol) was added very slowly over 3 h dropwise under reflux. When all amount of $TMSCF_3$ was added, the reaction mixture was refluxed for 1 h. Upon the completion of the conversion (monitored by ^{1}H NMR spectra of aliquots), the reaction mixture was cooled to rt, filtered, and evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (300 mL), the precipitate was

filtered off, and the filtrate was evaporated in *vacuo*. Product **14** was used in the next step without additional purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 – 3.48 (m, 2H), 1.73 – 1.49 (m, 3H), 1.36 – 1.25 (m, 1H), 0.99 – 0.88 (m, 1H), 0.09 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 113.4 (t, *J* = 285 Hz), 64.1 (d, *J* = 3.1 Hz), 19.5 (t, *J* = 15.4 Hz), 14.5 (t, *J* = 11.2 Hz), 11.2, 1.9, –0.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ –135.0 (d, *J* = 151 Hz), –135.5 (d, *J* = 151 Hz). GC/MS (EI): *m/z* = 134 [M]$^+$.

The crude silyl ether **14** (ca. 0.357 mol) from the previous step was dissolved in THF (700 mL), and diluted aq HCl (3 mL of conc. aq HCl in 90 mL H_2O) was added. The resulting mixture was stirred at rt for 30 min; the reaction progress was monitored by ^{1}H NMR spectra. After the disappearance of the TMS signal, the reaction mixture was diluted with H_2O (350 mL) and Et_2O (350 mL). The aqueous layer was separated and extracted with Et_2O (350 mL). The combined organic layers were washed with H_2O (350 mL) and brine (350 mL), dried over Na_2SO_4, filtered, and evaporated in *vacuo*. The residue was distilled in *vacuo*. Yield 32.8 g (69%, *dr* ≥95:5), colorless oil; bp 32–34 °C / 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 – 3.57 (m, 2H), 1.82 – 1.73 (m, 1H), 1.73 – 1.67 (m, 1H), 1.66 – 1.44 (m, 2H), 1.36 (dd, *J* = 8.2, 5.0 Hz, 1H), 0.99 (dt, *J* = 8.3, 5.1 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 113.3 (t, *J* = 285 Hz), 64.1 (d, *J* = 4.3 Hz), 19.5, 19.4 (t, *J* = 11.4 Hz), 14.5 (t, *J* = 11.3 Hz), 10.7 (d, *J* = 1.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –135.01 (d, *J* = 150.7 Hz), –135.64 (d, *J* = 150.8 Hz). GC/MS (EI): *m/z* = 117 [M–OH]$^+$, 134 [M]$^+$. Anal. Calcd. for $C_6H_8F_2O$: C 53.73; H 6.01. Found: C 53.42; H 5.83.

(±)-(1*S*,3*R*)-4,4-Difluorospiro[2.2]pentane-1-carboxylic acid (10). $RuCl_3{\cdot}H_2O$ (230 mg, 1.01 mmol) and $NaIO_4$ (53.9 g, 0.252 mol) were added in portions to a solution of **9** (13.5 g, 0.101 mol) in MeCN – H_2O (260 mL, 1:1, v/v) at rt. The reaction mixture was stirred at rt for 3 h, then the solid was filtered and washed with EtOAc (100 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated in *vacuo*. The residue was dissolved in CH_2Cl_2 (200 mL), dried over Na_2SO_4, filtered, and evaporated in *vacuo*. Yield 13.4 g (90%); colorless crystals, mp 96–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.13 (s, 1H), 2.30 (dd, *J* = 7.9, 5.2 Hz, 1H), 1.96 – 1.84 (m, 1H), 1.84 – 1.76 (m, 1H), 1.76 – 1.65 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.7, 112.6 (t, *J* = 287 Hz), 23.2 (t, *J* = 11.5 Hz), 19.8, 16.3 (t, *J* = 11.2 Hz), 14.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ –135.0, –135.0. GC/MS (EI): *m/z* = 131 [M–OH]$^+$, 148 [M]$^+$. Anal. Calcd. for $C_6H_6F_2O_2$: C 48.66; H 4.08. Found: C 48.42; H 3.77.

4-(Bromomethyl)-1,1-difluorospiro[2.2]pentane (15). Br_2 (28.4 g, 9.10 mL, 0.177 mol) was added dropwise to a stirred ice-cooled solution of Ph_3P (46.9 g, 0.179 mol) in CH_2Cl_2 (240 mL) maintaining the internal temperature below 10 °C. The resulting suspension was stirred at 0 °C for 45 min, then Et_3N (18.3 g, 25.2 mL, 0.180 mmol) was added, and the reaction mixture was stirred at 0 °C for 15 min. Next, the solution of alcohol **9** (20.0 g, 0.149 mol) in CH_2Cl_2 (30 mL) was added dropwise at 0 °C, and the reaction mixture was allowed to warm to rt and stirred for 16 h. Then, the reaction mixture was slowly diluted with water (300 mL), the organic layer was separated, washed with saturated aq Na_2CO_3 (100 mL), dried over Na_2SO_4, filtered, and concentrated at atmospheric pressure. The residue was triturated with pentane (250 mL), filtered, and washed with pentane (2 × 50 mL). The combined filtrate was concentrated at atmospheric pressure, and the residue was distilled in *vacuo*. Yield 21.4 g (73%, *dr* ≥95:5); colorless liquid; bp 55–56 °C / 19–20 mBar. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (dd, *J* = 10.3, 6.4 Hz, 1H), 3.28 (dd, *J* = 10.3, 8.3 Hz, 1H), 2.04 – 1.92 (m, 1H), 1.85 (td, *J* = 7.8, 3.0 Hz, 1H), 1.67 – 1.56 (m, 1H), 1.52 (dd, *J* = 8.3, 5.3 Hz, 1H), 1.10 – 0.99 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 112.2 (t, *J* = 285 Hz), 34.0, 33.9, 22.1 (t, *J* = 11.4 Hz), 19.4, 14.1, 13.6 (t, *J* = 11.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –135.1 (d, *J* = 152 Hz), –135.6 (d, *J* = 152 Hz). GC/MS (EI): *m/z* = 117 [M–HBr]$^+$, 196/198 [M]$^+$. Anal. Calcd. for $C_6H_7BrF_2$: C 36.58; H 3.58; Br 40.56. Found: C 36.61; H 3.43; Br 40.23.

***tert*-Butyl (±)-(1*S*,3*R*)-(4,4-difluorospiro[2.2]pentan-1-yl)carbamate (16).** 4,4-Difluorospiro[2.2]pentane-1-carboxylic acid (**10**, 5.43 g, 36.0 mmol) was dissolved in toluene (50 mL), and DPPA (11.8 g, 43.2 mmol), *t*-BuOH (26.0 g, 0.360 mol) were added. Then, Et_3N (6.50 mL, 46.8 mmol) was added dropwise, and the resulting mixture was heated at 80 °C overnight. Volatiles were evaporated in *vacuo*, and CH_2Cl_2 (100 mL) was added. The mixture was washed with 15% aq NaOH (2 × 50 mL), organic layer was dried oved Na_2SO_4, filtered, and evaporated in *vacuo*. The crude product was purified by flash column chromatography on silica gel using hexanes – EtOAc (6:1, v/v) as an eluent. Yield 4.80 g (62%); colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.70 (s, 1H), 3.27 – 3.02 (m, 1H), 1.74 (t, *J* = 8.5 Hz, 1H), 1.63 (t, *J* = 8.1 Hz, 1H), 1.59 – 1.54 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.9, 113.0 (t, *J* = 286 Hz), 80.0, 28.5, 28.2, 14.8 (t, *J* = 11.5 Hz), 14.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ –134.6 (d, *J* = 151 Hz), –135.4 (d, *J* = 151 Hz). Anal. Calcd. for $C_{10}H_{15}F_2NO_2$: C 54.79; H 6.90; N 6.39. Found: C 54.75; H 7.26; N 6.65.

(±)-(1*S*,3*R*)-4,4-Difluorospiro[2.2]pentan-1-aminium chloride (11). 4 M HCl in 1,4-dioxane (25 mL) was added to a solution of **16** (4.80 g, 21.9 mmol) in 1,4-dioxane (25 mL). The reaction mixture was stirred at rt overnight, then evaporated in *vacuo* to half of volume, and the residue was diluted with Et_2O (50 mL). The mixture was cooled to 4 °C for 3 h, the precipitate was filtered and washed with Et_2O (2 × 25 mL). Yield 3.27 g (96%); colorless solid; mp 185–187 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (s, 3H), 3.20 (dd, *J* = 6.8, 4.6 Hz, 1H), 2.04 (td, *J* = 8.7, 3.1 Hz, 1H), 1.96 – 1.89 (m, 1H), 1.65 – 1.49 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 113.2 (dd, *J* = 287, 284 Hz), 26.8, 17.9 (dd, *J* = 12.6, 10.7 Hz), 14.9 (t, *J* = 11.3 Hz), 11.0. ^{19}F NMR (376 MHz, DMSO-d_6) δ –133.2 (d, *J* = 150 Hz), –133.9 (d, *J* = 150 Hz). LC/MS (ES-API): *m/z* = 120 [M–HCl+H]$^+$. Anal. Calcd. for $C_5H_8ClF_2N$: C 38.60; H 5.18; N 9.00; Cl 22.79. Found: C 38.50; H 4.79; N 8.92; Cl 22.48.

(±)-(1*S*,3*R*)-(4,4-Difluorospiro[2.2]pentan-1-yl)methyl methanesulfonate (17). MsCl (15.0 mL, 0.189 mol) was added dropwise at 0 °C to a solution of (4,4-difluorospiro[2.2]pentan-1-yl)methanol (**9**, 23.0 g , 0.172 mol) and triethylamine (30.0 mL, 0.206 mol) in CH_2Cl_2 (250 mL). The mixture was stirred at rt for 1 h, then washed with citric acid (100 mL) and $NaHCO_3$ (100 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated in *vacuo*. Yield 29.9 g (82%); yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.32 (dd, *J* = 10.8, 6.6 Hz, 1H), 4.11 (dd, *J* = 10.8, 7.9 Hz, 1H), 3.01 (s, 3H), 1.96 – 1.86 (m, 1H), 1.74 (t, *J* = 8.3 Hz, 1H), 1.64 (t, *J* = 7.9 Hz, 1H), 1.47 (dd, *J* = 8.3, 5.3 Hz, 1H), 1.10 (dt, *J* = 8.3, 5.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 111.9 (t, *J* = 285 Hz), 70.8 (d, *J* = 4.8 Hz), 37.4, 19.4 (t, *J* = 11.5 Hz), 15.9, 14.1 (t, *J* = 11.6 Hz), 10.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ –135.0 (d, *J* = 152 Hz), –135.8 (d, *J* = 152 Hz). LC/MS (ES-API): *m/z* = 213 [M+H]$^+$. Anal. Calcd. for $C_7H_{10}F_2O_3S$: C 39.62; H 4.75; S 15.11. Found: C 39.72; H 4.82; S 14.73.

***di-tert*-Butyl (±)-(1*S*,3*R*)-((4,4-difluorospiro[2.2]pentan-1-yl)methyl)-dicarbamate (18).** Mesylate **17** (52.0 g, 0.245 mol) was dissolved in MeCN (500 mL), then K_2CO_3 (50.7 g, 0.367 mol) and *di-tert*-butyl-2-imidodicarbonade (58.5 g, 0.270 mmol) were added. The reaction mixture was stirred at 80 °C for 48 h, then cooled to rt, the precipitate was filtered off, and the filtrate was evaporated in *vacuo*. The crude product was purified by flash column chromatography on silica gel using hexanes – EtOAc (15:1, v/v) as an eluent. Yield 58.0 g (73%); yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (dd, *J* = 14.3, 6.1 Hz, 1H), 3.55 (dd, *J* = 14.3, 7.2 Hz, 1H), 1.86 – 1.74 (m, 1H), 1.67 – 1.61 (m, 1H), 1.58 – 1.52 (m, 1H), 1.47 (s, 18H), 1.25 (dd, *J* = 8.4, 4.8 Hz, 1H), 1.07 – 0.93 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7, 113.4 (t, *J* = 285 Hz), 82.5, 47.4 (t, *J* = 1.7 Hz), 28.0, 19.9 (t, *J* = 11.2 Hz), 17.5, 15.0 (t, *J* = 11.4 Hz), 11.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ –135.3. Anal. Calcd. for $C_{16}H_{25}F_2NO_4$: C 57.65; H 7.56; N 4.20. Found: C 57.44; H 7.74; N 4.27.

(±)-(1*S*,3*R*)-(4,4-Difluorospiro[2.2]pentan-1-yl)methanaminium chloride (12). 4 M HCl in 1,4-dioxane (500 mL) was added dropwise to the solution of **18** (58.0 g, 0.174 mol) in 1,4-dioxane (500 mL). The reaction mixture was stirred at rt overnight, then evaporated in *vacuo* to quarter of volume, and the residue was diluted with Et_2O (500 mL). The mixture was cooled to 4 °C for 3 h, the precipitate was filtered and washed with Et_2O (2 × 250 mL). Yield 27.7 g (94%). Colorless solid, mp

196–197 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 3H), 2.91 (dd, J = 13.2, 6.6 Hz, 1H), 2.72 (dd, J = 13.2, 7.5 Hz, 1H), 2.58 – 2.51 (m, 1H), 2.09 (t, J = 8.6 Hz, 1H), 1.85 – 1.58 (m, 2H), 1.38 (dd, J = 8.6, 4.9 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 114.4 (t, J = 285 Hz), 41.1 (d, J = 4.7 Hz), 20.2 (t, J = 10.8 Hz), 15.4, 14.6 (t, J = 10.9 Hz), 11.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ –132.7 (d, J = 148 Hz), –133.5 (d, J = 148 Hz). LC/MS (ES-API): m/z = 134 [M–HCl+H]$^+$. Anal. Calcd. for $C_6H_{10}ClF_2N$: C 42.49; H 5.94; N 8.26; Cl 20.90. Found: C 42.38; H 6.16; N 8.33; Cl 20.52.

(±)-(1*S*,3*R*)-*S*-((4,4-Difluorospiro[2.2]pentan-1-yl)methyl) ethanethioate (19). (4,4-Difluorospiro[2.2]pentan-1-yl)methyl methanesulfonate (**17**, 23.7 g, 0.111 mol) was dissolved in DMF (300 mL), and KSAc (25.5 g, 0.223 mol) was added. The reaction mixture was stirred at 75 °C for 48 h, then cooled to rt, diluted with EtOAc (300 mL), and washed with brine (4 × 200 mL). Organic layer was dried over Na_2SO_4, filtered, and evaporated in *vacuo*. The crude product was distilled in *vacuo*. Yield 13.9 g (65%); yellow liquid; 50–52 °C / 0.2 mbar. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (dd, J = 13.8, 6.8 Hz, 1H), 2.80 (dd, J = 13.8, 7.4 Hz, 1H), 2.29 (s, 3H), 1.61 – 1.56 (m, 2H), 1.52 (td, J = 7.6, 2.2 Hz, 1H), 1.32 (dd, J = 8.2, 5.1 Hz, 1H), 0.91 (dt, J = 7.8, 5.1 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 195.2, 113.1 (t, J = 285.2 Hz), 31.1 (d, J = 4.0 Hz), 30.4, 21.2 (t, J = 11.3 Hz), 17.4 (d, J = 1.2 Hz), 14.5 (t, J = 11.5 Hz), 13.2 (d, J = 2.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –134.7 (d, J = 151 Hz), –135.3 (d, J = 151 Hz). GC/MS (EI): 192 (M$^+$). Anal. Calcd. for $C_8H_{10}F_2OS$: C 49.99; H 5.24; S 16.68. Found: C 50.14; H 5.56; S 17.03.

(±)-(1*S*,3*R*)-(4,4-Difluorospiro[2.2]pentan-1-yl)methanesulfonyl chloride (20). Gaseous Cl_2 was bubbled through the solution of thioacetate (15.0 g, 0.780 mol) in CH_2Cl_2 – H_2O (250 mL, 3:2, v/v) at 10 °C for 30 min. The reaction mixture was stirred for additional 30 min, and argon was bubbled through the resulting mixture for 5 min. Then, organic layer was separated, aqueous layer was reextracted with CH_2Cl_2 (2 × 50 mL). Combined organic layers were washed with brine (2 × 75 mL), dried over Na_2SO_4, filtered, and evaporated in *vacuo*. The residue was dried in *vacuo* for 30 min. Yield 14.6 g (86%); yellow oil, which crystalized at –20 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (d, J = 7.1 Hz, 2H), 2.14 – 2.05 (m, 1H), 1.88 – 1.80 (m, 1H), 1.72 – 1.62 (m, 2H), 1.29 – 1.17 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 111.5 (t, J = 286 Hz), 67.0 (d, J = 4.0 Hz), 19.9 (t, J = 11.6 Hz), 14.4 (t, J = 11.7 Hz), 12.3, 11.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ –134.9 (d, J = 153 Hz), –135.5 (d, J = 153 Hz). LC/MS (ES-API): m/z = 197 [sulfonic acid–H]$^-$. Anal. Calcd. for $C_6H_7ClF_2O_2S$: C 33.27; H 3.26; S 14.80; Cl 16.36. Found: C 33.22; H 2.99; S 14.96; Cl 16.13.

(±)-(1*S*,3*R*)-(4,4-Difluorospiro[2.2]pentan-1-yl)methanethiol (21). All operations were performed under argon atmosphere. K_2CO_3 (43.1 g, 0.312 mol) was added to the solution of thioacetate (**14**, 20.0 g, 0.104 mol) in MeOH (150 mL). The mixture was vigorous stirred for 2 h; the completion of the reaction was monitored by NMR. Then, the reaction mixture was evaporated in *vacuo* at 32 °C, and the residue was diluted with H_2O (300 mL). Saturated aq $NaHSO_4$ (600 mL) was added upon stirring, and the resulting mixture was extracted with Et_2O (4 × 200 mL). Combined organic layers were dried over Na_2SO_4 upon stirring for 20 min, then filtered, evaporated in *vacuo* at 30 °C. The residue was distilled in *vacuo*. Yield 11.9 g (76%); colorless liquid; bp 52–54 °C / 17–18 mbar. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.71 – 2.59 (m, 1H), 2.58 – 2.49 (m, 1H), 1.77 – 1.65 (m, 2H), 1.60 – 1.55 (m, 1H), 1.45 (t, J = 7.6 Hz, 1H), 1.39 (dd, J = 8.2, 5.2 Hz, 1H), 0.92 (td, J = 5.2, 3.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 112.7 (t, J = 285 Hz), 26.4, 21.0 (t, J = 11.4 Hz), 20.6, 13.9 (t, J = 11.5 Hz), 12.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ –135.0. GC/MS (EI): m/z = 150 [M]$^+$. Anal. Calcd. for $C_6H_8F_2S$: C 47.98; H 5.37; S 21.35. Found: C 47.63; H 5.64; S 21.66.

General procedure for the preparation of anilides. DIPEA (389 mg, 3.00 mmol) was added to a mixture of the corresponding carboxylic acid (1.50 mmol), aniline (140 mg, 1.50 mmol), EDC (345 mg, 1.80 mmol) and DMAP (9.16 mg, 75.0 μmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at rt overnight, then diluted with CH_2Cl_2 (10 mL) and washed with 10% aq $NaHSO_4$ (2 × 5 mL) and saturated aq $NaHCO_3$ (2 × 5 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and evaporated in *vacuo*.

***N*-Phenylspiro[2.2]pentane-1-carboxamide (22c).** Yield 235 mg (84%); colorless solid; 159–161 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.99 (br s, 1H), 7.58 (d, J = 7.9 Hz, 2H), 7.27 (t, J = 7.9 Hz, 2H), 7.04 – 6.95 (m, 1H), 2.13 (dd, J = 7.5, 4.3 Hz, 1H), 1.42 – 1.36 (m, 1H), 1.29 (dd, J = 7.5, 3.3 Hz, 1H), 0.99 – 0.80 (m, 3H), 0.80 – 0.69 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.9, 139.9, 129.1, 123.2, 119.3, 22.3, 18.2, 13.6, 6.5, 5.3. LC/MS (ES-API): m/z = 188 [M+H]$^+$. Anal. Calcd. for $C_{12}H_{13}NO$: C 76.98; H 7; N 7.48. Found: C 76.67; H 6.90; N 7.24.

2,2-Difluoro-*N*-phenylspiro[2.2]pentane-1-carboxamide (23c). Yield 270 mg (81%); colorless solid; mp 155–156 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (s, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.34 – 7.27 (m, 2H), 7.05 (t, J = 7.4 Hz, 1H), 2.98 (d, J = 10.4 Hz, 1H), 1.44 – 1.29 (m, 2H), 1.28 – 1.18 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.5, 139.3, 129.2, 123.9, 119.5, 114.2 (dd, J = 292, 288 Hz), 31.3 (t, J = 10.5 Hz), 19.4 (t, J = 9.2 Hz), 7.0, 6.6. ^{19}F NMR (376 MHz, DMSO-d_6) δ –126.3 (d, J = 143 Hz), –139.9 (d, J = 143 Hz). LC/MS (ES-API): m/z = 224 [M+H]$^+$. Anal. Calcd. for $C_{12}H_{11}F_2NO$: C 64.57; H 4.97; N 6.27. Found: C 64.79; H 5.07; N 6.60.

4,4-Difluoro-*N*-phenylspiro[2.2]pentane-1-carboxamide (24). Yield 282 mg (84%); colorless solid; mp 152–153 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (br s, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.33 – 7.25 (m, 2H), 7.04 (t, J = 7.4 Hz, 1H), 2.49 – 2.43 (m, 1H), 1.94 (td, J = 8.2, 3.5 Hz, 1H), 1.73 (td, J = 8.3, 3.4 Hz, 1H), 1.68 – 1.56 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.2, 168.2, 139.5, 129.2, 123.7, 119.6, 114.7 (t, J = 287 Hz), 22.6 (t, J = 10.7 Hz), 21.7, 16.2 (t, J = 10.6 Hz), 13.0. ^{19}F NMR (376 MHz, DMSO-d_6) δ –132.8 (d, J = 150 Hz), –133.3 (d, J = 150 Hz). LC/MS (ES-API): m/z = 224 [M+H]$^+$. Anal. Calcd. for $C_{12}H_{11}F_2NO$: C 64.57; H 4.97; N 6.27. Found: C 64.80; H 5.12; N 5.96.

General procedure for the preparation of benzamides. A solution of benzoyl chloride (200 mg, 1.43 mmol) in CH_2Cl_2 (2 mL) was added dropwise at 0 °C to a stirred mixture of the corresponding amine (1.50 mmol) and Et_3N (379 mg, 3.75 mmol) in CH_2Cl_2 (4 mL). The reaction mixture was stirred at rt for 18 h. The reaction mixture was washed with 10% aq $NaHSO_4$ (2 × 5 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and evaporated in *vacuo*.

***N*-(Spiro[2.2]pentan-1-yl)benzamide (22d).** Yield 265 mg (94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.64 (m, 2H), 7.46 (t, J = 7.4 Hz, 1H), 7.38 (t, J = 7.4 Hz, 2H), 6.29 (br s, 1H), 3.61 – 2.98 (m, 1H), 1.34 (t, J = 6.1 Hz, 1H), 1.07 – 0.98 (m, 1H), 0.97 – 0.92 (m, 1H), 0.92 – 0.84 (m, 2H), 0.84 – 0.77 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.6, 134.4, 131.4, 128.5, 126.8, 29.0, 15.2, 14.3, 7.0, 3.6. LC/MS (ES-API): m/z = 188 [M+H]$^+$. Anal. Calcd. for $C_{12}H_{13}NO$: C 76.98; H 7; N 7.48. Found: C 77.24; H 7.07; N 7.83.

***N*-(2,2-Difluorospiro[2.2]pentan-1-yl)benzamide (23d).** Yield 261 mg (78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.6 Hz, 2H), 7.60 – 7.51 (m, 1H), 7.51 – 7.41 (m, 2H), 6.37 (s, 1H), 3.92 (dt, J = 8.9, 4.3 Hz, 1H), 1.51 – 1.42 (m, 1H), 1.40 – 1.32 (m, 1H), 1.27 – 1.12 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 133.0, 131.5, 128.2, 126.5, 112.4 (dd, J = 298, 288 Hz), 34.9 (dd, J = 13.4, 10.8 Hz), 20.5 (t, J = 9.7 Hz), 7.8, 4.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ –134.2 (d, J = 156 Hz), –143.2 (d, J = 156 Hz). LC/MS (ES-API): m/z = 224 [M+H]$^+$. Anal. Calcd. for $C_{12}H_{11}F_2NO$: C 64.57; H 4.97; N 6.27. Found: C 64.87; H 4.64; N 6.14.

***N*-(4,4-Difluorospiro[2.2]pentan-1-yl)benzamide (25).** Yield 290 mg (87%). Colorless solid, mp 119–121 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.73 (m, 2H), 7.51 (t, J = 7.5 Hz, 1H), 7.41 (t, J = 7.5 Hz, 2H), 6.58 (br s, 1H), 3.60 – 3.44 (m, 1H), 1.82 (td, J = 8.3, 2.3 Hz, 1H), 1.73 – 1.63 (m, 2H), 1.37 – 1.27 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 133.3, 131.3, 128.1, 126.5, 112.3 (dd, J = 287, 285 Hz), 28.1, 20.6 (t, J = 11.4

Hz), 14.5 (t, J = 11.6 Hz), 13.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −134.5 (d, J = 152 Hz), −135.2 (d, J = 152 Hz). LC/MS (ES-API): m/z = 224 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{11}F_2NO$: C 64.57; H 4.97; N 6.27. Found: C 64.25; H 4.79; N 6.61.

Acknowledgements

The work was funded by Enamine Ltd. An additional funding was received from Ministry of Education and Sciences of Ukraine, Grants No. 0121U100387 (21BF037-01M) and 0122U001962 (22BF037-02). The authors thank Andriy Skreminskiy for the Log*P* and S_w measurements, Olga Kovalenko and Margaryta Bolgova for the pK_a titrations, Dr. Eduard Rusanov for the X-ray diffraction studies, Prof. Andrey A. Tolmachev for his encouragement and support, and the people of Ukraine who made finalizing this publication possible.

Conflict of Interest

All the authors are employees, trainees, or consulting scientists of Enamine Ltd. (Kyiv, Ukraine) that offers the building blocks described in this work from the company's catalogue.

Keywords: bicyclic compounds • fluorine • building blocks • spiro compounds • *gem*-difluorocyclopropanation

[1] Z. Fang, Y. Song, P. Zhan, Q. Zhang, X. Liu, *Future Med. Chem.* **2014**, *6*, 885–901.
[2] A. Mann, in *The Practice of Medicinal Chemistry*, Elsevier, **2008**, pp. 363–379.
[3] K. Hiesinger, D. Dar'in, E. Proschak, M. Krasavin, *J. Med. Chem.* **2021**, *64*, 150–183.
[4] J. Meyers, M. Carter, N. Y. Mok, N. Brown, *Future Med. Chem.* **2016**, *8*, 1753–1767.
[5] K. Miyazawa, D. Demus, A. De Meijere, *Mol. Cryst. Liq. Cryst. Sci. Technol. Sect. A. Mol. Cryst. Liq. Cryst.* **2001**, *364*, 253–270.
[6] F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752–6756.
[7] M. Aldeghi, S. Malhotra, D. L. Selwood, A. W. E. Chan, *Chem. Biol. Drug Des.* **2014**, *83*, 450–461.
[8] H. P. Guan, M. B. Ksebati, Y. C. Cheng, J. C. Brach-, E. R. Kern, J. Zemlicka, *J. Org. Chem.* **2000**, *65*, 1280–1290.
[9] K. W. Lai, J. Liang, B. Zhang, S. Labadie, D. Ortwine, P. Dragovich, J. Kiefer, V. S. Gehling, J.-C. Harmange, PCT Int. Pat. WO2016057924, **2016**.
[10] P. Shah, A. D. Westwell, *J. Enzyme Inhib. Med. Chem.* **2007**, *22*, 527–540.
[11] E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315–8359.
[12] W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359–4369.
[13] S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330.
[14] A. Galano, J. R. Alvarez-Idaboy, A. Vivier-Bunge, *Theor. Chem. Acc.* **2007**, *118*, 597–606.
[15] L. D. Cripe, H. Uno, E. M. Paietta, M. R. Litzow, R. P. Ketterling, J. M. Bennett, J. M. Rowe, H. M. Lazarus, S. Luger, M. S. Tallman, *Blood* **2010**, *116*, 4077–4085.
[16] A. Alam, R. Kung, J. Kowal, R. A. McLeod, N. Tremp, E. V. Broude, I. B. Roninson, H. Stahlberg, K. P. Locher, *Proc. Natl. Acad. Sci.* **2018**, *115*, DOI 10.1073/pnas.1717044115.
[17] A. E. Sutton, T. E. Richardson, B. R. Huck, S. R. Karra, X. Chen, Y. Xiao, A. Goutopoulos, R. Lan, D. Perrey, G. Vandeveer, L. Harold, Liu-Bujalski, F. Stieber, B. L. Hodous, H. Qiu, R. C. Jones, B. Heasley, PCT Int. Pat. WO 2010/093419, **2010**.
[18] B. Buettelmann, B. Kocer, B. Kuhn, M. Prunotto, H. Richter, M. Ritter, M. Rudolph, A. L. Satz, PCT Int. Pat. WO 2017/005583, **2017**.
[19] H. Urabe, R. Shimono, T. Tamita, N. Hatton, K. Sakagami, Y. Matsuda, A. Yasuhara, S. Masuda, K. Konishi, S. Y. T. Nakamura, PCT Int. Pat. WO2013/062079, **2013**.
[20] R. Zahler, J. E. Vath, PCT Int. Pat. WO 2017/027684, **2017**.
[21] W. R. J. Dolbier, S. F. Sellers, B. H. Al-Sader, T. H. J. Fielder, S. Elsheimer, B. E. Smart, *Isr. J. Chem.* **1981**, *21*, 176–184.
[22] W. R. Dolbier, S. F. Sellers, B. H. Al-Sader, S. Elsheimer, *J. Am. Chem. Soc.* **1981**, *103*, 715–717.
[23] W. R. Dolbier, M. J. Seabury, *Tetrahedron* **1987**, *43*, 2437–2442.
[24] A. Gerasov, G. A. Dolgonos, A. Y. Mandzhulo, A. Ryabitsky, V. Fetyukhin, O. Lukin, A. Shivanyuk, *Synthesis* **2020**, *52*, 1015–1024.
[25] P. S. Nosik, A. O. Gerasov, R. O. Boiko, E. Rusanov, S. V. Ryabukhin, O. O. Grygorenko, D. M. Volochnyuk, *Adv. Synth. Catal.* **2017**, *359*, 3126–3136.
[26] P. S. Nosik, S. V. Ryabukhin, O. O. Grygorenko, D. M. Volochnyuk, *Adv. Synth. Catal.* **2018**, *360*, 4104–4114.
[27] F. Wang, T. Luo, J. Hu, Y. Wang, H. S. Krishnan, P. V. Jog, S. K. Ganesh, G. K. S. Prakash, G. A. Olah, *Angew. Chem. Int. Ed.* **2011**, *50*, 7153–7157.
[28] H. Imgartinger, S. Gries, P. Klaus, R. Gleiter, *Chem. Ber.* **1992**, *125*, 2503–2512.
[29] J. M. Birchall, R. Fields, R. N. Haszeldine, R. J. McLean, *J. Fluor. Chem.* **1980**, *15*, 487–495.
[30] M. J. Bunegar, R. Fields, R. N. Haszeldine, *J. Fluor. Chem.* **1980**, *15*, 497–509.
[31] J. T. Pechacek, T. M. Bargar, M. R. Sabol, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2665–2668.
[32] W. R. Dolbier, C. R. Burkholder, A. Lucia Chaves, A. Green, *J. Fluor. Chem.* **1996**, *77*, 31–37.
[33] W. R. Dolbier, S. F. Sellers, B. E. Smart, *Tetrahedron Lett.* **1981**, *22*, 2953–2956.
[34] K. Okuma, Y. Tanaka, K. Yoshihara, A. Ezaki, G. Koda, H. Ohta, K. Hara, S. Kashimura, *J. Org. Chem.* **1993**, *58*, 5915–5917.
[35] Z. Yu, Q. Lin, *J. Am. Chem. Soc.* **2014**, *136*, 4153–4156.
[36] N. Hayashi, Y. Hirokawa, I. Shibata, M. Yasuda, A. Baba, *J. Am. Chem. Soc.* **2008**, *130*, 2912–2913.
[37] A. García-Domínguez, T. H. West, J. J. Primozic, K. M. Grant, C. P. Johnston, G. G. Cumming, A. G. Leach, G. C. Lloyd-Jones, *J. Am. Chem. Soc.* **2020**, *142*, 14649–14663.
[38] A. V. Chernykh, K. P. Melnykov, N. A. Tolmacheva, I. S. Kondratov, D. S. Radchenko, C. G. Daniliuc, D. M. Volochnyuk, S. V. Ryabukhin, Y. O. Kuchkovska, O. O.

Grygorenko, *J. Org. Chem.* **2019**, *84*, 8487–8496.
[39] S. Holovach, K. P. Melnykov, A. Skreminskiy, M. Herasymchuk, O. Tavlui, D. Aloshyn, P. Borysko, A. B. Rozhenko, S. V. Ryabukhin, D. M. Volochnyuk, O. O. Grygorenko, *Chem. Eur. J.* **2022**, *28*, e202200331.
[40] O. O. Grygorenko, K. P. Melnykov, S. Holovach, O. Demchuk, *ChemMedChem* **2022**, submitted.
[41] O. O. Grygorenko, P. Babenko, D. M. Volochnyuk, O. Raievskyi, I. V. Komarov, *RSC Adv.* **2016**, *6*, 17595–17605.
[42] O. O. Grygorenko, D. Demenko, D. M. Volochnyuk, I. V. Komarov, *New J. Chem.* **2018**, *42*, 8355–8365.
[43] W. L. F. Armarego, C. Chai, *Purification of Laboratory Chemicals*, Elsevier: Oxford, **2003**.

WILEY-VCH

RESEARCH ARTICLE

Bicyclo[m.n.k]alkane Building Blocks as Promising Benzene and Cycloalkane Isosteres: Multigram Synthesis, Physicochemical and Structural Characterization

Volodymyr V. Semeno,[a,b] Vadym O. Vasylchenko,[a] Ihor M. Fesun,[a] Liudmyla Yu. Ruzhylo,[a,c] Mykhailo O. Kipriianov,[a,c] Dr. Kostiantyn P. Melnykov,[a,b] Artem Skreminskyi,[a] Dr. Rustam Iminov,[a] Dr. Pavel Mykhailiuk,[a] Dr. Bohdan V. Vashchenko,[a,b] Dr. Oleksandr O. Grygorenko*[a,b]

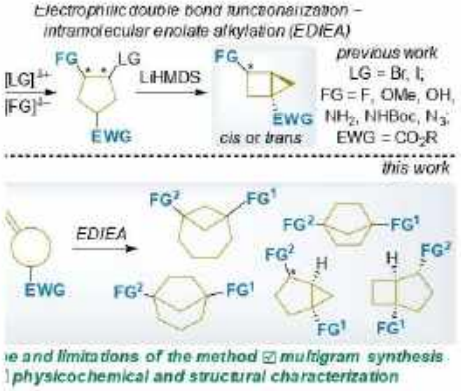
Dedicated to the memory of Kyrylo Burmagin, a student at Taras Shevchenko National University, a trainee at Enamine Ltd., and a volunteer who died under Severodonetsk on November 10, 2023

[a] Enamine Ltd.
Chervonotkatska Street 78, Kyiv 02094, Ukraine
URL: www.enamine.net
[b] Taras Shevchenko National University of Kyiv
Volodymyrska Street 60, Kyiv 01601, Ukraine
E-mail: gregor@univ.kiev.ua
URL: www.grygorenko.com
[c] National Technical University of Ukraine «Igor Sikorsky Kyiv Polytechnic Institute»
Beresteiskyi Ave. 37, Kyiv 03056, Ukraine
Supporting information for this article is given via a link at the end of the document

Abstract: Electrophilic double bond functionalization – intramolecular enolate alkylation sequence was used to obtain a series of bridged and fused bicyclo[m.n.k]alkane derivatives (i.e., bicyclo[4.1.1]octanes, bicyclo[2.2.1]heptanes, bicyclo[3.2.1]octanes, bicyclo[3.1.0]hexanes, and bicyclo[4.2.0]heptanes). The scope and limitations of the method were established, and applicability to the multigram synthesis of target bicyclic compounds was illustrated. Using the developed protocols, over 50 mono- and bifunctional building blocks relevant to medicinal chemistry were prepared. The synthesized compounds are promising isosteres of benzene and cycloalkane rings, which is confirmed by their physicochemical and structural characterization (pK_a, Log*P*, and exit vector parameters (EVP)). "Rules of thumb" for the upcoming isosteric replacement studies were proposed.

Introduction

Bicyclic saturated compounds have reached leading positions in the modern design of organic molecules. This phenomenon could be addressed to the molecular rigidity and the distinct spatial arrangement of substituents connected to the sp^3-enriched non-planar bicyclic scaffolds.[1–4] Nature itself widely utilizes carbocyclic molecules with mono- and bicyclic framework that have a wide range of biological activities.[5–11] The rigidity of bicyclic scaffolds has noticeable features in drug discovery since it may decrease the enthalpic penalty of the protein-ligand binding and improve overall physicochemical properties of the molecule.[5–7,12–14] In the last few years, bicyclo[m.n.k]alkanes have attracted much attention in medicinal chemistry as non-classical isosteres of benzene and cycloalkanes that allow improve pharmacokinetic parameters of the compound and fine-tune its affinity to the biological target.[15–21] In this view, bicyclo[1.1.1]pentanes (BCPs),[22,23] -[2.1.1]hexanes,[24] -[2.2.1]-heptanes (norbornanes), -[3.1.1]heptanes,[25] -[2.2.2]octanes,[26] or -[2.2.0]hexanes ([2]-ladderanes)[27] can be particularly outlined (Scheme 1, *A*).



Scheme 1. (*A*) Some examples of the known bicyclic benzene/cycloalkane isosteres. (*B*) Electrophilic double bond desymmetrization – intramolecular enolate alkylation sequence for the synthesis of 1,3-disubstituted bicyclo[2.1.0]pentanes (housanes). (*C*) The main targets of this work.

To date, synthetic approaches to bicyclic saturated ring systems were typically unique for each bicyclo[m.n.k]alkane, especially if

a required substitution of the parent scaffold is taken into account. General strategies allowing for the construction of various properly functionalized saturated bicyclic systems using the same synthetic approach are very rare but highly desirable. In our previous work, we have shown that electrophilic double bond desymmetrization (functionalization) – intramolecular enolate alkylation (*EDIEA*) is a very efficient method for the preparation of 1,3-disubstituted bicyclo[2.1.0]pentanes (housanes) from properly functionalized cyclopentanes (Scheme 1, *B*).[28] The synthetic sequence allowed for the preparation of both *cis*- and *trans*-1,3-disubstituted housane-1-carboxylic acids in a diastereoselective manner on up to 80 g scale.

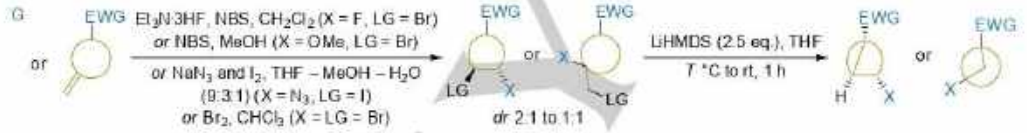
Herein, we demonstrate the utility of the *EDIEA* sequence for the preparation of various fused and bridged saturated bicyclic ring systems starting from the corresponding cyclic esters bearing an endo- or exocyclic double bond (Scheme 1, *C*). We show the scope and limitations of the method, as well as its applicability for the multigram synthesis. Furthermore, we illustrate the potential of the synthesized mono- and bifunctional building blocks as benzene/cycloalkane isosteres by characterization of their physicochemical (pK_a, Log*P*[29]) and structural (exit vector parameters, EVP[20,30]) properties.

Results and Discussion

Preliminary synthetic experiments: scope and limitations

We started our study with application of the *EDIEA* reaction sequence to 11 model cycloalka(e)ne carboxylic acid derivatives bearing an exo- or endocyclic double bond (Table 1). All preliminary experiments were performed at 10 mmol scale. Three model electrophilic functionalization reactions were used at the first step: fluorobromination, methoxybromination, and iodoazidation. In particular, fluorobromination was performed by action of $Et_3N{\cdot}3HF$ and NBS in CH_2Cl_2. The method worked well with all cyclic esters with exocyclic double bond (except cyclobutane derivative **1**), as well as symmetric cycloalkene derivatives **19** (previous work[28]) and **26** (Table 1, Entries 2–8). In the case of ester **1**, considerable formation of elimination by-product was observed (Entry 1). Methoxybromination was performed with NBS in MeOH and worked well with all the substrates mentioned above (Table 1, Entries 1–8). Finally, iodoazidation was carried out upon action of NaN_3 and I_2 in THF – MeOH – H_2O (9:3:1, v/v/v), and the method was efficient with all substrates discussed (Table 1, Entries 1–8).

Table 1. Preliminary synthetic experiments on the *EDIEA* reaction sequence



Entry	Substrate	Intermediate[a]	Product[a]	Yield of product, % (over two steps)		
				X = F, LG = Br	X = OMe, LG = Br	X = N_3, LG = I
1				*complex mixture* (*T* = –70 °C)	*complex mixture* (*T* = –70 °C)	–
2				*no reaction* (*T* = –70 °C or –40 °C) *complex mixture*[b]	*complex mixture*[b]	–
3				*complex mixture* (*T* = –50 °C)	*complex mixture* (*T* = –20 °C)	–
4				55 (*T* = –10 °C)	51 (*T* = –10 °C)	68 (*T* = –10 °C)

WILEY-VCH

Entry	Substrate	Intermediate[a]	Product[a]	Yield of product, % (over two steps)		
				X = F, LG = Br	X = OMe, LG = Br	X = N_3, LG = I
5				23 (*T* = –10 °C)	29 (*T* = –10 °C)	21 (*T* = –10 °C)
6				37 (*T* = –10 °C)	57 (*T* = –10 °C)	69 (*T* = –10 °C)
7[b]				44 (*T* = –70 °C)	54 (*T* = –70 °C)	24 (*T* = –70 °C)
8				70 (*T* = –10 °C)	71 (*T* = –10 °C)	61 (*T* = –10 °C)
9				69 (*T* = –70 °C; X = LG = Br)[e]	41 (*T* = –70 °C)[f]	37 (*T* = –70 °C)[f]
10		*complex mixture*	–		–	
11		*complex mixture*	–		–	

[a] Relative configurations are shown. All intermediates mentioned in Entries 1–9 were successfully obtained (see Supporting Information)

[b] Results of the previous work.[28]

[c] Conditions for the second step: LiHMDS (1.4 eq.), –10 °C, 1 h, reverse addition; or LDA (1.2 eq.), –78 °C to rt, 2 h, or LDA (1.5 eq.), HMPTA (4 eq.), –78 °C to rt, 2 h.

[d] Conditions for the second step: LDA (1.5 eq.), HMPTA (7 eq.), –78 °C to rt, 2 h.

[e] The corresponding products **26a** and **27a** (X = LG = Br) were obtained with bromine in $CHCl_3$ as the electrophile at the first step.

[f] Methoxybromination and azidoiodination gave mixtures of regioisomers **26b,c** and **28b,c** (ca. 1:1 ratio) according to LC-MS and ^{1}H NMR spectra. Only compounds **26b** and **26c** underwent cyclization at the second step.

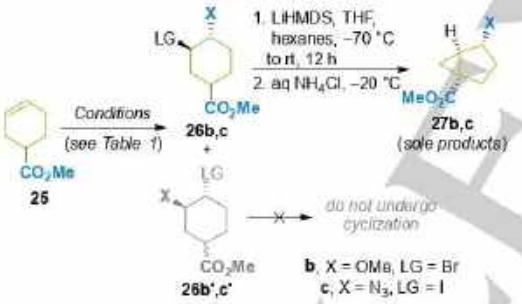
In all the above cases, the reactions proceeded regioselectively (where appropriate), while the diastereoselectivity relatively to the configuration at the carboxylate (nitrile) moiety was modest (*dr* 2:1 to 1:1; note *anti* addition for the endocyclic double bonds in **19** and **22**). Nevertheless, the observed diastereomeric ratio had no impact at the further step, i.e., intramolecular enolate alkylation, since the stereogenic center near the EWG group disappeared upon the deprotonation with a base.

Initially, the optimized conditions from the previous work were implemented for the cyclization step (2.5-fold excess of LiHMDS, THF, –70 °C to rt, 1 h).[28] As was found, the construction of the methylene bridge could be achieved for the relatively large ring systems, i.e., bicyclo[4.1.1]-, -[2.2.1]-, and -[3.2.1]alkanes (albeit the reaction was performed at higher temperature, i.e., –10 °C to rt) (Table 1, Entries 4–6). Notably, norbornane (bicyclo[2.2.1]-alkane) derivatives were obtained in modest yield (21–29%), which might be related to unfavorable geometry of the transition

state for the cyclization. Furthermore, all attempts to obtain even more strained bicyclo[1.1.1]pentane, -[2.1.1]hexane, and -[3.1.1]-heptane derivatives were unfruitful (Entries 1–3). Meanwhile, the method worked well for intermediates **20** (previous work[20]) and **23** derived from substrates with endocyclic double bond (Entries 7 and 8).

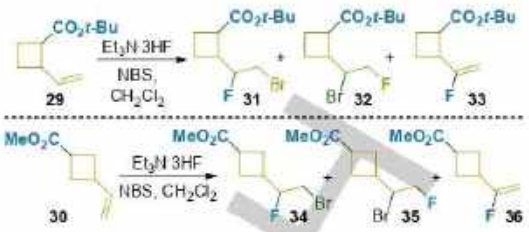
As might be expected, cyclohexene derivative **25** reacted non-regioselectively at the electrophilic functionalization conditions mentioned above. Nevertheless, an elegant solution for this problem was envisaged and implemented successfully. Thus, compound **25** was involved into the simple bromination reaction to give dibromide **26a**. In principle, intramolecular enolate alkylation could provide two possible products depending on the bromine atom involved into the reaction, i.e., bicyclo[3.1.0]-hexane or bicyclo[2.2.0]hexane derivative. Luckily for us, only bicyclo[3.1.0]hexane **27a** was formed in 69% yield upon reaction of compound **26a** with 2.5-fold excess of LiHMDS in THF at –70 °C to rt.

Being inspired by excellent cyclization regioselectivity observed in the case of dibromide **26a**, we put a closer look on the products of non-symmetric electrophilic functionalization of unsaturated ester **25**. Thus, the regioisomeric mixtures of methoxybromination (**26b** and **26b'**) and iodoazidation (**26c** and **26c'**) products were introduced into the intramolecular enolate alkylation step under the conditions described above for the compound **26a** (Scheme 2). It was found that only isomers **26b** and **26c** underwent the cyclization providing bicyclo[3.1.0]hexane derivatives **27b** and **27c** in 41% and 37% yield, respectively.



Scheme 2. Chemoselective formation of bicyclo[3.1.0]hexane derivatives **27** starting from unsaturated ester **25**

Unfortunately, vinyl-substituted cyclobutanes **29** and **30** were not suitable for the *EDIEA* reaction sequence since at the first step (electrophilic functionalization), complex mixtures were obtained (Table 1, Entries 10 and 11). According to LC-MS and ^{1}H NMR spectra of these mixtures, they presumably contained target regioisomers **31**/**32** or **34**/**35** (as mixtures of diastereomers), elimination products **33** or **36**, and other unidentified by-products (Scheme 3). The reaction was not fruitful even when bromine was used as the electrophile.



Scheme 3. Unsuccessful attempts on the fluorobromination of unsaturated esters **29** and **30** (the structures of the plausible products are proposed according to LC-MS and ^{1}H NMR spectra)

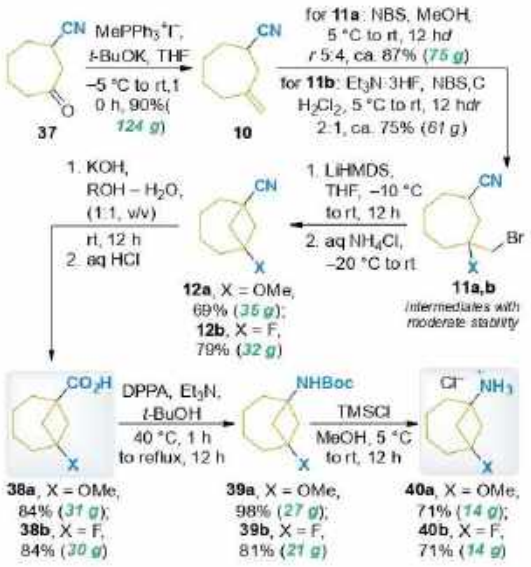
Multigram synthesis of target building blocks

With the optimized protocols, as well as scope and limitation of the method in hands, we have performed multigram synthesis of building blocks derived from bicyclic scaffolds that were successfully prepared in the preliminary experiments.

Synthesis of 1,6-disubstituted bicyclo[4.1.1]octanes. The proposed reaction sequence commenced from commercially available 3-oxocycloheptane-1-carbonitrile (**37**) that was involved into the Wittig reaction with $MePPh_3^+I^-$ in the presence of *t*-BuOK to give methylenecycloheptane **10** in 90% yield on up to 124 g scale in a single run (Scheme 4). The subsequent methoxy- and fluorobromination of **10** proceeded smoothly with good yields of the target bromomethyl-substituted intermediates **11a** and **11b** that had moderate stability towards attempted purification and storage. Therefore, it was advantageous to perform the subsequent cyclization immediately with halogenides **11** (and the following related homologs and isomers) isolated with over 90% purity. Notably, the formation of bicyclo[4.1.1]octane system proceeded in good yields (69% for **12a**, 79% for **12b**) on up to 35 g scale. The mild alkaline hydrolysis of nitrile group of **12** followed by the treatment with aq HCl was successfully performed to obtain two carboxylic acids **38a** and **38b**, both in 84% yield.

The modified DPPA-mediated Curtius rearrangement in the presence of *t*-BuOH was suitable to obtain *N*-Boc protected amines **39a** and **39b** in good to excellent yields. The subsequent carbamate group cleavage was performed with *in-situ* generated HCl (TMSCl – MeOH), and amines **40a** and **40b** were obtained as hydrochlorides both in 71% yield on up to 14 g scale.

Iodoazidation of methylenecycloheptane **10** was performed on up to 300 g scale; no diastereoselectivity was observed (Scheme 5). Iodomethyl derivative **11c** was immediately involved in the LiHMDS-mediated cyclization without additional purification, and the target bifunctional azido nitrile **12c** was obtained in 77% yield on 129 g scale in a single run. The subsequent alkaline hydrolysis provided azido carboxylic acid **38c** (57% yield, 140 g scale), which was transformed into ester **41** using CDI – MeOH (97% yield). Azide reduction was performed via the mild catalytic hydrogenation in the presence of Boc_2O, which gave *N*-Boc-protected amino ester **42** in 79% yield. Compound **42** served as a precursor for the preparation of amino ester **43** (via acidic carbamate cleavage), and *N*-Boc-protected amino acid **44** via reflux in the presence of $LiOH·H_2O$ in MeOH – H_2O (2:1, v/v) in good yields. Finally, free amino acid **45** was synthesized from compound **44** in 91% yield on up to 24 g scale as hydrochloride.

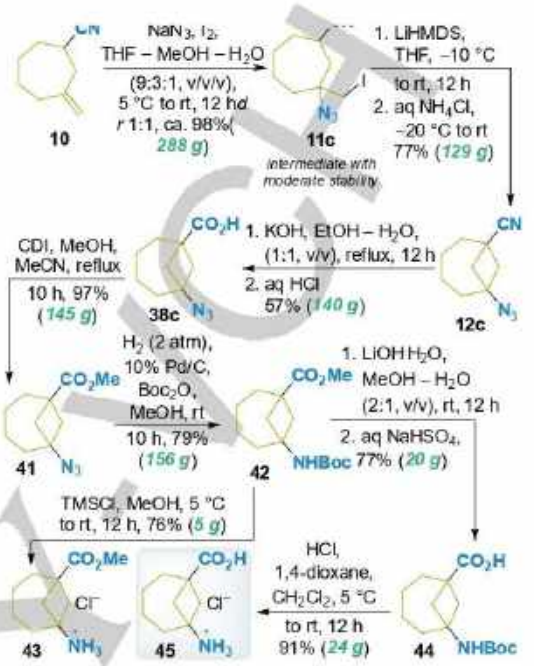


Scheme 4. Synthesis of bicyclo[4.1.1]octane-derived building blocks **38a**, **38b**, **40a**·HCl, and **40b**·HCl.

Synthesis of 1,4-disubstituted bicyclo[2.2.1]heptanes. Notably, synthesis of 1,4-disubstituted bicyclo[2.2.1]heptanes by intramolecular enolate alkylation was documented in the literature, albeit different retrosynthetic disconnections were used.[31–36] Our approach commenced with a known preparation of 4-methylenecyclohexane carboxylate **13** based on the use of $MePPh_3^+Br^-$ and *n*-BuLi in the reaction with **46** (Scheme 6).[37] In our hands, better results for the scaled-up synthesis of **13** were obtained with *t*-BuOK as a base for this step. Alkoxybromination was performed with MeOH or EtOH as the alcohol component, providing derivatives **14a** and **14d** both in ca. 90% yield on up to 465 g scale. The fluorobromination also proceeded with good efficiency to give fluorinated intermediate **14b**. The subsequent LiHMDS-mediated cyclization of bromoalkyl carboxylates **14a**, **14b**, and **14d** provided target norbornane carboxylates **15a**, **15b**, and **15d** in relatively low yields (31–36%). Nevertheless, the proposed method was suitable for the scaled-up synthesis of bicyclic carboxylate intermediates for a series of further functional group transformations on up to 68 g scale in a single run.

KOH-mediated hydrolysis of carboxylates **15a**, **15b**, and **15d** proceeded smoothly and gave the corresponding carboxylic acids **47a** (90% yield), **47b** (86% yield), and **47d** (77% yield). The Curtius rearrangement of derivatives **47a–d** was performed by the action of DPPA and *t*-BuOH in the presence of Et_3N (80–88% yield of *N*-Boc-protected derivatives **48a–d**), while the carbamate group cleavage with *in situ* generated HCl allowed for the preparation of norbornane amines **49a**, **49b**, and **49d** in good yields (71–75%).

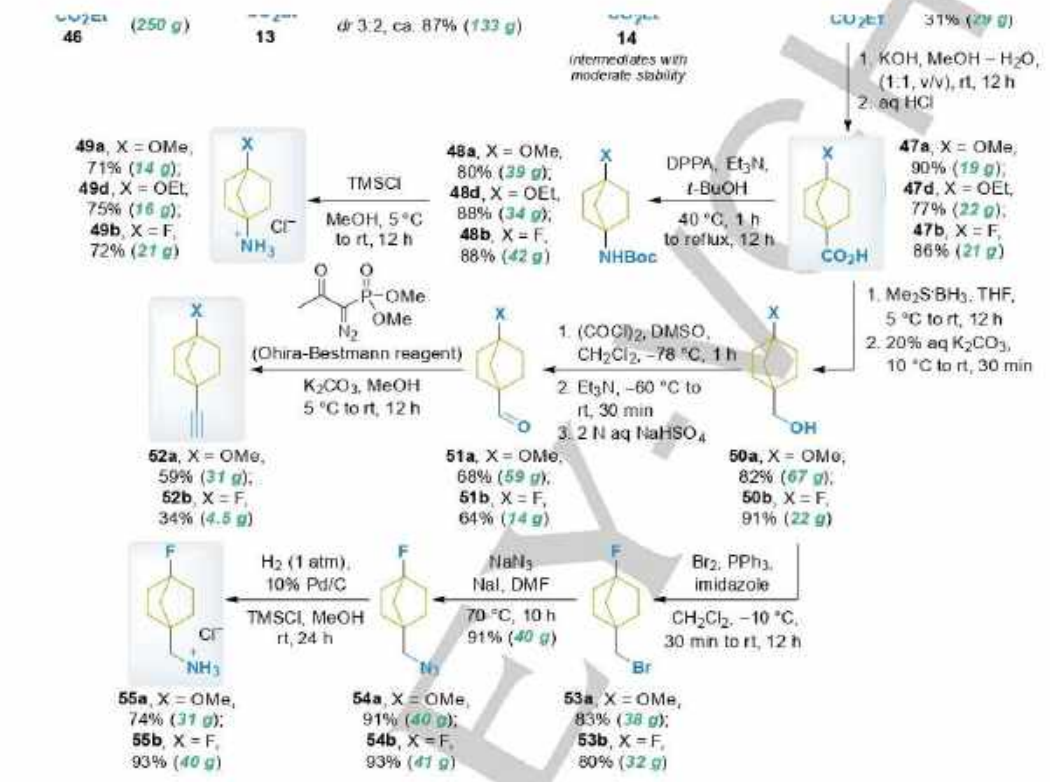
Reduction of the carboxylic group in compounds **47a** and **47b** was easily achieved with borane – dimethylsulfide complex and gave primary alcohols **50a** and **50b**. Further Swern oxidation of these products provided aldehydes **51a** and **52b**, that were transformed into acetylenes **52a** and **52b** using Ochira-Bestmann reagent. Also, alcohols **50** were subjected to Appel bromination providing intermediates **53** that was introduced into reaction with NaN_3 (giving azides **54**) and then – catalytic hydrogenation giving amines **55** as hydrochlorides.



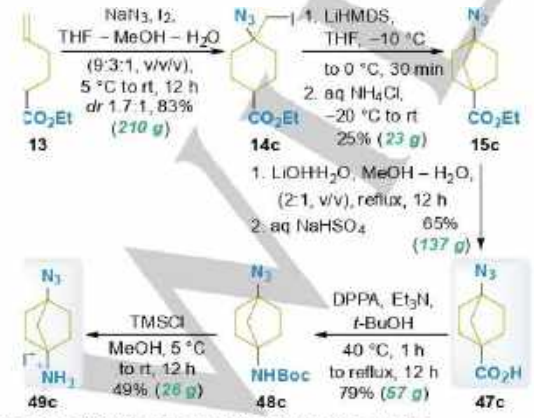
Scheme 5. Synthesis of bicyclo[4.1.1]octane-derived amino acid **45** and its derivatives.

The iodoazidation of intermediate **13** proceeded smoothly to give iodide **14c** in 83% yield on up to 210 g scale in a single run (Scheme 7). The cyclization of carbanion formed from **14c** proceeded with comparable efficiency to that of **14a**, **14b**, and **14d** and provided norbornane derivative **15c** in 25% yield. Mild alkaline hydrolysis and the subsequent Curtius reaction of carboxylic acid **47c** thus obtained provided amino azide **49c** (26 g scale in a single run) after *N*-Boc deprotection.

In order to further expand the present scope of known 1,4-difunctionalized norbornanes, we have also prepared 4-hydroxybicyclo[2.2.1]heptane-1-carboxylic acid (**47e**) and the corresponding amino alcohol **49e** (Scheme 8). The synthesis started with hydroxybromination of alkene **13** giving bromohydrin **14e** that required an additional *O*-protection step prior to the cyclization. The corresponding *O*-TBDMS-protected derivative **14f** was easily obtained on up to 81 g scale and then subjected to carbanion-mediated cyclization. Notably, the reaction proceeded much higher efficiently as compared to analogs **14a–d** – norbornane **15f** was obtained in 68% yield. This result might be addressed to the bulkiness of the OTBDMS substituent favoring axial disposition of the CH_2Br moiety necessary for the cyclization step. After alkaline hydrolysis of compound **15f**, compound **56** transformed into carboxylic acid **47e** and amino alcohol **49e** (in three steps via **48f** and **57**) using the standard functional group transformations.



Scheme 6. Synthesis of bicyclo[2.2.1]octane-derived building blocks **47a–55**

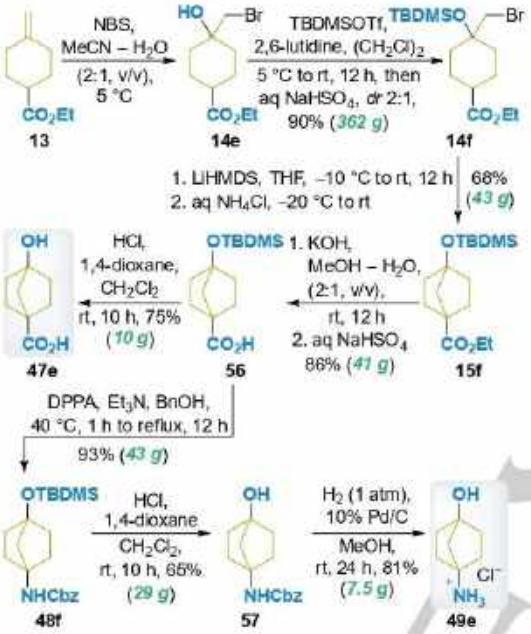


Scheme 7. Synthesis of building blocks **47c** and **49c**.

Synthesis of 1,5-disubstituted bicyclo[3.2.1]octanes. A series of bicyclo[3.2.1]octane-derived building blocks were obtained from 4-oxocycloheptane-1-carboxylic acid (**58**), which was introduced into the Wittig reaction (88% yield of **59**, 97 g scale) and then – esterification (63% yield of **16**, 93 g scale) (Scheme 9). Next, methoxy- and fluorobromination of unsaturated ester **16** were performed to obtain bromides **17a** and **17b** that were successfully involved into the cyclization reaction upon the common conditions to give bicyclo[3.2.1]octanes **18a** and **18b** in 72% and 57% yield, respectively, on up to 30 g scale. The target building blocks were obtained by the treatment of esters **18a** and **18b** with LiOH·H_2O in MeOH – H_2O. The corresponding carboxylic acids **60a** and **60b** thus formed were introduced into the Curtius rearrangement in the presence of BnOH, which gave *N*-Cbz-amines **61a** and **61b** for the further catalytic deprotection. The latter steps for the preparation of bicyclic primary amines **62a** and **62b** could be performed on over 50 g scale in a single run.

In addition to that, amino acid derivatives was obtained in an analogous manner to that of bicyclo[4.1.1]octane counterparts (Scheme 10). The reaction sequence included iodoazidation of

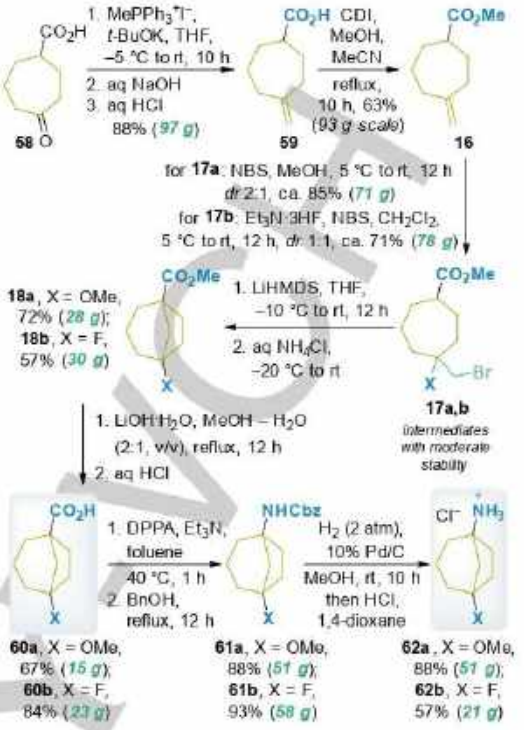
unsaturated ester **16** and further cyclization of intermediate **17c** thus obtained into 5-azidobicyclo[3.2.1]octane-1-carboxylate **18c**. Compound **18c** was subjected to catalytic hydrogenation in the presence of Boc_2O in order to obtain *N*-Boc-protected amino ester **63** (61% yield over three steps, 6 g scale). The latter derivative was used to obtain amino ester **64** (91% yield), *N*-Boc-amino acid **65** (71% yield), as well as amino acid hydrochloride **66** (61% yield from **65**).



Scheme 8. Synthesis of building blocks **47e** and **49e**.

Synthesis of 1,4-disubstituted bicyclo[3.2.0]heptanes. Cyclization of vicinal *trans*-4,5-disubstituted cycloheptane carboxylates **23a** and **23b** (obtained from cycloheptene derivative **22** with *dr* 2:1) proceeded in a diastereoselective manner under the common conditions to give bicyclic compounds **24a** and **24b** (Scheme 11). After hydrolysis, carboxylic acids **67a** and **67b** were obtained in 75–89% yield on up to 16 g scale (53% and 63% yield, respectively, over three steps).

The iodoazidation – LiHMDS-mediated cyclization sequence was suitable for the diastereoselective preparation of azido ester **24c** in 66% yield on up to 75 g scale in a single run, also starting from cycloheptene derivative **22** via intermediate **24c** (Scheme 12). The following transformation of **24c** into amino ester **68** was performed via the Staudinger reaction (71% yield, 77 g scale). Compound **68** was subjected to *N*-Boc-protection (87% yield of intermediate **69**, 114 g scale), alkaline hydrolysis (for the preparation of *N*-Boc-amino acid **70** in 76% yield), and acid-mediated cleavage of the carbamate group (81% yield of amino acid **71**).

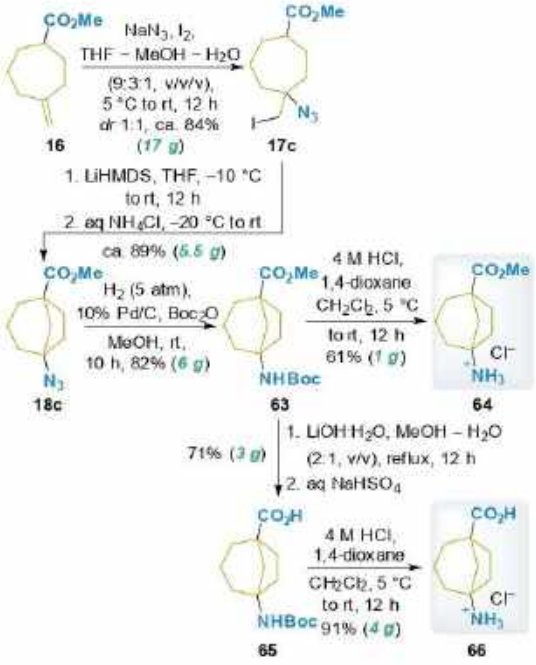


Scheme 9. Synthesis of bicyclo[3.2.1]octane-derived building blocks **60a**, **60b**, **62a**, and **62b**.

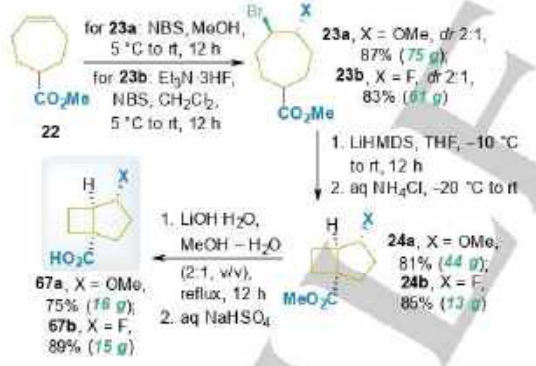
Bromohydroxylation of alkene **22** upon action of NBS in MeCN – H_2O (2:1, v/v) provided alcohol **23e** as a ca. 2:1 mixture of diastereomers in 99% yield on up to 62 g scale in a single run (Scheme 13). The subsequent treatment of compound **23e** with TBDMSCl in the presence of DMAP and imidazole in DMF gave *O*-protected intermediate **23f** in 90% yield. The cyclization of **23f** under the conditions described above provided bis-protected fused bicyclic derivative **24f** (68% yield). The cleavage of both protecting groups was achieved via the alkaline hydrolysis in the presence of LiOH·H_2O in refluxing MeOH – H_2O (2:1, v/v) and gave target compound **72** in 82% yield on up to 23 g scale.

Synthesis of 1,4-disubstituted bicyclo[3.1.0]hexanes. As mentioned above, bromination of unsaturated ester **25** was the key transformation for the successful synthesis of 1,4-disubstituted bicyclo[3.1.0]hexane derivatives. The reaction provided dibromide **26a** in 88% yield on up to 107 g scale in a single run (Scheme 14). The subsequent cyclization gave *cis*-4-bromobicyclo[3.1.0]hexane-1-carboxylate (**27a**) in 83% yield.

According to the initial plan, nucleophilic substitution in bromide **27a** was envisaged to introduce the required functional groups into the bicyclo[3.1.0]hexane scaffold. Indeed, the reaction of compound **27a** with KSAc in DMF apparently proceeded according to S_N2 mechanism and resulted in expected *trans*-isomeric thioacetate **73** in 89% yield (Scheme 15). Oxidative chlorination of compound **73** provided sulfonyl chloride **74**.

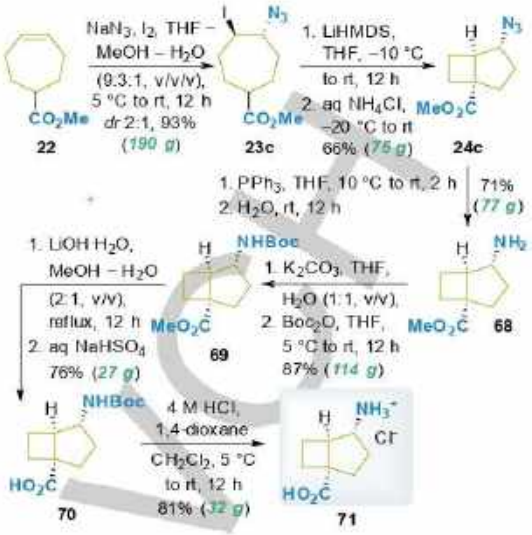


Scheme 10. Synthesis of bicyclo[3.2.1]octane amino acid derivatives **63**–**66**.

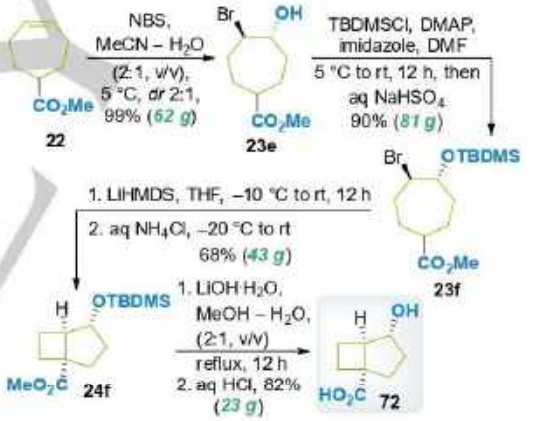


Scheme 11. Synthesis of bicyclo[3.2.0]heptane carboxylic acids **67a** and **67b** (relative configurations are shown).

In a similar manner, the reaction of bromide **27a** with NaN_3 gave corresponding azide *trans*-**27c**, albeit the diastereoselectivity was somewhat lower in this case (*dr* 6:1, with *trans* isomer being the major one). After alkaline hydrolysis, diastereopure carboxylic acid *trans*-**75** was obtained. Further transformations included the catalytic hydrogenation of the azide group (for the preparation of amino acid *trans*-**76**), followed by the esterification with $SOCl_2$ and MeOH giving amino ester *trans*-**77**.



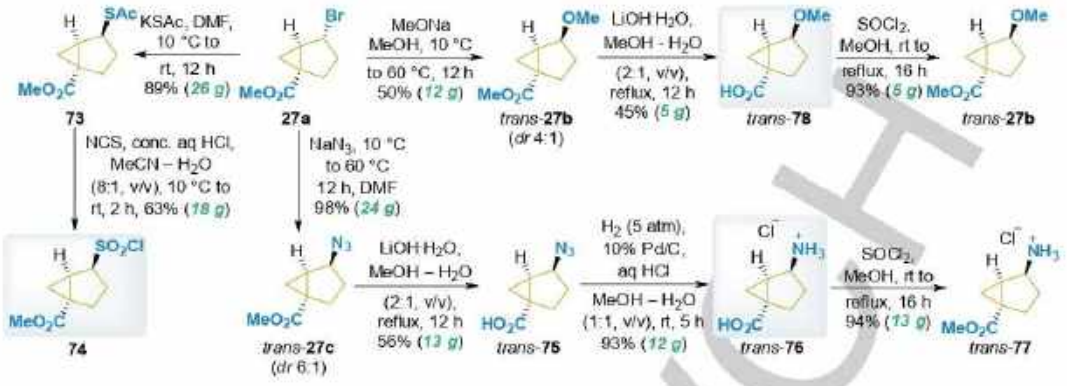
Scheme 12. Synthesis of bicyclo[3.2.0]heptane-derived amino acid **71** (relative configurations are shown).



Scheme 13. Synthesis of bicyclo[3.2.0]heptane-derived building block **72** (relative configurations are shown).



Scheme 14. Synthesis of *cis*-4-bromobicyclo[3.1.0]hexane-1-carboxylate (**27a**) (relative configurations are shown).

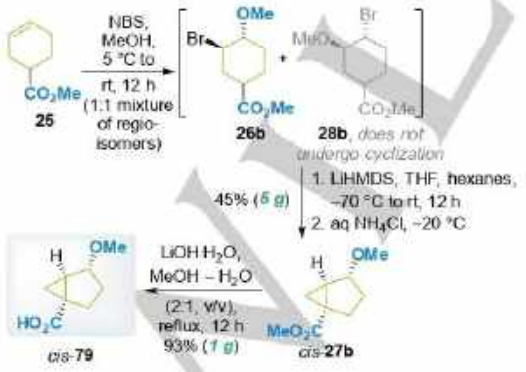


Scheme 15. Synthesis of *trans*-1,4-disubstituted bicyclo[3.1.0]hexane building blocks (relative configurations are shown).

Furthermore, the reaction of bromide **27a** with sodium methoxide provided ester ***trans*-27b** (*dr* 4:1, with *trans* isomer being the major one). As in the previous case, pure carboxylic acid ***trans*-78** was obtained after hydrolysis of compound ***trans*-27b** and recrystallization. Pure ***trans*-27b** could be obtained from ***trans*-78** after esterification.

Unfortunately, an attempted nucleophilic substitution reaction of **26a** with cyanide ion resulted in the formation of a complex mixture, while the reaction with fluoride ion provided mostly the product of the elimination reaction (according to LC-MS and ^{1}H NMR spectra).

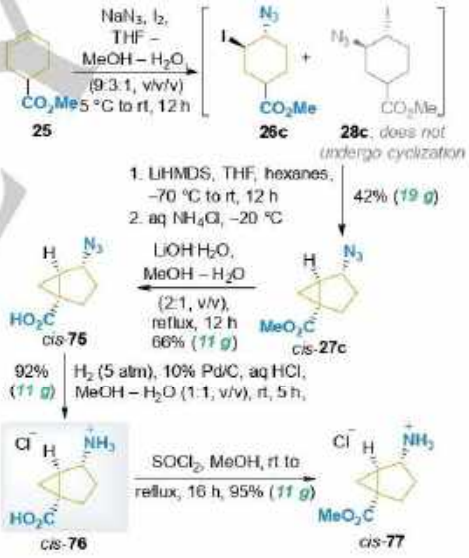
To obtain *cis*-isomeric 1,4-disubstituted bicyclo[3.1.0]hexane derivatives, selectivity of the intramolecular enolate alkylation shown in Scheme 2 was exploited. Thus, methoxybromination of compound **25** gave ca. 1:1 mixture of regioisomers **26b** and **28b**, and only one of them (**26b**) underwent cyclization into bicyclic derivative **27b** (Scheme 16). The latter compound was obtained in 45% yield (5 g scale) after chromatographic purification. Hydrolysis of ester **27b** gave carboxylic acid ***cis*-78** 93% yield.



Scheme 16. Synthesis of building block *cis*-**78** (relative configurations are shown).

In a similar manner, azidoiodination of compound **25** was used to obtain bicyclic azide **27c** (42% yield, 19 g scale) (Scheme 17).

After alkaline hydrolysis of compound **27c** and further catalytic hydrogenation of resulting intermediate ***cis*-75** (66% yield), *cis* isomer of amino acid ***cis*-76** was obtained (92% yield, 11 g scale, as hydrochloride). Esterification of ***cis*-76** provided amino ester ***cis*-77** (95% yield ,11 g scale, as hydrochloride).



Scheme 17. Synthesis of amino acid *cis*-**76** and its derivative *cis*-**77** (relative configurations are shown).

Physicochemical properties. The pK_a measurements were performed with methoxy-substituted carboxylic acids described in this work (**38a**, **47a**, **60a**, **67a**, ***cis*-78**, and ***trans*-78**), known benzene isostere **79**, cycloalkane derivatives **80**–**82**, and methoxybenzoic acids **83a**, **84a** according to the previously reported protocol[28] (Table 2).

Table 2. Physicochemical parameters values of model derivatives studied in

this work (measured at 22 °C)

Carboxylic acid[a]	pK_a (R = OMe)	Log$P^{[b]}$ (R = OMe)	Log$P^{[b]}$ (R = F)
	4.00±0.05	2.31±0.01	2.60±0.04
	4.23±0.04	1.83±0.01	2.35±0.02
	4.30±0.02	2.06±0.02	2.43±0.04
	4.44±0.03	2.43±0.01	2.11±0.01
	4.67±0.03	1.56±0.07	–
	4.38±0.05	1.55±0.06	–
	4.40±0.03	2.02±0.01	–
	4.63±0.07	2.01±0.03	–
	4.37±0.02	2.06±0.01	–
	4.20±0.05	2.07±0.02	–
	4.32±0.04	1.88±0.01	–
	4.40±0.05	1.81±0.01	–
	4.68±0.10	2.70±0.05	2.26±0.03
	3.79±0.04	2.82±0.02	2.68±0.06

[a] Relative configurations are shown.

[b] Measured for anilide derivatives.

[c] The compound was available as a mixture of diastereomers and was used in this form.

The obtained pK_a values for all saturated carboxylic acids varied in the range of 4.0–4.6 units and were between the corresponding values for *m*- and *p*-methoxybenzoic acids (3.8 and 4.7, respectively). The length and number of through-bond pathways between the methoxy and carboxy moieties was the main factor determining the compound's acidity. Thus, the compound **38b** having two C–CH_2–C units between the above functional groups was most acidic among the non-aromatic representatives (pK_a = 4.0). These results confirm that inductive electronic effect is the most important factor defining the compound's acidity in the series studied. Nevertheless, stereoelectronic effects also had a considerable impact on the pK_a value. For example, the compounds with *cis* orientation of the methoxy and carboxy groups were by 0.1–0.2 pK_a units slightly less acidic than the *trans* counterparts (compare the data for the *cis*- and *trans*-isomers of **78a**, **80**, or **82**). One of the reasons behind this might be destabilization of the negatively charged form for the *cis* isomers due to unfavorable dipole moment orientations.

Obviously but still notably, switching to saturated ring systems allowed eliminating resonance effects responsible for higher acidity of *m*-methoxybenzoic acid (pK_a = 3.8) and lower – of the *p*-isomer (pK_a = 4.7).

Log*P* measurements were performed for anilides **85** of the above carboxylic acids using the standard shake-flask method (Table 2).[29] In addition to that, anilides **85b**, **85d**, **85f**, **85h**, **85o**, and **85q** of corresponding fluorine-substituted carboxylic acids **38b**, **47b**, **60b**, **67b**, as well as *p*- and *m*-fluorobenzoic acids **83b**, **84b** were included in this part of the study (since lipophilicity is a more complex phenomenon, and it is preferable to have more data points here). For the methoxy-substituted series, it was found that the bicyclic derivatives were considerably less lipophilic than their aromatic counterparts (Log*P* = 1.55–2.43 *vs* 2.70–2.82,

respectively). Furthermore, the bicyclic compounds had somewhat lower Log*P* value than the corresponding monocylic analogs with the same number of carbon atoms or even those having one less carbon atom (i.e., **78a**/**82** or **47**/**80** anilide pairs). This interesting effect has been already precedented in the literature;[36,38] together with our results, these data suggest that it might have a general nature.

For the bicyclic compounds, increasing the number of carbon atoms typically resulted in higher Log*P* values, but this effect was not general. In particular, for methoxy-substituted derivatives, the lipophilicity increased in the following series:

[3.1.0] (*6*) < [2.2.1] (*7*) < [2.2.2] (*8*) ≈ [3.2.1] (*8*) <
< [4.1.1] (*8*) < [3.2.0] (*7*)

(the numbers correspond to the lengths of the bridges (square brackets) and the total number of the carbon atoms (round brackets) in the bicyclic system). In other words, bicyclo[3.2.0]-heptane-derived anilide of **67a** was an outlier with higher Log*P* value.

Notably, the corresponding fluorine-substituted derivatives were somewhat more lipophilic than methoxy-substituted ones, but the general Log*P* trend remained nearly the same:

[3.2.0] (*7*) < [2.2.1] (*7*) < [3.2.1] (*8*) < [4.1.1] (*8*).

Again, bicyclo[3.2.0]heptane-derived anilide of **67b** was an outlier, with lower Log*P* value this time. We believe that somewhat higher flexibility of the bicyclo[3.2.0]heptane scaffold might be responsible for the observed differences. Since the dipole moment of the C–F bond is directly attached to the ring system, the polarity fluorinated derivatives should be more sensitive to the molecular geometry variations.

Another interesting feature is related to the Log*P* values of stereoisomeric anilides of **78a, 80**, and **82**: the differences were negligible for the methoxy-substituted series. This is contrary to the behavior of monocyclic fluorinated compounds studied previously,[40,41] which might be again related to the higher sensitivity of organofluorine derivatives polarity to the molecular geometry changes.

The lipophilicity of anilides derived from *m*- and *p*-fluorobenzoic acids (**83b** and **84b**) should be also commented. Both compounds were less lipophilic than the corresponding methoxy derivatives, and this effect was more significant for the *p*-isomer (Log*P* = 2.68 and 2.26, respectively). We address this feature to the resonance effects increasing the overall dipole moment of the molecule. These results show that benzene derivatives are not necessarily less lipophilic than their saturated counterparts in the series studied, and fine effects of the functional groups should be also taken into account.

The Craig-type pK_a – Log*P* plot for the methoxy-substituted compound series is shown in Figure 1. These generalized data show that the bicyclic scaffolds studied in this work allow fine-tuning acidity of cycloalkane and benzene derivatives upon isosteric replacements within a range of *ca.* 0.6 pK_a units. In addition to that, the compound's lipophilicity can be also varied within a range of *ca.* 0.9 Log*P* units (and is likely to be decreased, especially for the case of benzene replacement).

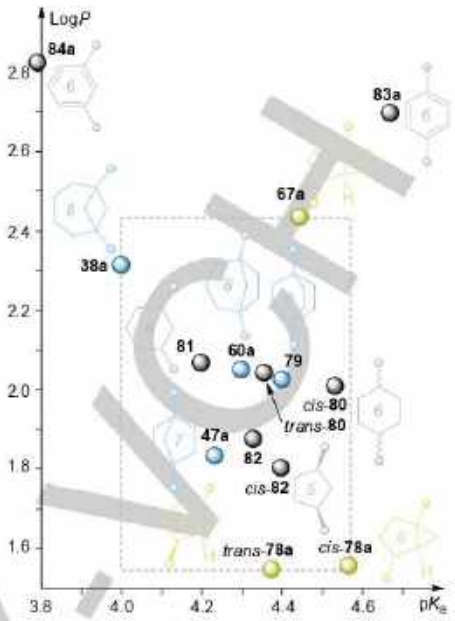


Figure 1. pK_a – Log*P* plot for methoxy-substituted carboxylic acids and their derivatives studied in this work (the numbers inside the rings correspond to the number of carbon atoms in the scaffold).

Structural characterization. To evaluate molecular geometry of the proposed scaffolds, X-Ray diffraction studies were performed with amino acid derivatives **44**, **70**, *cis*-**86**, and *trans*-**86** (Figure 2, *A*). For the corresponding bicyclo[2.2.1]heptane, -[3.2.1]- and -[2.2.2]octane, and benzene derivatives, three-dimensional structures were generated using the Conformer tool of Marvin package.[42] For further discussions, exit vector parameter (EVP)-based method was used,[43,44] which had been applied by our group for analysis of various cyclic systems previously[45-51] and is being adopted by a wider chemical community.[25,27,52-54] The basic idea of this approach is simulating the functional groups mounted onto the scaffold by two exit vectors. Carbon atoms of the (bi)cyclic ring system bearing the functional groups are used as the starting points of these vectors, whereas the direction is defined by the attached bonds (Figure 2, *A*). Relative orientation of two exit vectors can be described by four geometric parameters *r*, φ_1, φ_2, and θ as shown in Figure 2, *B*. For flattened structures, the absolute value of θ tends to be close to 0° or 180°, whereas for linear ones, the φ_1/φ_2 angles are equal to 0°.

Exit vector plots depicted in $r - \theta$ *and* $\theta - \varphi_1/\varphi_2$ coordinates and containing the data for the studied bicyclic scaffolds are shown in Figure 3 and Table 3). It is apparent that geometrically, bridged bicyclic systems synthesized in this work (i.e., bicyclo[2.2.1]heptanes, bicyclo[4.1.1]- and -[3.2.1]octanes) are close mimetics of *m*- and (to lesser extent) *p*-disubstituted benzene, as well as *cis*-1,3-disubstituted cyclohexane scaffold (all located in the β region of exit vector plots). *cis*-Isomeric bicyclo[3.2.0]heptane and especially -[3.1.0]hexane scaffolds are found on the other side of

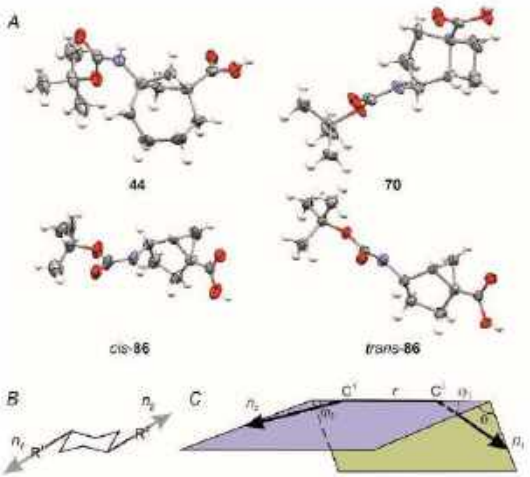


Figure 2. (*A*) Molecular structures of compounds **44**, **70**, *cis*-**86**, and *trans*-**86** according to X-Ray diffraction studies (thermal ellipsoids are shown at 50% probability level). (*B*) Definition of exit vectors $\boldsymbol{n}_1$ and $\boldsymbol{n}_2$ (1,4-disubstituted cyclohexane scaffold is taken as an example). (*C*) Definition of geometric parameters r, φ_1, φ_2, and θ.

Table 3. Geometric parameters r, φ_1, φ_2, and θ of the scaffolds studied in this work.

Entry	Scaffold	r, Å	φ_1, °[a]	φ_2, °	θ, °[b]
1		2.17	42	42	1
2		2.23	21	21	0
3		2.40	30	30	0
4		2.48	73	53	19
5		2.39	72	40	41
6		2.44	39	38	121
7		2.70	0	0	N/D[d]
8[c]		2.97	70	24	4
9[c]		2.96	30	28	177
10[c]		2.52	36	34	5
11[c]		2.53	82	35	116
12[c]		2.42	56	47	13
13[c]		2.45	67	46	151
14		2.85	0	0	N/D[d]
15		2.46	30	30	0

[a] Since the choice of φ_1 and φ_2 is deliberate, we set $\varphi_1 \geq \varphi_2$.

[b] Absolute values are given.

[c] Average values for the cycloalkane scaffolds are retrieved from ref. [43].

[d] For the scaffolds with colinear orientation of exit vectors, the θ angle is undefined.

WILEY-VCH

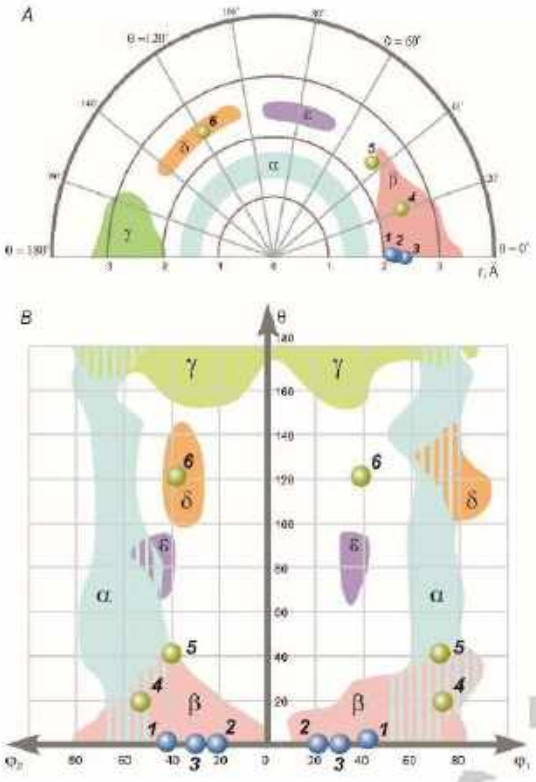
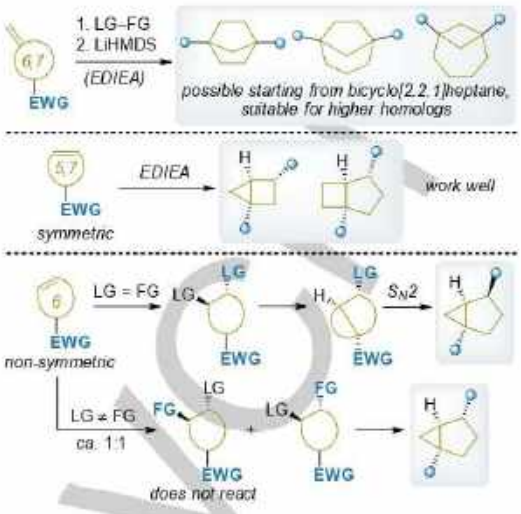


Figure 3. Bicyclic scaffolds synthesized in this work shown in $r-\theta$ (*A*) and $\theta-\varphi_1/\varphi_2$ (*B*) coordinates. Bold italic numbers corresponds to entry numbers in Table 3: ***1*** – bicyclo[4.1.1]octane, ***2*** – bicyclo[2.2.1]heptane, ***3*** – bicyclo[3.2.1]-octane, ***4*** – bicyclo[3.2.0]heptane, ***5*** and ***6*** – *cis*- and *trans*-isomeric bicyclo[3.1.0]hexanes. For the definition of EVP regions α–ε, see ref. [44].

the β EVP region; they can be considered as three-dimensional analogs of *cis*-1,3-disubstituted cyclohexanes and cyclopentanes. Finally, the *trans* isomer of 1,4-disubstituted bicyclo[3.1.0]hexane scaffold demonstrates a close resemblance to *trans*-1,3-disubstituted cyclohexane and (to a lesser extent) cyclopentane scaffolds (all located in the δ EVP region).

Conclusions

Electrophilic double bond functionalization – intramolecular enolate alkylation (*EDIEA*) sequence is an efficient approach for the construction of disubstituted bicyclo[m.n.k]alkane scaffolds starting (where k = 0 or 1) from the appropriate unsaturated cyclic carboxylic acids derivatives (i.e., esters or nitriles) (Scheme 18). The scope of the substrates with exocyclic double bonds (leading to bridged bicyclic ring systems) is limited by the size of the scaffold formed. Thus, bicyclo[2.2.1]heptane (formed from 4-methylenecyclohexane carboxylate) is the smallest ring system that can be constructed using this approach, albeit with moderate yield. Symmetric five- and seven-membered cycloalkenecarboxylic acid derivatives work well in the *EDIEA* sequence, giving the corresponding fused bicyclo[m.n.0]alkanes.



Scheme 18. Summary of the electrophilic double bond functionalization – intramolecular enolate alkylation (*EDIEA*) sequence scope and limitations

With non-symmetric substrates having an endocyclic double bond (e.g., cyclohexene derivative), regioselectivity of the first step becomes an issue. Luckily, the cyclization step is highly selective in this case. Therefore, using a symmetric modification for the electrophilic addition step (e.g., bromination) followed by regioselective intramolecular enolate alkylation and nucleophilic substitution can an approach to obtain *trans*-isomeric derivatives of the corresponding fused bicyclic system (i.e., bicyclo[3.1.0]hexane). On the other hand, non-symmetric electrophilic functionalization can be also used since only one of the regioisomeric addition products undergoes the cyclization at the second step. In this way, *cis* stereoisomers of the above scaffold can be synthesized.

The developed method was amendable for multigram synthesis of mono- and bifunctional bicyclo[4.1.1]- and -[3.2.1]octane, bicyclo[2.2.1]- and -[3.2.0]heptane, bicyclo[3.1.0]hexane, and bicyclo[2.1.0]pentane (housane; previous work) derivatives, including fluorinated amines and carboxylic acids, amino acids, monoprotected diamines, and many other building blocks for medicinal chemistry.

The above bicyclic scaffolds can allow fine-tuning acidity of cycloalkane and benzene derivatives upon isosteric replacements in a range of 0.6 pK_a units. In addition to that, the compound's lipophilicity can be varied in a ca. 0.9 Log*P* unit range; it is likely to be decreased or affected insignificantly. For both parameters, the conjugation effects present in the aromatic series are eliminated.

According to exit vector parameter (EVP) analysis, bicyclo[2.2.1]-heptanes, bicyclo[4.1.1]- and -[3.2.1]octanes are close structural analogs of *m*- and (to lesser extent) *p*-disubstituted benzene, as well as *cis*-1,3-disubstituted cyclohexane scaffold (Figure 4). Fused *cis*- and *trans*-isomeric bicyclo[3.m.0]alkanes (m = 1 or 2) can be used as three-dimensional mimetic of *cis*- and *trans*-1,3-disubstituted cycloalkanes (C_5/C_6), respectively. Of course, a wider range of isosteric replacements can be also envisaged for the synthesized bicyclic derivatives.

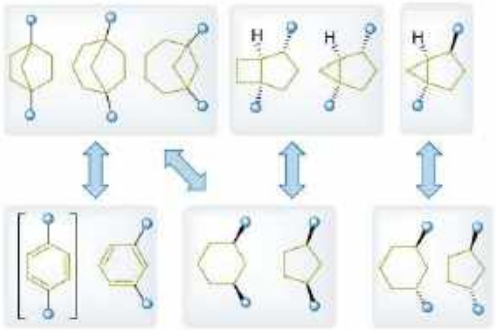


Figure 4. Potential for isosteric replacements using saturated bicyclic ring systems described in this work.

The title bicyclic benzene and cycloalkane isosteres have now become readily available to the scientific community, and with their physicochemical and structural characteristics known, we believe that these and similar ring systems accessible through the *EDiEA* reaction sequence will find their wider application in early drug discovery in the nearest future.

Experimental Section

Compounds **1**, **4**, **7**, **22**, **25**, **46**, **58**, and other reagents were available from Enamine Ltd. or purchased from other commercial sources. Log*P* and pK_a values were measured as described previously [28] Melting points were measured on MPA100 OptiMelt automated melting point system. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on an Agilent ProPulse 600 spectrometer (at 600 MHz for ^{1}H NMR, 151 MHz for ^{13}C NMR), Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR and 470 MHz for ^{19}F NMR) or Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-*d*$_6$. Coupling constants (*J*) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)). pK_a(H) measurements were performed using a SI Analytics TitroLine 7000 automated titrator. Agilent 1260 HPLC instrument equipped with diode-array detector (G1365A) and Agilent 6120B Quadrupole LC-MS with ESI ionisation (Zorbax SB C18 column (2.1×50 mm, 1.8 μm), gradient 0.1% HCO_2H in H_2O – 0.1% HCO_2H in MeCN (90:10 to 0:100) as eluent) was used for Log*P* measurements. Deposition Numbers <url href="https://www.ccdc.cam.ac.uk/services/structures?id=doi:10.1002/chem.202303859"> 2308293 (a single crystal of compound **44** obtained by crystallization from THF), 2308294 (a single crystal of compound **70** obtained by crystallization from MeCN), 2308295 (a single crystal of compound *cis*-**87** obtained by crystallization from EtOAc), and 2308296 (a single crystal of compound *trans*-**87** obtained by crystallization from MeOH) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe <url href="http://www.ccdc.cam.ac.uk/structures">Access Structures service</url>.

Acknowledgements

This work has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (grant agreement No. 101000893 – BENOVELTY), was supported by Enamine Ltd. and Ministry of Education and Science of Ukraine (Grants No. 0121U100387 (21BF037-01M) and 0122U001962 (22BF037-02)). The authors thank Ms. Olga Kovalenko and Ms. Margaryta Bolgova for pK_a measurements, Dr. Eduard Rusanov for X-Ray diffraction studies, Illia O. Doroshenko, Bohdan Sosunovych, and Oleksandr S. Liashuk for their help with manuscript preparation, Prof. Andrey A. Tolmachev for his encouragement and support, and all the brave people of Ukraine for making this publication possible.

Conflict of Interest

Most authors are employees, trainees, or consulting scientists of Enamine Ltd. that offers the building blocks described in this paper in the company's catalog.

Keywords: bicyclic compounds • acidity • lipophilicity • isosteres • enolate alkylation

[1] F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752–6756.
[2] M. Aldeghi, S. Malhotra, D. L. Selwood, A. W. E. Chan, *Chem. Biol. Drug Des.* **2014**, *83*, 450–461.
[3] F. Lovering, *Med. Chem. Commun.* **2013**, *4*, 515–519.
[4] O. O. Grygorenko, D. M. Volochnyuk, S. V. Ryabukhin, D. B. Judd, *Chem. Eur. J.* **2020**, *26*, 1196–1237.
[5] E. K. Davison, M. A. Brimble, *Curr. Opin. Chem. Biol.* **2019**, *52*, 1–8.
[6] L. A. Wessjohann, W. Brandt, T. Thiemann, *Chem. Rev.* **2003**, *103*, 1625–1648.
[7] V. M. Dembitsky, *J. Nat. Med.* **2008**, *62*, 1–33.
[8] L. Wang, Z. Zhang, H. Han, X. Liu, Z. Bu, Q. Wang, *Chinese J. Org. Chem.* **2020**, *41*, 51.
[9] A. Nelson, G. Karageorgis, *RSC Med. Chem.* **2021**, *12*, 353–362.
[10] G. S. Cremosnik, J. Liu, H. Waldmann, *Nat. Prod. Rep.* **2020**, *37*, 1497–1510.
[11] M. Kaiser, S. Wetzel, K. Kumar, H. Waldmann, *Cell. Mol. Life Sci.* **2008**, *65*, 1186–1201.
[12] Z. Fang, Y. Song, P. Zhan, Q. Zhang, X. Liu, *Future Med. Chem.* **2014**, *6*, 885–901.
[13] I. V. Komarov, V. A. Bugrov, A. Cherednychenko, O. O. Grygorenko, *Chem. Rec.* **2023**, e202300276.
[14] A. Mann, in *The Practice of Medicinal Chemistry*, Elsevier, **2008**, pp. 363–379.
[15] O. O. Grygorenko, D. M. Volochnyuk, B. V. Vashchenko, *Eur. J. Org. Chem.* **2021**, 6478–6510.
[16] P. K. Mykhailiuk, *Org. Biomol. Chem.* **2019**, *17*, 2839–2849.
[17] N. A. Meanwell, *Chem. Res. Toxicol.* **2016**, *29*, 564–616.
[18] N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529–2591.
[19] M. A. M. Subbaiah, N. A. Meanwell, *J. Med. Chem.* **2021**, *64*,

14046–14128.

[20] O. O. Grygorenko, P. Babenko, D. M. Volochnyuk, O. Raievskyi, I. V. Komarov, *RSC Adv.* **2016**, *6*, 17595–17605.

[21] Y. P. Auberson, C. Brocklehurst, M. Furegati, T. C. Fessard, G. Koch, A. Decker, L. La Vecchia, E. Briard, *ChemMedChem* **2017**, *12*, 590–598.

[22] A. F. Stepan, C. Subramanyam, I. V. Efremov, J. K. Dutra, T. J. O'Sullivan, K. J. Dirico, W. S. McDonald, A. Won, P. H. Dorff, C. E. Nolan, S. L. Becker, L. R. Pustilnik, D. R. Riddell, G. W. Kauffman, B. L. Kormos, L. Zhang, Y. Lu, S. H. Capetta, M. E. Green, K. Karki, E. Sibley, K. P. Atchison, A. J. Hallgren, C. E. Oborski, A. E. Robshaw, B. Sneed, C. J. O'Donnell, *J. Med. Chem.* **2012**, *55*, 3414–3424.

[23] J. X. Zhao, Y. X. Chang, C. He, B. J. Burke, M. R. Collins, M. Del Bel, J. Elleraas, G. M. Gallego, T. P. Montgomery, J. J. Mousseau, S. K. Nair, M. A. Perry, J. E. Spangler, J. C. Vantourout, P. S. Baran, *Proc. Natl. Acad. Sci. U. S. A.* **2021**, *118*, e2108881118.

[24] A. Denisenko, P. Garbuz, Y. Makovetska, O. Shablykin, D. Lesyk, C. Galeb Al-Maali, R. Korzh, I. V Sadkova, P. K. Mykhailiuk, A. Denisenko, P. Garbuz, Y. Makovetska, O. Shablykin, G. Al-Maali, R. Korzh, I. V Sadkova, P. K. Mykhailiuk, O. V. Shablykin Kukhar, *ChemRxiv* **2023**, DOI: 10.26434/CHEMRXIV-2023-78Z7P.

[25] N. Frank, J. Nugent, B. R. Shire, H. D. Pickford, P. Rabe, A. J. Sterling, T. Zarganes-Tzitzikas, T. Grimes, A. L. Thompson, R. C. Smith, C. J. Schofield, P. E. Brennan, F. Duarte, E. A. Anderson, *Nature* **2022**, *611*, 721–726.

[26] M. Zhong, E. Peng, N. Huang, Q. Huang, A. Huq, M. Lau, R. Colonno, L. Li, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5731–5737.

[27] R. C. Epplin, S. Paul, L. Herter, C. Salome, E. N. Hancock, J. F. Larrow, E. W. Baum, D. R. Dunstan, C. Ginsburg-Moraff, T. C. Fessard, M. K. Brown, *Nat. Commun.* **2022**, *13*, 1–5.

[28] V. V. Semeno, V. O. Vasylchenko, B. V. Vashchenko, D. O. Lutsenko, R. T. Iminov, O. B. Volovenko, O. O. Grygorenko, *J. Org. Chem.* **2020**, *85*, DOI 10.1021/acs.joc.9b03044.

[29] S. Holovach, K. P. Melnykov, A. Skreminskiy, M. Herasymchuk, O. Tavlui, D. Aloshyn, P. Borysko, A. B. Rozhenko, S. V. Ryabukhin, D. M. Volochnyuk, O. O. Grygorenko, *Chem. – A Eur. J.* **2022**, *28*, e202200331.

[30] O. O. Grygorenko, D. Demenko, D. M. Volochnyuk, I. V. Komarov, *New J. Chem.* **2018**, *42*, 8355–8365.

[31] E. Della, A. Knill, *Aust. J. Chem.* **1994**, *47*, 1833.

[32] Y. Iwaki, A. Ohhata, S. Nakatani, K. Hisaichi, Y. Okabe, A. Hiramatsu, T. Watanabe, S. Yamamoto, T. Nishiyama, J. Kobayashi, Y. Hirooka, H. Moriguchi, T. Maeda, M. Katoh, Y. Komichi, H. Ota, N. Matsumura, M. Okada, T. Sugiyama, H. Saga, A. Imagawa, *ACS Med. Chem. Lett.* **2020**, *11*, 1335–1341.

[33] E. W. Della, A. M. Knill, P. E. Pigou, *J. Org. Chem.* **1993**, *58*, 2110–2114.

[34] R. Al Hussainy, J. Verbeek, D. van der Born, A. H. Braker, J. E. Leysen, R. J. Knol, J. Boos, J. (Koos) D. M. Herscheid, *J. Med. Chem.* **2011**, *54*, 3480–3491.

[35] Y. Liu, S. R. Turner, *J. Polym. Sci. Part A Polym. Chem.* **2010**, *48*, 2162–2169.

[36] E. Della, J. Tsanaktsidis, *Aust. J. Chem.* **1985**, *38*, 1705.

[37] L. Perez, M. Mettry, S. S. Hinman, S. R. Byers, K. S. McKeating, B. G. Caulkins, Q. Cheng, R. J. Hooley, *Soft Matter* **2017**, *13*, 3966–3974.

[38] S. L. Degorce, M. S. Bodnarchuk, J. S. Scott, *ACS Med. Chem. Lett.* **2019**, *10*, 1198–1204.

[39] S. L. Degorce, M. S. Bodnarchuk, I. A. Cumming, J. S. Scott, *J. Med. Chem.* **2018**, *61*, 8934–8943.

[40] K. P. Melnykov, K. Nazar, O. Smyrnov, A. Skreminskyi, S. Pavlenko, O. Klymenko-Ulianov, S. Shishkina, D. M. Volochnyuk, O. O. Grygorenko, *Chem. – A Eur. J.* **2023**, *29*, e202301383.

[41] D. O'Hagan, *Chem. – A Eur. J.* **2020**, *26*, 7981–7997.

[42] MarvinView v. 20.13, can be found under www.chemaxon.com.

[43] O. O. Grygorenko, P. Babenko, D. M. Volochnyuk, O. Raievskyi, I. V. Komarov, *RSC Adv.* **2016**, *6*, 17595–17605.

[44] O. O. O. Grygorenko, D. Demenko, D. M. Volochnyuk, I. V. Komarov, *New J. Chem.* **2018**, *42*, 8355–8365.

[45] Y. A. Skalenko, T. V. Druzhenko, A. V. Denisenko, M. V. Samoilenko, O. P. Dacenko, S. A. Trofymchuk, O. O. Grygorenko, A. A. Tolmachev, P. K. Mykhailiuk, *J. Org. Chem.* **2018**, *83*, 6275–6289.

[46] A. V. Denisenko, T. Druzhenko, Y. Skalenko, M. Samoilenko, O. O. Grygorenko, S. Zozulya, P. K. Mykhailiuk, *J. Org. Chem.* **2017**, *82*, 9627–9636.

[47] O. O. Grygorenko, R. Prytulyak, D. M. Volochnyuk, V. Kudrya, O. V. Khavryuchenko, I. V. Komarov, *Mol. Divers.* **2012**, *16*, 477–487.

[48] I. O. Feskov, A. V. Chernykh, Y. O. Kuchkovska, C. G. Daniliuc, I. S. Kondratov, O. O. Grygorenko, *J. Org. Chem.* **2019**, *84*, 1363–1371.

[49] K. P. Melnykov, D. M. Volochnyuk, S. V. Ryabukhin, E. B. Rusanov, O. O. Grygorenko, *Amino Acids* **2019**, *51*, 255–261.

[50] D. S. Radchenko, S. O. Pavlenko, O. O. Grygorenko, D. M. Volochnyuk, S. V. Shishkina, O. V. Shishkin, I. V. Komarov, *J. Org. Chem.* **2010**, *75*, 5941–5952.

[51] V. S. Yarmolchuk, I. L. Mukan, O. O. Grygorenko, A. A. Tolmachev, S. V. Shishkina, O. V. Shishkin, I. V. Komarov, *J. Org. Chem.* **2011**, *76*, 7010–7016.

[52] E. Smith, K. D. Jones, L. O'Brien, S. P. Argent, C. Salome, Q. Lefebvre, A. Valery, M. Bocu, G. N. Newton, H. W. Lam, *J. Am. Chem. Soc.* **2023**, *145*, 16365–16373.

[53] S. Paul, D. Adelfinsky, C. Salome, T. Fessard, M. K. Brown, *Chem. Sci.* **2023**, *14*, 8070–8075.

[54] A. Denisenko, P. Garbuz, N. M. Voloshchuk, Y. Holota, G. Al-Maali, P. Borysko, P. K. Mykhailiuk, *Nat. Chem.* **2023**, *15*, 1155–1163.

[55] G. M. Sheldrick, *Acta Crystallogr. Sect. A* **2007**, *64*, 112–122.

DOI 10.1007/s10593-020-02829-8

Chemistry of Heterocyclic Compounds **2020**, *56*(11), 1411–1413

HETEROCYCLES IN FOCUS

Synthesis of α-spirocyclic pyrrolidines (microreview)

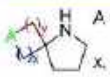
Kostiantyn P. Melnykov[1,2], **Sergey V. Ryabukhin**[1,2]*

[1] *Taras Shevchenko National University of Kyiv, 64 Volodymyrska St., Kyiv 01601, Ukraine; e-mail: s.v.ryabukhin@gmail.com*

[2] *Enamine Ltd., 78 Chervonotkatska St., Kyiv 02094, Ukraine*

Published in Khimiya Geterotsiklicheskikh Soedinenii, 2020, *56*(11), 1411–1413

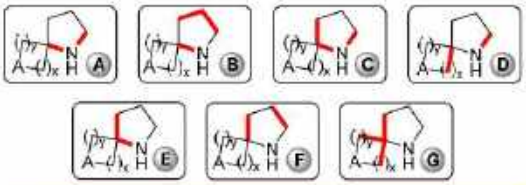
Submitted April 26, 2020
Accepted May 11, 2020



Different approaches and recent advances in methodologies for the synthesis of α-spirocyclic pyrrolidines are presented. The microreview covers the latest selected examples (2009–2019) on the synthesis of such compounds based on pyrrolidine ring construction. The advantages and features of the methods are discussed.

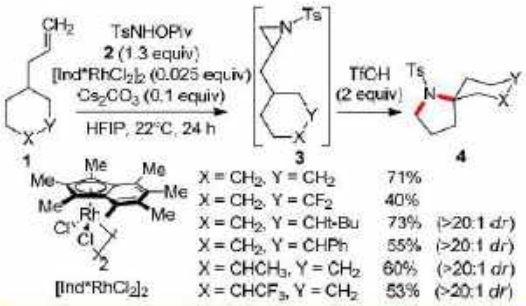
Introduction

The concept of conformational restriction is a modern trend in organic chemistry.[1] sp^3-Enriched, 3D-shaped templates become the place of "traditional" drug design based mainly on (hetero)aromatic cores. This fact prompts for more sophisticated methodologies to produce conformationally restricted analogs and derivatives of common aliphatic heterocycles as medicinally relevant molecules. Low molecular weight spirocyclic motifs as an examples of such building blocks were outlined as a class of compounds highly relevant to drug discovery by Carreira and coworkers in 2010.[2] In this microreview, various methods for the synthesis of α-spirocyclic pyrrolidines are described. All these methods can be divided into groups depending on how the pyrrolidine ring is assembled.



Method A

A prominent example of method A for the synthesis of α-spirocyclic pyrrolidines was described by Lee and coworkers.[3] Alkene **1** reacts with nitrene precursor **2** and forms aziridine intermediate **3** which under the reaction conditions undergoes rearrangement with the formation of the desired compound **4**. Furthermore, regardless of the *trans*/*cis* ratio of the starting allylcyclohexane **1**, the reaction shows excellent diastereoselectivity: in the major product, NTs group and the cyclohexane ring substituent are in equatorial positions.





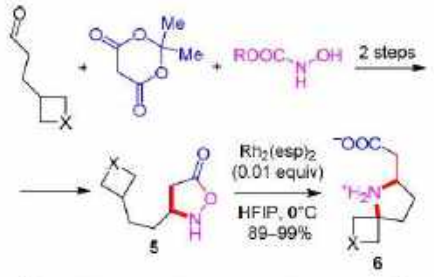
Kostiantyn P. Melnykov was born in 1990 in Mykolaiv, Ukraine. He graduated with honors from the Taras Shevchenko National University of Kyiv, obtaining his MSc degree in 2013. At present, he is a synthetic chemist at Enamine Ltd. He obtained the PhD with a thesis on medicinal chemistry relevant *gem*-difluorocycloalkane building blocks at the Institute of High Technologies, Taras Shevchenko National University of Kyiv. His scientific interests include modern methods in organic synthesis, organofluorine chemistry, organometallic chemistry, chemistry of heterocycles, and medicinal chemistry.



Sergey V. Ryabukhin is a Professor in the Institute of High Technologies, Taras Shevchenko National University of Kyiv. He obtained his PhD in Taras Shevchenko National University of Kyiv in 2008. He has more than 15 years of experience in managing Combinatorial Chemistry Departments as well as chemical outsourcing projects having previously worked in contract research organizations. Now he is also working at Enamine Ltd. as a scientific advisor. Dr. S. V. Ryabukhin is an expert in combinatorial methods in organic chemistry, elaboration of new synthetic methodologies, modern drug discovery. His research interests include organometallics, organofluorine and heterocyclic chemistry, medicinal chemistry, multicomponent reactions.

Method A (continued)

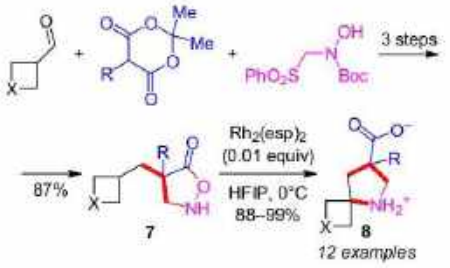
Another approach was developed by Espinosa and coworkers.[4] The target product **6** was formed as a result of the rearrangement of 3-substituted isoxazolidin-5-one **5** with the formation of a homoproline derivative **6**. Precursor **5** can be obtained by the method described by Berini and coworkers.[5]



X = $(CH_2)_4$, $(CH_2)_2Y(CH_2)_2$; Y = CH_2, NCbz, O

Method B

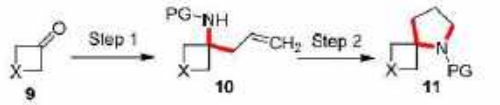
Espinosa and coworkers have developed a method with another type of disconnection from a very close intermediate **7**.[4] The method is based on the rearrangement of 4-substituted isoxazolidin-5-one **7** into the desired product **8**. The yield of this step was quantitative in most cases.



X = $(CH_2)_n$, $(CH_2)_2Y(CH_2)_2$; Y = NBoc, S, O, $C(O(CH_2)_2O)$
R = Me, CH_2CN, $(CH_2)_2COOBn$

Method C

Various methods were described for obtaining target compounds from cyclic ketones.[6–9] All these methods are based on a similar idea: ketones **9** are converted into 1-allyl-1-aminocycloalkanes **10**, after which the latter undergo cyclization with the formation of spirocyclic pyrrolidines **11**. Methods for the synthesis of various α-spirocyclic pyrrolidines **11** with moderate to good overall yields have been developed by our group.[10]



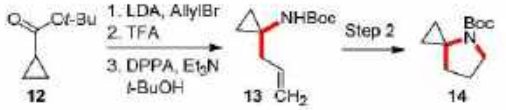
X = $(CH_2)_n$, $(CH_2)_xO(CH_2)_y$, $CH_2SO_2CH_2$; n = 1–4; x,y = 0, 1
PG = Bn; X = y = O; 42–74%*
Step 1: $BnNH_2$, then AllylMgCl
Step 2: aq. HBr, then Br_2, then Et_3N, then $LiAlH_4$

X = $Y(CH_2)_2$, $CH_2CF_2CH_2$; Y = S, SO_2**
PG*** = Cbz, CO_2Et; 25–56%*
Step 1: $PGNH_2$, $AllylSiMe_3$, BF_3
Step 2: I_2, NaBH; then H_2O_2, then MsCl, DIPEA, then NaH

X = $NBoc(CH_2)_2$, CH_2YCH_2, ZCH_2; Y = O, S, NBoc; Z = S, SO_2**
PG*** = Boc, $COCF_3$; 31–49%*
Step 1: AllylBPin, NH_3; then protection
Step 2: I_2, $NaBH_4$, then H_2O_2, then MsCl, DIPEA, then NaH

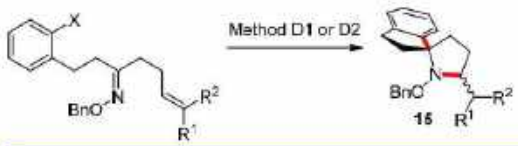
* Overall yield after deprotection.
** SO_2-containing derivative is obtained by oxidation of S-containing derivative by $NaIO_4$, $RuCl_3$ before deprotection.
*** The choice of PG depends on X.

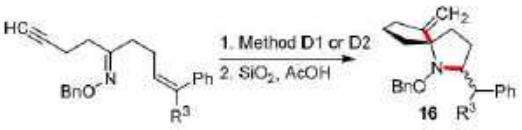
Furthermore, we described the method for the synthesis of 4-azaspiro[2.4]heptane **14**. The key difference compared to the previous scheme is inaccessibility of cyclopropanone. So, another route to key intermediate **13** was needed, starting from cyclopropanecarboxylic acid derivative **12**. The next steps were analogous to the general method. The target compound **14** was obtained in a 24% overall yield.[10]



Method D

Guerrero-Caicedo and coworkers proposed the methods D1 and D2 for the synthesis of 1-azaspiro[4.4]nonanes **15** and **16** using domino radical bicyclization with moderate to good yields.[11] These methods give higher yields compared to the others. Method D1 has shown better diastereoselectivity and higher yields than method **A**. The *N*-protecting group can be easily removed by reduction with Zn/HOAc.[12]



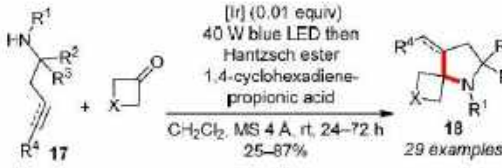


Method D1:
TBTH, AIBN, Δ, 6–8 h, 11–66%
X = Br, I; R^1, R^2 = H, Me, Ph, CN, CO_2Et
R^3 = H 66% 1.1:1 *dr*
R^3 = Ph 64% >20:1 *dr*
trans/*cis*: from 1.4:1 to >20:1

Method D2:
TBTH, Et_3B, rt, 3 h, 23–65%
X = I
R^1, R^2 = H, Ph, CN, CO_2Et
R^3 = H 45% 1.9:1 *dr*
R^3 = Ph 49% >20:1 *dr*
trans/*cis*: from 2.3:1 to >20:1

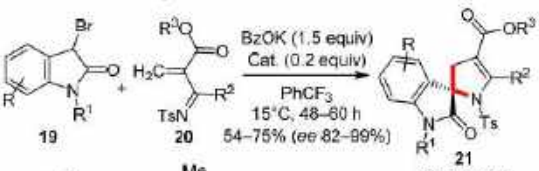
Method E

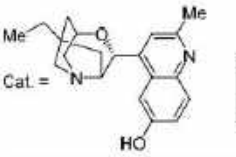
Homoallylamines and homopropargylamines **17** can be converted to the corresponding α-spirocyclic 3-methyl-(methylene)pyrrolidines **18** by Ir^{3+}-catalyzed photochemical reaction.[13] In most cases, this method gives high yields, but low diastereoselectivity.



R^1 = Bn, $(CH_2)_2CN$, Ph, etc.; R^2, R^3 = H, $(CH_2)_nY(CH_2)_m$, CH_2OTIPS; R^4 = H, Me, Ph, Br; X = $(CH_2)_pZ(CH_2)_m$
Y = direct bond, O, NPG, other spirocyclic system
Z = direct bond, O, NPG, SO_2, CF_2; n, m > 0; 2 < n + m < 8

Another similar method was developed for the enantioselective synthesis of spiro[indoline-3,2'-pyrrolidin]-2-one **21** starting from 3-bromooxindole **19** and 1-azadiene **20**.[14] Quinine derivative was used as a chiral catalyst. In most cases enantiomeric excess was excellent. Dihydropyrrole ring can be easily reduced to a pyrrolidine ring with various diastereoselectivity.

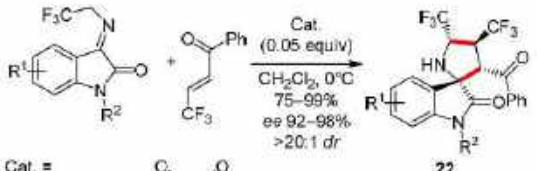


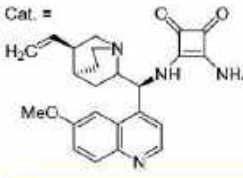


R = H, 5-Cl, 6-Cl, 7-F, 5-Me, 5-MeO, 5,7-Me_2; R^1 = Me, Bn, Ph
R^2 = Ar, Hetar; R^3 = Me, Et, *t*-Bu

Method F

Another enantioselective method for the synthesis of spiro-[indoline-3,2'-pyrrolidin]-2-one **22** is based on [3+2] cycloaddition.[15] Analogously to the previous one this reaction is catalyzed by quinine derivative.

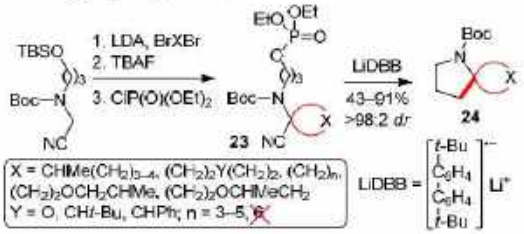




R^1 = H, 4-Cl, 5-Me, 5-MeO, 5-F, 5-Cl, 5-Br, 5-NO_2, 6-Cl, 7-Cl
R^2 = H, Me, Et, Bn, Allyl, Bn

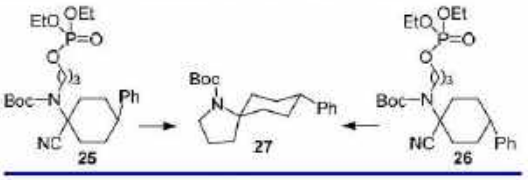
Method G

Perry and coworkers reported a new method for the synthesis of target spirocyclic derivatives **24**.[16,17]



X = CHMe$(CH_2)_{3-4}$, $(CH_2)_2Y(CH_2)_2$, $(CH_2)_n$, $(CH_2)_2OCH_2CHMe$, $(CH_2)_2OCHMeCH_2$
Y = O, CH*t*-Bu, CHPh; n = 3–5, 6

At the key step, LiDBB (it can be stored at –25°C at least for 37 weeks without any loss of reactivity[18]) was used and the pyrrolidine ring was formed. This method showed excellent diastereoselectivity: NBoc group and the cyclohexane ring substituent are located in equatorial position in the major product. It was shown on a series of compounds that the reaction of both possible diastereomers of the intermediate compound **23** (e.g., compounds **25** and **26**) leads to the formation of the sole diastereomer **27**.



References

1. Wipf, P.; Skoda, E. M.; Mann, A. In *The Practice of Medicinal Chemistry*; Wermuth, C.; Aldous, D.; Raboisson, P.; Rognan, D., Eds.; Academic Press, 2015, 4th ed., Chap. 11, p. 279.
2. Burkhard, J. A.; Wagner, B.; Fischer, H.; Schuler, F.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3524.
3. Lee, S.; Lei, H.; Rovis, T. *J. Am. Chem. Soc.* **2019**, *141*, 12536.
4. Espinosa, M.; Noda, H.; Shibasaki, M. *Org. Lett.* **2019**, *21*, 9296.
5. Berini, C.; Sebban, M.; Oulyadi, H.; Sanselme, M.; Levacher, V.; Brière, J.-F. *Org. Lett.* **2015**, *17*, 5408.
6. Bonjoch, J.; Diaba, F.; Puigbó, G.; Solé, D.; Segarra, V.; Santamaría, L.; Beleta, J.; Ryder, H.; Palacios, J.-M. *Bioorg. Med. Chem.* **1999**, *7*, 2891.
7. Bonjoch, J.; Diaba, F.; Puigbó, G.; Peidró, E.; Solé, D. *Tetrahedron Lett.* **2003**, *44*, 8387.
8. Diaba, F.; Puigbò, G.; Bonjoch, J. *Eur. J. Org. Chem.* **2007**, 3038.
9. Jenkins, I. D.; Lacrampe, F.; Ripper, J.; Alcaraz, L.; Van Le, P.; Nikolakopoulos, G.; de Almeida Leone, P.; White, R. H.; Quinn, R. J. *J. Org. Chem.* **2009**, *74*, 1304.
10. Melnykov, K. P.; Artemenko, A. N.; Ivanenko, B. O.; Sokolenko, Y. M.; Nosik, P. S.; Ostapchuk, E. N.; Grygorenko, O. O.; Volochnyuk, D. M.; Ryabukhin, S. V. *ACS Omega* **2019**, *4*, 7498.
11. Guerrero-Caicedo, A.; Soto-Martínez, D. M.; Osorio, D. A.; Novoa, M.; Loaiza, A. E.; Jaramillo-Gómez, L. M. *ACS Omega* **2019**, *4*, 21100.
12. Witkowski, G.; Kowalski, M.; Szyszka, L.; Potopnyk, M. A.; Jarosz, S. *Tetrahedron Asymmetry* **2016**, *27*, 747.
13. Flodén, N. J.; Trowbridge, A.; Willcox, D.; Walton, S. M.; Kim, Y.; Gaunt, M. J. *J. Am. Chem. Soc.* **2019**, *141*, 8426.
14. Zheng, P.-F.; Ouyang, Q.; Niu, S.-L.; Shuai, L.; Yuan, Y.; Jiang, K.; Liu, T.-Y.; Chen, Y.-C. *J. Am. Chem. Soc.* **2015**, *137*, 9390.
15. You, Y.; Lu, W.-Y.; Wang, Z.-H.; Chen, Y.-Z.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2018**, *20*, 4453.
16. Perry, M. A.; Hill, R. R.; Rychnovsky, S. D. *Org. Lett.* **2013**, *15*, 2226.
17. Perry, M. A.; Hill, R. R.; Leong, J. J.; Rychnovsky, S. D. *Org. Lett.* **2015**, *17*, 3268.
18. Hill, R. R.; Rychnovsky, S. D. *J. Org. Chem.* **2016**, *81*, 10707.

RESEARCH ARTICLE

α-CF_3-Substituted Saturated Bicyclic Amines: Advanced Building Blocks for Medicinal Chemistry

Oleh Smyrnov,[a,b] Dr. Kostiantyn P. Melnykov,[a,b] Volodymyr Semeno,[a,b] Oleksandr S. Liashuk,[a,b] and Prof. Dr. Oleksandr O. Grygorenko*[a,b]

Dedicated to the people of Ukraine

[a] Enamine Ltd.
Winston Churchill Street 78, Kyiv 02094, Ukraine
URL: www.enamine.net
[b] Taras Shevchenko National University of Kyiv
Volodymyrska Street 60, Kyiv 01601, Ukraine
E-mail: gregor@univ.kiev.ua
URL: www.grygorenko.com

Supporting information for this article is given via a link at the end of the document.

Abstract: A straightforward approach to α-CF_3-substituted saturated bicyclic amines starting from commercially available compounds is proposed. The key steps include addition of the Ruppert-Prakash reagent to imine moiety and $AlMe_3$-promoted intramolecular heterocyclization. The reaction sequence provides an access to fluorine-containing azabicyclo[n.2.1]alkane (n = 1–3) or azabicyclo[2.2.2]-octane derivatives in 10–42% overall yield. The physicochemical properties of the prepared compounds or their model derivatives (*i.e.*, pK_a and Log*P*) were measured and compared to those for the parent monocyclic or non-fluorinated saturated heterocycles. As expected, amine basicity was lowered considerably upon introduction of the CF_3 group ($\Delta pK_a \approx 4$), while the lipophilicity increased (by ca. 0.5 Log*P* units). The summarized data provides a convenient guideline for application of the synthesized compounds in drug discovery programs.

Introduction

In the last decades, hopping to rigidified structures and enrichment of the sp^3 carbon atom content were found to be effective instruments for fine-tuning the physicochemical properties of a potential drug candidate.[1–6] In particular, bridged bicyclic motifs are widely represented among both natural compounds and synthetic drugs (Figure 1, *A*). On the other hand, introducing fluorine-containing substituents may lead to enhanced metabolic stability, binding affinity, lipophilicity, and aqueous solubility of the developed compound.[7–9] As a result, over 20% of the drug market is occupied by fluorine-containing molecules (Figure 1, *B*);[10–13] which is accompanied by an increased interest to the synthesis of novel fluorine-containing building blocks.[14–18] A combination of two design concepts mentioned above leads to bicyclic fluorine-containing saturated heterocyclic amines, e.g., compounds of general formulae **1** (Figure 2, *A*). While both α-CF_3-substituted monocyclic[19] and non-fluorinated bicyclic[20–22] counterparts of compounds **1a–d** are well-known in the literature, only one of them (**1a**) was synthesized previously through an eight-step photochemical approach (Figure 2, *B*).[16] In view of that, we intended to develop a unified convenient approach to the multigram synthesis of fluorinated amines **1a–d** (Figure 2, *C*). Furthermore, we assessed their key physicochemical properties (i.e., pK_a(H), hereafter denoted simply as pK_a, and Log*P*) and compared to those for the prototype molecules shown in Figure 2, *A*, thus demonstrating their potential as advanced building blocks for medicinal chemistry.

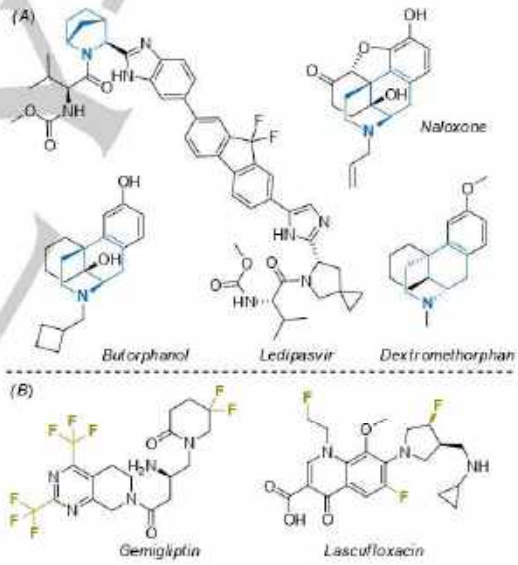


Figure 1. Marketed drugs with bridged (*A*) and fluorinated (*B*) saturated heterocyclic amine moieties.

Results and Discussion

Synthesis. The synthesis of amines **1a–d** was very straightforward and commenced from corresponding commercially available keto esters **2a–d** (Scheme 1). The fluorinated substituents was introduced by addition of the Ruppert-Prakash reagent (CF_3SiMe_3) to the C=N double bond of *N*-benzyl imines **3a–d** according to the reported protocol.[23] Compounds **3a–d** were obtained by reaction of ketones **2a–d** with

benzylamine in the presence of $MgSO_4$. None of the intermediates **3a–d** or **4a–d** were isolated in pure form; instead, amino esters **5a–d** were obtained in 17–65% yield after the catalytic hydrogenolysis step.

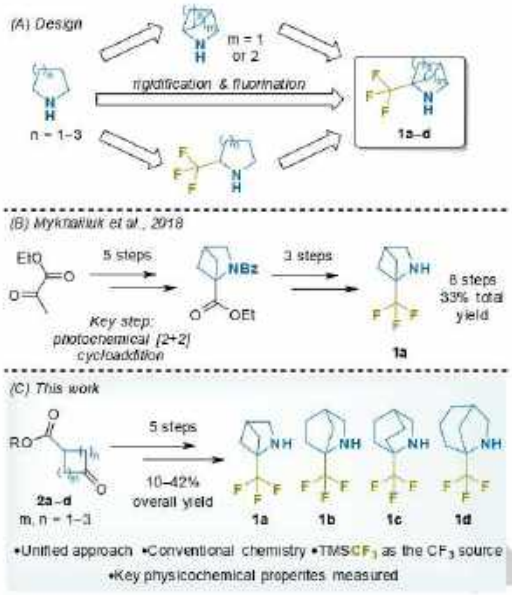
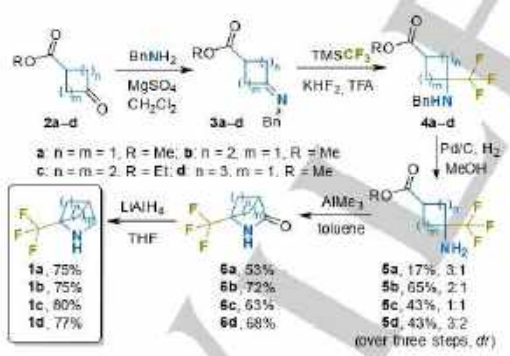


Figure 2. (*A*) Design of α-CF_3-substituted bicyclic amines **1a–d**. (*B*) A reported approach to the synthesis of CF_3-substituted bicyclic amine **1a**. (*C*) Results presented in this work.



Scheme 1. Synthesis of α-CF_3-substituted bicyclic amines **1a–d**.

Notably, the Ruppert – Prakash reagent addition step proceeded with no to moderate diastereoselectivity, so that the products **5a–d** were obtained with *dr* = 1:1 to 3:1. Expectedly, *cis* isomer (which is, fortunately, required for the further cyclization step) was major in most cases, which was confirmed by heteronuclear NOE experiments with compound **5b** (Figure 3, for more details see the Supporting Information).

After some experimentations, it was found that optimal conditions for the construction of the bicyclic system included heating of amino esters **5a–d** with $AlMe_3$ in toluene.[24] In this way, corresponding bicyclic lactams **6a–d** were obtained in 53–72% yields. Surprisingly, the complete conversion of the starting material **5a–d** (both *cis* and *trans* isomers) was observed. This fact can be explained either by intermolecular amide-forming condensations of minor isomer *trans*-**5** or its Me_3Al-promoted epimerization under the reaction conditions. The second hypothesis is confirmed by relatively high yield of the target product, as well as constant *dr* of the starting material during the reaction progress (similar observations were made by Nagao and co-workers[25]).

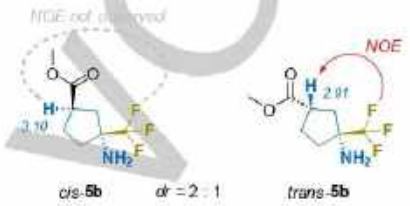


Figure 3. Important correlations in ^1H-^{19}F heteronuclear NOE spectra of compound **5b**.

The final step of the synthetic scheme included the standard $LiAlH_4$-mediated reduction of the amide moiety in the molecules of **6a–d** giving bicyclic amines **1a–d** that were isolated as hydrochlorides in 75–80% yield. Notably, the target compounds were obtained on up to 20 g scale.

Basicity. The pK_a values for amines **1a–d** and their non-fluorinated analogs were measured by standard acid-base titration; for the monocyclic counterparts, the data was retrieved from our previous work[19] (Figure 4). Expectedly, the introduction of the α-CF_3 group resulted in a significant drop of the basicity (by 4.2–4.4 pK_a units), which is obviously due to the strong negative inductive effect of the fluorine atoms and consistent with the previous observations for the monocyclic ring systems.[19,26] At the same time, introducing the α-CH_3 fragment led to a considerable rise in the compound's basicity (ΔpK_a up to 0.59 for the **1n/o** pair). Notably, while imposing the conformation restriction resulted in a slightly decreased basicity for the non-fluorinated series, an opposite trend was typically observed for the fluorine-containing counterparts (i.e., compounds **1a** and **1c**; note also a smaller difference for the **1b/1i** pair as compared to **1k/1m**). A possible explanation might include a partial disruption of the CF_3 group inductive effect transmission pathways due to the distortion of the molecule imposed by the bicyclic system.

Lipophilicity. Log*P* values were measured for benzamides **7a–o** (prepared by benzoylation of amines **1a–o** under the standard reaction conditions) using the classical shake-flask method combined with HPLC quantitative analysis as reported previously (Figure 5).[27] For benzamides **7e**, **7g**, **7l**, and **7m**, the corresponding data was retrieved from our previous work.[19] As should be expected, introducing the CF_3 substituent into the bicyclic ring system resulted in increased compound's lipophilicity.[28] However, this effect was less pronounced as compared to the monocyclic ring

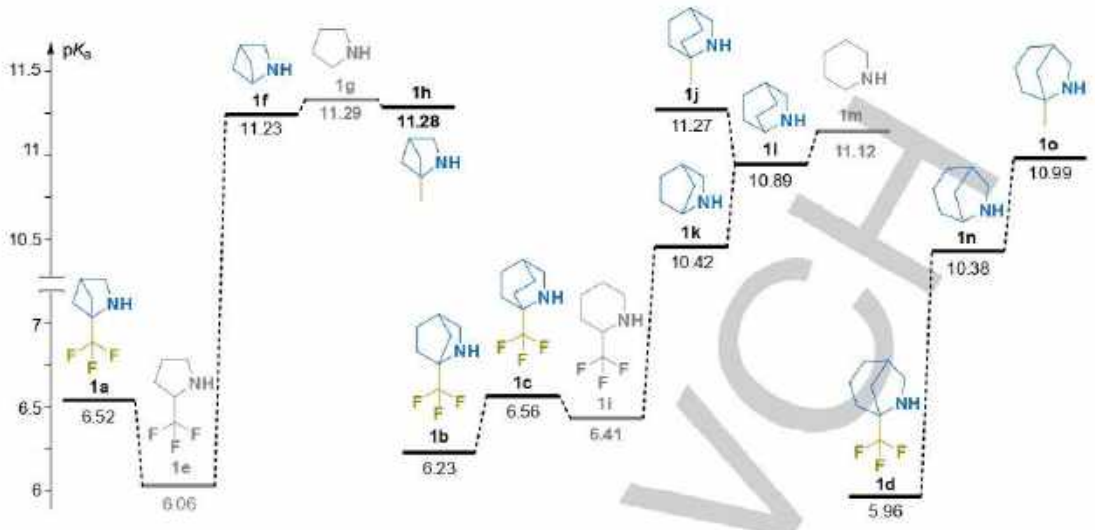


Figure 4. pK_a values of CF_3-substituted bicyclic amines **1a–d**, non-fluorinated bicyclic amines **1f**, **1h**, **1j–l**, **1n**, **1o**, CF_3-substituted amines **1e**, **1i**, and parent heterocycles **1g**, **1m**.

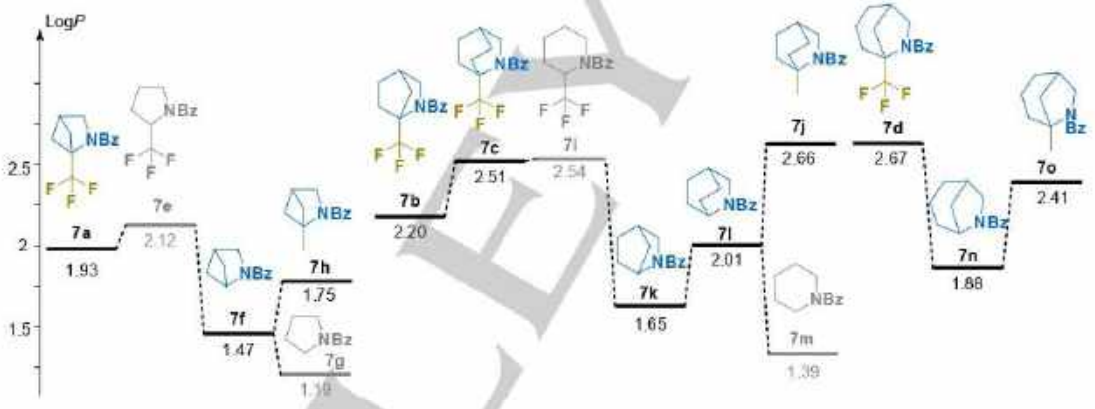


Figure 5. Log*P* values of CF_3-substituted bicyclic amides **7a–d**, non-fluorinated bicyclic amides **7f**, **7h**, **7j–l**, **7n**, **7o**, CF_3-substituted amides **7e**, **7i**, and parent derivatives **7g**, **7m**.

systems (ΔLog*P* = 0.46–0.82 and 0.93–1.15 for the bi- and monocyclic series, respectively). Furthermore, whereas non-fluorinated bicyclic amines were more lipophilic as compared to the parent monocyclic derivatives (which may be expected because of the additional CH_2 groups), an opposite trend was observed for the CF_3-substituted series. At the same time, expected increase of the lipophilicity upon introducing of methyl group on the lipophilicity in bicyclic compounds **7h**, **7j** and **7o** should be also mentioned. On the other hand, the corresponding CF_3-substituted counterparts were typically even more lipophilic. A possible explanation might include a rigid fixation of the corresponding functional group dipole moments by the bicyclic systems increasing the overall molecule's polarization (Figure 6), which is less prominent in monocyclic counterparts. Alternatively, the conformational equilibrium around the amide bond might be affected.[29] Notably, similar experimental results were obtained for bicyclic morpholine and piperazine analogs.[2]

The above results illustrate that simple additive models based on the structural fragment increments can give only approximate values of pK_a and especially Log*P* within the series studied. In other words, the impact of both fluorinated substituent and bicyclic system should be considered simultaneously.

Craig-type (Log*P* – pK_a) plot. Isosteric replacement optimization studies often require simultaneous control of several physico-chemical properties rather than one. In this view, pK_a – Log*P* plots (analogous to the classical Craig plots[30]) can be useful representation for the compound series studied in this work (Figure 7).

WILEY-VCH



Figure 6. Functional group dipole moments in mono- and bicyclic α-CF_3-substituted amines (schematic representation).

Expectedly, the fluorinated bicyclic amines **1a–d** proposed in this work occupy the low-pK_a area characteristic for amines bearing the fluorinated substituent closely to the basic center (pK_a = 5.96–6.56, Log*P* = 1.93–2.67). As it can be seen from the plot, compounds **1a–d** provide a nice complementation to this scarcely populated part of the chemical space and can be useful for fine-tuning physicochemical properties within this area.

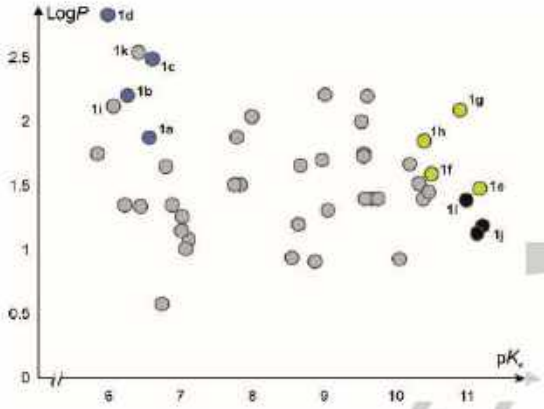


Figure 7. Key compounds of this work shown in the Log*P* – pK_a(H) plot along with other fluorinated saturated heterocyclic amines described previously.[13] Data point colors: blue – α-CF_3-substituted bicyclic amines **1a–d**; yellow – non-fluorinated bicyclic amines **1f**, **1h**, **1j–l**, **1n**, **1o**; gray – monocyclic fluorine-substituted amines, including **1e** and **1i**; black – parent saturated heterocyclic amines, including pyrrolidine (**1g**) and piperidine (**1m**).

Conclusions

A combination of fluorination and rigidification can be a promising concept in design of advanced building blocks relevant to medicinal chemistry, in particular, when applied to saturated heterocyclic ring systems. In this work, this strategy is illustrated by design, synthesis, and physicochemical evaluation of α-CF_3-substituted bridged bicyclic amines. It is shown that the target amines can be obtained in multigram quantities (up to 20 g) in only five steps starting from commercially available oxocycloalkane carboxylates; the key steps of the reaction sequence included the Ruppert-Prakash reagent addition to the imine C=N double bond and Me_3Al-promoted lactam formation.

Expectedly, the title compounds occupy the part of chemical space characteristic for amines bearing the fluorinated substituent closely to the basic center (pK_a = 5.96–6.56, Log*P* = 1.93–2.67). They nicely complement this scarcely populated area, thus allowing to fine-tune the corresponding physicochemical properties in medicinal chemistry optimization studies. Interesting trends were observed when the conformational restriction imposed by the bicyclic ring system was applied to CF_3-containing and non-fluorinated compound series. Thus, non-fluorinated bicyclic compounds were slightly less basic and more lipophilic than the parent saturated heterocycles (i.e., pyrrolidine and piperidine), whereas the opposite trends were observed for the fluorine-containing counterparts. These results show that the impact of simultaneous fluorination and rigidification can be complex in these systems, and only approximate estimations of the physicochemical properties can be made when these effects are considered separately.

The title compounds comply with recent criteria for the design of building blocks relevant to drug discovery (i.e., they are low-molecular-weight, sp^3-enriched, rigid, and fluorine-containing).[31,32]Taking into account this fact, as well as their current synthetic accessibility and interesting physicochemical properties, we expect their implementation by medicinal chemistry community in the nearest future.

Experimental Section

The solvents were purified according to the standard procedures.[33] Compounds **1f**, **1h**, **1j–l**, **1n**, **1o** were obtained from Enamine stock; all other starting materials were available commercially. Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^1H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^1H NMR, 126 MHz for ^{13}C NMR and 470 MHz for ^{19}F NMR) and Varian Unity Plus 400 spectrometer (at 400 MHz for ^1H NMR, 101 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^1H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^1H and ^{13}C in DMSO-d_6. Coupling constants (*J*) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and Agilent 5890 Series II 5972 MS instrument (electron impact ionization (EI)). High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer.

General procedure for the synthesis of amino esters 5

A mixture of ketone **1** (0.703 mol), benzylamine (75.4 g, 0.703 mol), and powdered anhydrous magnesium sulphate (253 g, 2.11 mol) in dichloromethane (1200 mL) was stirred at rt for 96 h. The suspension was filtered, the organic solvent was removed under reduced pressure, and the residue was dried under vacuum (1 mmHg) for 2 h. The crude residue containing imine **3** was used in the next step without any purification.

Imine **3** (ca. 0.703 mol) was dissolved in CH_3CN (1300 mL), and the solution was cooled to 0 °C in an ice/water bath. Trifluoroacetic acid (70.5 mL, 0.914 mol), KHF_2 (43.9 g, 0.563 mol), and DMF (200 mL) were subsequently added to the reaction mixture with intensive stirring. Me_3SiCF_3 (162.1 mL, 1.05 mol) was carefully added to the reaction mixture in a dropwise manner, and the resulting suspension was stirred at ambient temperature for 12 h. After the reaction was completed (monitored by ^1H NMR spectroscopy), the organic solvents were evaporated under reduced pressure, and the crude residue was treated with sat aq Na_2CO_3 (500 mL) with additional stirring for 5 min. The resulting mixture was diluted with water (500 mL) and extracted with EtOAc (3 × 400 mL). The combined organic layers were washed with water (3 × 100 mL) and brine (3 × 100

mL), dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was dissolved in minimum amounts of dioxane and treated with anhydrous HCl (ca. 5 M in dioxane, 400 mL), and the volatiles were removed under reduced pressure. Trituration of the viscous residue with *t*-BuOMe, filtration of the obtained suspension, and drying under high vacuum (1 mmHg) resulted in a brownish solid containing amine **4**. The crude material was used in the next step without additional purification.

Compound **4** (ca. 0.58 mol) was dissolved in MeOH (1600 mL), and Pd/C (10% w/w, 17.5 g) was added in one portion. The reaction vessel was evacuated and backfilled with H_2 from a balloon (repeated 3 times), and the resulting mixture was kept under H_2 atmosphere with intensive stirring overnight. After the reaction was completed (monitored by ^{1}H NMR spectroscopy), the suspension was filtered through a celite pad, and the organic solvent was evaporated under reduced pressure. The residue was dissolved in 5% aq HCl (ca. 1 L) and washed with CH_2Cl_2 (3 × 500 mL). Aqueous layer was basified with solid Na_2CO_3 to pH = 9 and extracted with CH_2Cl_2 (3 × 500 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated on vacuo to afford crude material, which was purified by fractional distillation under reduced pressure to give amine **5**.

General procedure for the synthesis of lactams 6

Compound **5** (47.4 mmol) was dissolved in toluene (400 mL) under argon atmosphere. Me_3Al (2 M in heptane, 47.4 mL, 94.8 mmol) was added via syringe in a dropwise manner, and the resulting mixture was stirred at 80 °C overnight. After the reaction was completed (monitored by ^{1}H NMR spectroscopy; additional amounts of Me_3Al were added if necessary), the reaction mixture was cooled to rt and poured onto 15% aq $NaHSO_4$ (400 mL). The precipitate formed was removed by filtration and washed with EtOAc (3 × 100 mL). The aqueous layer was extracted with EtOAc (4 × 300 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was redissolved in a minimal amount of CH_2Cl_2 and passed through a silica gel pad (ca. 150 g) using *t*-BuOMe as eluent. Obtained filtrate was concentrated under reduced pressure and dried on air to afford compound **6** as yellow solid.

General procedure for the synthesis of amines 1a–d (as hydrochlorides)

$LiAlH_4$ (4.32 g, 0.114 mol) was suspended in THF (200 mL) under argon atmosphere, and the mixture was cooled to 0 °C. Compound **6** (55.8 mmol) was dissolved in THF (40 mL) and added to the $LiAlH_4$ suspension in a dropwise manner, keeping the internal temperature below 5 °C. After completion of the addition, the reaction mixture was gradually heated to reflux (over ca. 90 min) and stirred for 8 h at the same temperature. The resulting suspension was cooled to 0 °C in an ice/water bath and quenched by the dropwise addition of water (5 mL). Insoluble inorganic salts were filtered off, washed with *t*-BuOMe (3 × 50 mL), and discarded. The obtained filtrate was concentrated under reduced pressure, the residue was diluted with 15% aq HCl (ca. 200 mL), washed with CH_2Cl_2 (3 × 50 mL), basified with 10% aq NaOH to pH = 14, and extracted with Et_2O (3 × 200mL). The combined ethereal solutions were dried over Na_2SO_4, transferred into flask, and triturated with anhydrous HCl (ca. 5 M in dioxane, 100 mL). Turbid solution was concentrated under reduced pressure and triturated with Et_2O (150 mL). The precipitate formed was collected by filtration and dried in high vacuo (1 mmHg) to give compound **1**·HCl as beige solid.

General procedure for the synthesis of benzamides 7

To a pre-cooled to 0 °C solution of amine hydrochloride **1**·HCl (1.50 mmol) and NEt_3 (3.00 mmol) in CH_2Cl_2 (5 mL) pure benzoyl chloride (0.17 mL, 1.45 mmol) was added in a dropwise manner. Resulted mixture was stirred at rt overnight, then diluted with sat aq $NaHCO_3$ (15 mL) and CH_2Cl_2 (10mL). The layers were separated, organic solution was washed with sat aq $NaHCO_3$ (3 × 10 mL), 10% aq $NaHSO_4$ (3 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford crude product, which was crystallized from hexane to afford analytically pure amides **7**.

Acknowledgements

The work was supported by Enamine Ltd. and Ministry of Education and Science of Ukraine (Grants No. 0121U100387 (21BF037-01M) and 0122U001962 (22BF037-02)). The authors thank Dr. Andriy Kozytskyi for advanced NMR experiments, Ms. Olga Kovalenko and Ms. Margaryta Bolgova for pK_a titrations, Mr. Andriy Skreminskyi for Log*P* measurements, Prof. Andrey A. Tolmachev for his encouragement and support, and all the brave people of Ukraine for making finalizing this publication possible.

Supporting Information

The authors have cited ref.[16] in the Supporting Information.

Conflict of Interest

The authors are / have been employees, trainees, or consulting scientists of Enamine Ltd. that offers all the building blocks described in this paper in the company's catalog.

Keywords: fluorine • saturated compounds • nitrogen heterocycle • bicyclic compounds • physicochemical properties

[1] F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752–6756.

[2] S. L. Degorce, M. S. Bodnarchuk, I. A. Cumming, J. S. Scott, *J. Med. Chem.* **2018**, *61*, 8934–8943.

[3] J. Meyers, M. Carter, N. Y. Mok, N. Brown, *Future Med. Chem.* **2016**, *8*, 1753–1767.

[4] Z. Fang, Y. Song, P. Zhan, Q. Zhang, X. Liu, *Future Med. Chem.* **2014**, *6*, 885–901.

[5] A. Mann, in *The Practice of Medicinal Chemistry*, Elsevier, **2008**, pp. 363–379.

[6] M. Aldeghi, S. Malhotra, D. L. Selwood, A. W. E. Chan, *Chem. Biol. Drug Des.* **2014**, *83*, 450–461.

[7] K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886.

[8] K. Müller, *Fluorination Patterns in Small Alkyl Groups: Their Impact on Properties Relevant to Drug Discovery*, Academic Press, **2019**.

[9] N. A. Meanwell, *J. Med. Chem.* **2018**, *61*, 5822–5880.

[10] M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633–10640.

[11] J. Han, A. M. Remete, L. S. Dobson, L. Kiss, K. Izawa, H. Moriwaki, V. A. Soloshonok, D. O'Hagan, *J. Fluor. Chem.* **2020**, *239*, 109639.

[12] C. Rizzo, S. Amata, I. Pibiri, A. Pace, S. Buscemi, A. Palumbo Piccionello, *Int. J. Mol. Sci.* **2023**, *24*, 7728.

[13] J. He, Z. Li, G. Dhawan, W. Zhang, A. E. Sorochinsky, G. Butler, V. A. Soloshonok, J. Han, *Chinese Chem. Lett.* **2023**, *34*, 107578.

[14] O. O. Grygorenko, K. P. Melnykov, S. Holovach, O. Demchuk, *ChemMedChem* **2022**, *17*, e202200365.

[15] K. P. Melnykov, O. V Voloshyna, B. V Vashchenko, O. P. Demchuk, O. V Hryshchuk, O. O. Grygorenko, *Eur. J. Org. Chem.* **2022**, e202200863.

[16] V. V Levterov, O. Michurin, P. O. Borysko, S. Zozulya, I. V Sadkova, A. A. Tolmachev, P. K. Mykhailiuk, *J. Org. Chem.* **2018**, *83*, 14350–14361.

[17] D. van der Born, A. Pees, A. J. Poot, R. V. A. Orru, A. D. Windhorst,

D. J. Vugts, *Chem. Soc. Rev.* **2017**, *46*, 4709–4773.

[18] D. Cahard, J.-A. Ma, Eds. , *Emerging Fluorinated Motifs: Synthesis, Properties and Applications*, Wiley-VCH, **2020**.

[19] K. P. Melnykov, O. Tavlui, A. Skreminskiy, Y. O. Kuchkovska, O. O. Grygorenko, *Chem. Eur. J.* **2022**, *28*, e202201601.

[20] A. Heesing, W. Herdering, *Chem. Ber.* **1983**, *116*, 1081–1096.

[21] G. R. Krow, R. Edupuganti, D. Gandla, F. Yu, M. Sender, P. E. Sonnet, M. J. Zdilla, C. DeBrosse, K. C. Cannon, C. W. I. I. I. Ross, A. Choudhary, M. D. Shoulders, R. T. Raines, *J. Org. Chem.* **2011**, *76*, 3626–3634.

[22] L. H. Werner, S. J. Ricca, *J. Am. Chem. Soc.* **1958**, *80*, 2733–2736.

[23] D. S. Radchenko, O. M. Michurin, A. V Chernykh, O. Lukin, P. K. Mykhailiuk, *Tetrahedron Lett.* **2013**, *54*, 1897–1898.

[24] J. Li, K. Subramaniam, D. Smith, J. X. Qiao, J. J. Li, J. Qian-Cutrone, J. F. Kadow, G. D. Vite, B.-C. Chen, *Org. Lett.* **2012**, *14*, 214–217.

[25] S. Sano, H. Shimizu, Y. Nagao, *Tetrahedron Lett.* **2005**, *46*, 2887–2891.

[26] M. Morgenthaler, E. Schweizer, A. Hoffmann-Röder, F. Benini, R. E. Martin, G. Jaeschke, B. Wagner, H. Fischer, S. Bendels, D. Zimmerli, J. Schneider, F. Diederich, M. Kansy, K. Müller, *ChemMedChem* **2007**, *2*, 1100–1115.

[27] S. Holovach, K. P. Melnykov, A. Skreminskiy, M. Herasymchuk, O. Tavlui, D. Aloshyn, P. Borysko, A. B. Rozhenko, S. V Ryabukhin, D. M. Volochnyuk, O. O. Grygorenko, *Chem. Eur. J.* **2022**, *28*, e202200331.

[28] K. Müller, in *Fluorine in Life Sciences: Pharmaceuticals, Medicinal Diagnostics, and Agrochemicals*, Elsevier, **2019**, pp. 91–139.

[29] B. Linclau, Z. Wang, B. Jeffries, J. Graton, R. J. Carbajo, D. Sinnaeve, J.-Y. Le Questel, J. S. Scott, E. Chiarparin, *Angew. Chem. Int. Ed.* **2022**, *61*, e202114862.

[30] P. N. Craig, *J. Med. Chem.* **1971**, *14*, 680–684.

[31] O. O. Grygorenko, D. M. Volochnyuk, B. V. Vashchenko, *Eur. J. Org. Chem.* **2021**, 6478–6510.

[32] O. O. Grygorenko, D. M. Volochnyuk, S. V. Ryabukhin, D. B. Judd, *Chem. Eur. J.* **2020**, *26*, 1196–1237.

[33] W. L. F. Armarego, C. Chai, *Purification of Laboratory Chemicals*, Elsevier: Oxford, **2003**.

WILEY-VCH

N-Difluorocyclopropyl-substituted pyrazoles: synthesis and reactivity

Pavel S. Nosik,[a,b] Andrii S.Poturai,[a,b] Mykola O. Pashko,[a,b] Kostiantyn P. Melnykov,[a,b] Dr. Sergey V. Ryabukhin,[b] Dr. Dmitriy M. Volochnyuk[c,*] and Dr. Oleksandr O. Grygorenko[a, b*]

Abstract: Difluorocyclopropanation of *N*-vinylazoles with the CF_3SiMe_3 – NaI system was studied. It was found that *N*-vinylpyrazoles could be transformed into the corresponding *N*-difluorocyclopropyl-substituted derivatives. The method was efficient on a 100 g scale and could be applied for the preparation of various functionalized regioisomeric pyrazole derivatives bearing a *gem*-difluorocyclopropane moiety, e.g. amines, carboxylic acids, aldehydes, bromides, and boronic ester. It was found that *N*-difluorocyclopropylpyrazole moiety tolerated many common reagents including nitrating mixture, bromine, aqueous acids and alkali, $KMnO_4$, $LiBH_4$, and $Pd^{(0)}$ complexes; it was unstable towards $AlCl_3$, catalytic hydrogenation and lithiation conditions. The products obtained are advanced building blocks which of potential importance to medicinal and agrochemistry.

Introduction

Fluorinated cyclopropanes have become extraordinary structural motifs which attracted much attention in organic synthesis, drug discovery and agrochemistry over the last years.[1–10] In particular, highly potent compounds bearing a *gem*-difluorocyclopropyl substituent were disclosed in recent patents, **e.g.** as highly potent metabotropic glutamate receptor 2 (mGluR2) agonists **1**,[11] glycine transporter 1 (GlyT1) inhibitor **2**,[12] extracellular signal-regulated kinase 2 (ERK2) inhibitors **3**,[13] or macrocyclic factor XIa (FXIa) inhibitor **4**[14] (Figure 1).

While a number of papers describe synthetic approaches to the compounds having a *gem*-difluorocyclopropyl group attached to the carbon atom,[15–24] as well as their chemical transformations,[6,25–29] the corresponding *N*-substituted analogues are much less studied. Most of them referred to the parent *gem*-difluorocyclopropylamine (**5**) or its derivatives (Scheme 1);[26,30–33] it should be noted that similar aliphatic amines (**e.g. 6**) were reported to have limited stability.[34] In a recent paper by Xiao and co-workers, a few *N*-difluorocyclopropyl-substituted indole, benzimidazole and benzotriazole derivatives of general formula **7** were synthesized by *N*-alkylation of the corresponding heterocyclic anions with tosylate **8**.[35] In the current work we describe an alternative approach to *N*-difluorocyclopropyl-substituted azo-

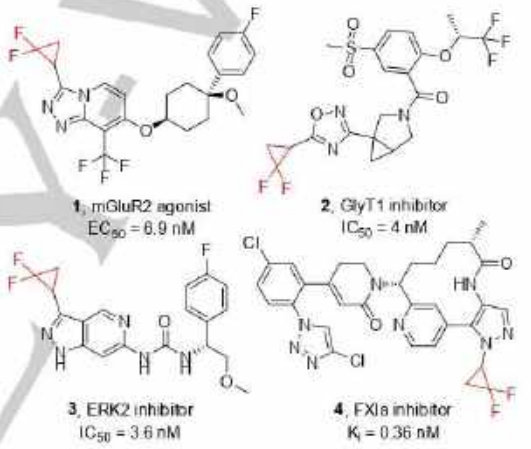
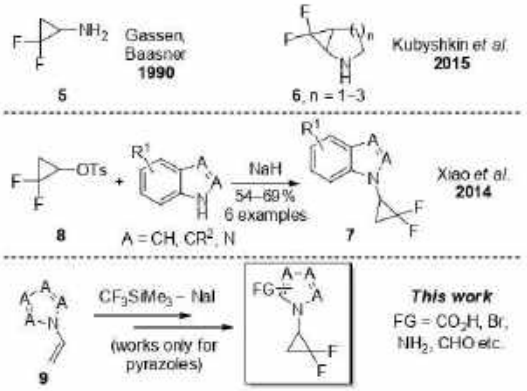


Figure 1. Biologically active heterocyclic compounds bearing a *gem*-difluorocyclopropyl substituent



Scheme 1. Synthesis of compounds bearing a *gem*-difluorocyclopropyl substituent at the nitrogen atom

[a] P.S. Nosik, A. S.Poturai, M. O. Pashko, K. P. Melnykov, Dr. O. O. Grygorenko
Enamine Ltd. (www.enamine.net)
Chervonotkatska Street 78, Kyiv 02094, Ukraine
[b] P.S. Nosik, A. S.Poturai, M. O. Pashko, K. P. Melnykov, Dr. S. V. Ryabukhin, Dr. O. O. Grygorenko*
Taras Shevchenko National University of Kyiv
Volodymyrska Street 60, Kyiv 01601, Ukraine
E-mail: gregor@univ.kiev.ua (O.O.G.)
URL: https://orcid.org/0000-0002-6036-5859
[c] Dr. D. M. Volochnyuk
Institute of Organic Chemistry, National Academy of Sciences of Ukraine
Murmanska Street 5, Kyiv 02094, Ukraine
E-mail: d.volochnyuk@gmail.com (D.M.V.)

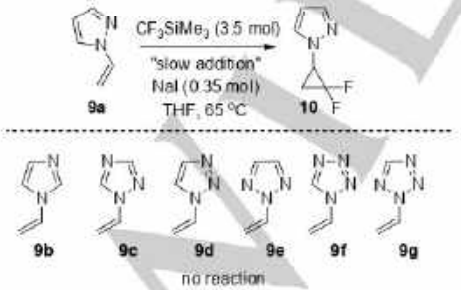
Supporting information for this article is given via a link at the end of the document.

les, which is based on the difluorocyclopropanation of the corresponding *N*-vinylazoles **9** with the CF_3SiMe_3 – NaI system, which was initially developed by Hu, Prakash, Olah and co-workers in 2011,[15] and has been used by many other groups since then.[16–19,36–38] Although this method appeared to be suitable only for the pyrazole derivatives, a wide range of functionalized compounds could be obtained, which are valuable low-molecular-weight building blocks for drug discovery and agrochemistry. In addition to that, tolerance of the *N*-difluorocyclopropyl-substituted azole moiety towards the conditions of common organic reactions is studied herein.

Results and Discussion

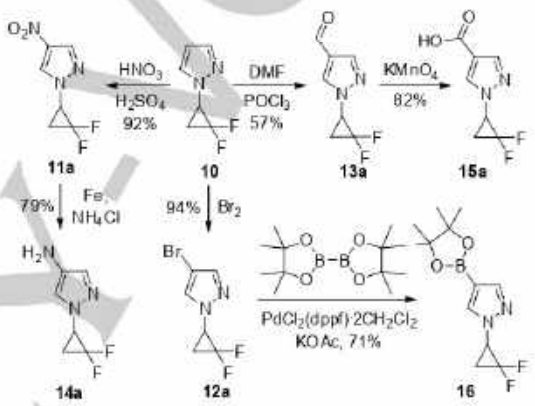
First of all, the conditions of Xiao and co-workers[36] (*i.e.* reaction of tosylate **8** with azole anion) were tested for the case of pyrazole. It was found that the method was unfruitful in this case. Therefore, we have prepared the parent *N*-vinylazoles **9a–g** using the known procedures[39,40] and evaluated them in the reaction with the CF_3SiMe_3 – NaI system. It was found that pyrazole derivative **9a** reacted smoothly when "slow addition" protocol was used (CF_3SiMe_3 (3.5 mol, added over 12–16 h), NaI (0.35 mol, reflux),[15,19] and the corresponding product **10** was obtained in 83% yield (Scheme 2). It should be noted that this transformation was performed at up to 128 g scale without considerable changes in the yield. In some cases, however, the reaction proceeded vigorously after addition of *ca.* 0.8–1.2 equivalents of CF_3SiMe_3; an induction period was observed. This is yet another fact showing that the reaction cannot be described simply as difluorocarbene cycloaddition;[18,20] in particular, some type of radical mechanism might be involved.

Unfortunately, other azole derivatives **9b–g** were unreactive towards the Ruppert–Prakash reagent with the use of either "one-batch" or "slow addition" protocol;[18,19] no conversion of **9b–g** was observed. Although the reason behind this result is unclear, it might be addressed either to the presence of a nucleophilic nitrogen atom (especially in the case of **9b**) or to electronic effects (for other representatives). Therefore, further study was focused on the preparation of various *N*-(difluorocyclopropyl)pyrazoles.



Scheme 2. Difluorocyclopropanation of parent *N*-vinylazoles

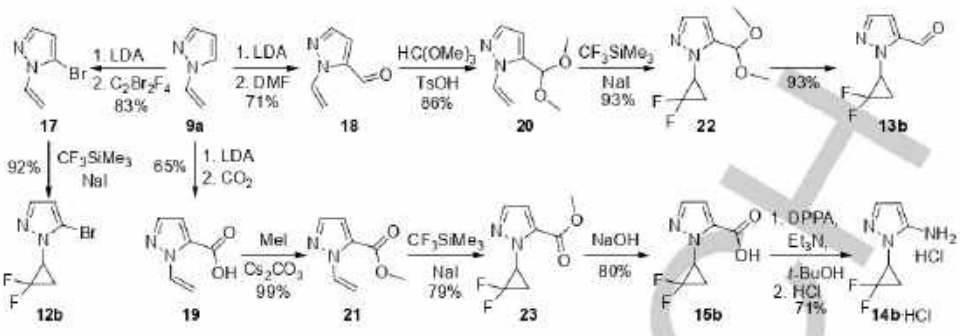
Initially, the product **10** was envisaged as the key intermediate for the preparation of the corresponding functionalized derivatives. Indeed, it was found that common electrophilic substitution reactions (*i.e.* nitration, bromination, and the Vilsmeier – Haack formylation) proceeded smoothly and gave the corresponding 1,4-disubstituted pyrazole derivatives **11a–13a** in 57–94% yields (Scheme 3). Further transformations of these products allowed for the preparation of some other important building blocks. In particular, amine **14a** was obtained in 79% yield by reduction of the nitro derivative **11a** with Fe – NH_4Cl in aq EtOH, whereas oxidation of aldehyde **13a** with $KMnO_4$ in 1,4-dioxane – H_2O gave the corresponding carboxylic acid **15a** (82% yield). It should be noted that catalytic hydrogenation of **11a** (H_2 (1 atm), Pd-C, rt) was unfruitful; a complex mixture of products was obtained, apparently due to instability of the difluorocyclopropane moiety at these conditions. Boronic ester **16** was prepared from the bromide **12a** by reaction with bis(pinacolato)diboron in the presence of $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ and KOAc in DMSO at 80 °C (71% yield).



Scheme 3. Functionalization of *N*-(*gem*-difluorocyclopropyl)pyrazole (**10**)

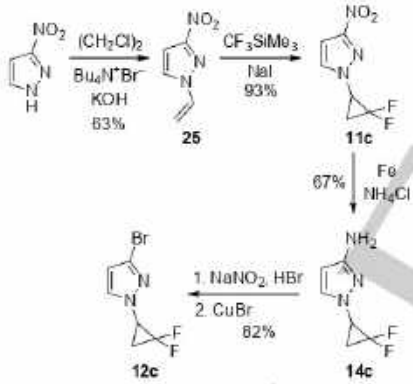
Unfortunately, the compound **10** appeared to be unstable under the Friedel – Crafts acylation conditions (AcCl, $AlCl_3$, CH_2Cl_2, 0 °C); a complex mixture of products was obtained in this case. In addition to that, stability of **10** towards aqueous acids and alkali was studied. It was found that the compound remained intact upon heating with either 2 M or conc aq. HCl, as well as with 2 M aq NaOH at 100 °C for 1 h.

On the contrary, functionalization of the compound **10** at the position 5 of the pyrazole ring *via* lithiation was not fruitful; a complex mixture of unidentified products was formed instead, which clearly indicated instability of the *N*-*gem*-difluorocyclopropyl group towards the reaction conditions tested (*n*-BuLi, LiHMDS, LDA or *i*-PrMgCl·LiCl, THF, –78 °C; LiTMP, THF, –100°C). Therefore, we decided to introduce the corresponding functional groups into the starting material **9a** prior the difluorocyclopropanation step. In particular, bromide **17**, aldehyde **18**, and carboxylic acid **19** were obtained by lithiation of **9a** and subsequent trapping of the organolithium species with the corresponding electrophile (65–83% yield) (Scheme 4). Since the free aldehyde and carboxylic functions are not compatible with the difluorocyclopropanation conditions, the products **18** and **19** were transformed into the corresponding protected derivatives **20** (86% yield) and **21** (99% yield), respectively. Difluorocyclopropanation of **17**, **20** and **21** gave the correspon-



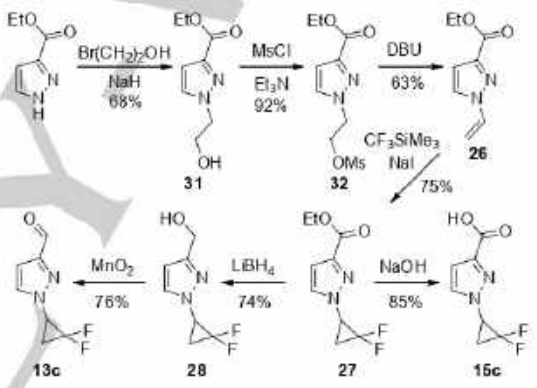
Scheme 4. Synthesis of 1,5-disubstituted *N*-(*gem*-difluorocyclopropyl)pyrazole derivatives

ding products **12b**, **22** and **23** (92%, 93% and 79% yield, respectively). The compounds **22** and **23** were transformed into the target building blocks **13b** and **15b** in 93% and 80% yield, respectively, upon deprotection. Finally, amine **14b** was obtained in 71% yield though a modified Curtius rearrangement via the corresponding *N*-Boc derivative **24**.

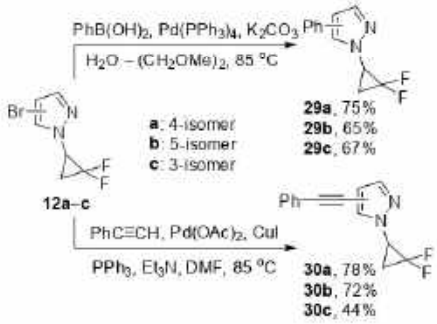


Scheme 5. Synthesis of 1,3-disubstituted *N*-(*gem*-difluorocyclopropyl)pyrazole derivatives **11c**, **12c** and **14c**

An approach to the remaining *N*-(*gem*-difluorocyclopropyl)pyrazole derivatives, *i.e.* 1,3-disubstituted isomers, relied on a synthesis of the corresponding *N*-vinylpyrazoles **25** and **26**. It should be noted that only compound **26** was described in the literature to date;[41] nevertheless, we have used our own methods for the preparation of both derivatives (Schemes 5 and 6). Difluorocyclopropanation of **25** and **26** occurred under standard conditions described above and gave the corresponding products **11c** and **27** in 93% and 75% yield, respectively. Transformations of the nitro derivative **11c** included reduction with Fe – NH_4Cl giving amine **14c** (67% yield), as well as subsequent diazotation of **14c** and Sandmeyer reaction leading to the formation of bromide **12c** (82% yield). Ester **27** was transformed into the corresponding carboxylic acid **15c** (85% yield) by alkaline hydrolysis; alternatively, it was reduced to alcohol **28** with $LiBH_4$ (74% yield), which in turn was oxidized to aldehyde **13c** with MnO_2 (76% yield).



Scheme 6. Synthesis of 1,3-disubstituted *N*-(*gem*-difluorocyclopropyl)pyrazole derivatives **13c** and **15c**



Scheme 7. Palladium-catalyzed couplings in the *N*-(*gem*-difluorocyclopropyl)pyrazole series

Since it is known from the literature *that gem*-difluorocyclopropanes are susceptible to palladium-catalyzed ring opening,[26] we

have studied common C–C and C–N coupling reactions with bromides **12a–c** (Scheme 7). It was found that the Suzuki – Miyaura and Sonogashira reactions were effective with **12a–c**, so that the corresponding products of C–C coupling **29a–c** and **30a–c** were obtained in 44–78% yield. Notably, the difluorocyclopropane ring tolerated the presence of palladium- and copper-containing species at 85 °C.

Conclusions

Difluorocyclopropanation of *N*-vinylpyrazoles with subsequent modification of the products obtained is a convenient method for the regioselective synthesis of various functionalized *N*-(*gem*-difluorocyclopropyl)pyrazoles, including amines, carboxylic acids, aldehydes, bromides, and boronic derivative (Figure 2). The method is not fruitful for the preparation of other azole derivatives studied (*i.e.* imidazole and 1,2,4-triazole). The *N*-*gem*-difluorocyclopropyl moiety attached to the pyrazole ring tolerates a number of typical organic transformations including nitration, bromination, treatment with acids and alkali, mild oxidation and reduction, as well as Pd-catalyzed couplings; it is unstable towards action of metallation agents like *n*-BuLi or lithium amides, strong Lewis acids like $AlCl_3$, or catalytic hydrogenolysis (Table 1). The building blocks described in this work were obtained on up to 50 g scale. Therefore, they can be considered as readily available to scientific community and are promising reagents for drug discovery and agrochemistry, which are fully compatible with even the strictest compound selection criteria.[42,43]

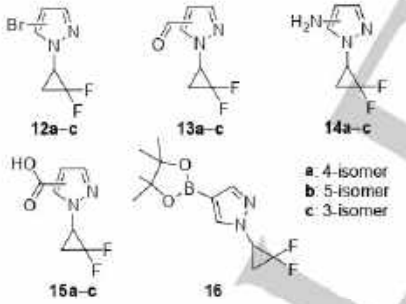


Figure 2. The key building blocks obtained in this work

Table 1. Tolerance of *N*-(*gem*-difluorocyclopropyl)pyrazoles to common organic reactions

Tolerate		Unstable towards
$HNO_3 – H_2SO_4$	2/12 M aq. HCl, 100 °C	*n*-BuLi, LiHMDS, LDA or *i*-PrMgCl·LiCl, THF, –78 °C
Br_2	2 M aq. NaOH, 100 °C	LiTMP, THF, –100°C
DMF – $POCl_3$	Pd(dppf)Cl_2, B_2Pin_2, 80 °C*	H_2 (1 atm), Pd-C, rt
$LiBH_4$	$Pd(PPh_3)_4$, 85 °C	$CH_3C(O)Cl$, $AlCl_3$
$KMnO_4$ or MnO_2	$Pd(OAc)_2$, PPh_3, CuI, 85 °C	

a) B_2Pin_2 – bis(pinacolato)diboron

Experimental Section

General. The solvents were purified according to the standard procedures.[44] All starting materials were purchased from commercial sources. Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^1H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 499.9 MHz for Protons and 124.9 MHz for Carbon-13) and Varian Unity Plus 400 spectrometer (at 400.4 MHz for protons and 100.7 MHz for Carbon-13). Chemical shifts are reported in ppm downfield from TMS as an internal standard. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, National Taras Shevchenko University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI), electrospray ionization (ESI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)).

General procedure for the preparation of 10, 11c, 12b, 22, 23, and 27.
NaI (26.2 g, 0.175 mol) was added to a solution of the corresponding *N*-vinylpyrazole (0.500 mol) in THF (500 mL) under nitrogen atmosphere, and the mixture was heated to reflux. CF_3SiMe_3 (249 g, 1.75 mol) was added dropwise over 12–16 h at this temperature (CAUTION! In some cases, the reaction proceeded vigorously after addition of ca. 0.4–0.6 mol of CF_3SiMe_3). The reaction mixture was heated overnight, and the conversion was monitored by ^1H NMR and/or GCMS. After the completion of the reaction, the solvent was evaporated in *vacuo*, the residue was diluted with CH_2Cl_2 (500 mL), the precipitate was filtered off, and the combined filtrates were evaporated or subjected to distillation in *vacuo*.

1-(2,2-Difluorocyclopropyl)-1*H*-pyrazole (10). The compound was purified by distillation in *vacuo*. Yield 59.1 g (82%); yellowish liquid; bp 46–48 °C / 13 mmHg. ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 1.9 Hz, 1H), 7.48 (d, *J* = 2.4 Hz, 1H), 6.28 (t, *J* = 2.1 Hz, 1H), 4.06 (tdd, *J* = 9.6, 5.8, 2.3 Hz, 1H), 2.18 (ddt, *J* = 14.7, 9.6, 5.8 Hz, 1H), 2.11–1.99 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.4, 130.5, 109.3 (t, *J* = 286 Hz), 106.5, 38.7 (dd, *J* = 16.2, 9.8 Hz), 18.0 (t, *J* = 11.0 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –130.7 (d, *J* = 163 Hz), –143.3 (d, *J* = 163 Hz). GC/MS (EI): *m/z* = 144 [M]$^+$. Anal. Calcd. for $C_6H_6F_2N_2$: C, 50.00; H, 4.20; N, 19.44. Found: C, 49.78; H, 4.37; N, 19.26.

5-Bromo-1-(2,2-difluorocyclopropyl)-1*H*-pyrazole (12b). The compound was purified by distillation in *vacuo*. Yield 103 g (92%); yellowish oil; bp 71–73 °C / 13 mmHg. ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 1.9 Hz, 1H), 6.35 (d, *J* = 1.9 Hz, 1H), 3.94 (dddd, *J* = 10.3, 7.8, 5.8, 1.9 Hz, 1H), 2.51 – 2.39 (m, 1H), 2.12 (dtd, *J* = 12.4, 10.3, 7.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.9 (d, *J* = 0.7 Hz), 115.4, 109.6, 108.9 (dd, *J* = 287, 286 Hz), 37.9 (dd, *J* = 16.3, 9.9 Hz), 17.2 (t, *J* = 11.3 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –132.0 (d, *J* = 162 Hz), –144.0 (d, *J* = 162 Hz). GC/MS (EI): *m/z* = 222/224 [M]$^+$. Anal. Calcd. for $C_6H_5BrF_2N_2$: C, 32.31; H, 2.26; N, 12.56; Br, 35.83. Found: C, 32.69; H, 1.95; N, 12.89; Br, 35.59.

1-(2,2-Difluorocyclopropyl)-5-(dimethoxymethyl)-1*H*-pyrazole (22). Yield 101 g (93%); yellowish oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 1.8 Hz, 1H), 6.34 (d, *J* = 1.8 Hz, 1H), 5.52 (s, 1H), 4.01–4.07 (m, *J* = 10.0, 8.2, 5.9, 1.8 Hz, 1H), 3.37 (s, 3H), 3.28 (s, 3H), 2.48 (ddt, *J* = 14.4, 10.0, 5.9 Hz, 1H), 2.01 (ddd, *J* = 12.8, 10.0, 7.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.3, 138.7, 109.4 (dd, *J* = 288, 285 Hz), 107.3, 53.5, 52.3, 38.2 (dd, *J* = 15.7, 9.7 Hz), 16.6 (t, *J* = 11.1 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ –131.3 (dddd, *J* = 161, 12.8, 5.9, 1.8 Hz), –144.3 (ddd, *J* = 161, 14.4, 8.2 Hz). Anal. Calcd. for $C_8H_{12}F_2N_2O_2$: C, 49.54; H, 5.54; N, 12.84. Found: C, 49.42; H, 5.16; N, 12.86.

Methyl 1-(2,2-difluorocyclopropyl)-1*H*-pyrazole-5-carboxylate (23). Yield 79.9 g (79%); yellowish oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 2.0 Hz, 1H), 6.88 (d, *J* = 2.0 Hz, 1H), 4.40 (dddd, *J* = 10.4, 8.4, 5.9, 2.1

Hz, 1H), 3.91 (s, 3H), 2.46 (ddt, *J* = 13.9, 8.4, 5.9 Hz, 1H), 2.12 – 2.06 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6, 138.9, 134.3, 112.2, 108.8 (dd, *J* = 288, 284 Hz), 52.1, 39.8 (dd, *J* = 15.8, 9.7 Hz), 16.9 (t, *J* = 11.2 Hz). ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ –132.0 (d, *J* = 163 Hz), –144.6 (d, *J* = 163 Hz). LC/MS (CI): *m/z* = 203 [M+H]$^+$. Anal. Calcd. for $C_8H_{12}F_2N_2O_2$: C, 49.54; H, 5.54; N, 12.84. Found: C, 49.50; H, 5.32; N, 12.64.

1-(2,2-Difluorocyclopropyl)-3-nitro-1*H*-pyrazole (11c). The compound was purified by flash chromatography on silica gel using hexanes – EtOAc (4:1) as eluent. Yield 67.1 g (71%); yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 2.7 Hz, 1H), 6.94 (d, *J* = 2.7 Hz, 1H), 4.22 (dddd, *J* = 10.9, 8.8, 5.5, 2.4 Hz, 1H), 2.40 – 2.31 (ddt, 14.4, 10.9, 5.5 Hz, 1H), 2.21 (dtd, *J* = 12.6, 8.8, 7.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2, 133.7, 108.3 (dd, *J* = 289, 286 Hz), 103.6, 39.7 (dd, *J* = 16.4, 9.7 Hz), 17.9 (t, *J* = 11.2 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ –130.4 (dddd, *J* = 165, 12.6, 8.8, 5.5 Hz), –142.3 (dddd, *J* = 165, 14.4, 7.1, 2.4 Hz). LC/MS (CI): *m/z* = 190 [M+H]$^+$. Anal. Calcd. for $C_6H_5F_2N_3O_2$: C, 38.11; H, 2.66; N, 22.22. Found: C, 38.09; H, 2.85; N, 22.52.

Ethyl 1-(2,2-difluorocyclopropyl)-1*H*-pyrazole-3-carboxylate (27). Yield 81.1 g (75%), yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 2.4 Hz, 1H), 6.78 (d, *J* = 2.4 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.13 (dddd, *J* = 9.7, 6.9, 6.1, 2.3 Hz, 1H), 2.24 (ddt, *J* = 14.7, 9.7, 5.7 Hz, 1H), 2.09 (dtd, *J* = 12.2, 9.8, 6.1 Hz, 1H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8, 144.8, 132.0, 109.4, 108.8 (dd, *J* = 288, 286 Hz), 61.1, 39.3 (dd, *J* = 16.3, 9.7 Hz), 18.2 (t, *J* = 11.0 Hz), 14.3. ^{19}F NMR (470 MHz, $CDCl_3$) δ –130.3 (dddd, *J* = 164, 12.2, 9.8, 5.7 Hz), –142.3 (ddd, *J* = 164, 14.7, 6.9 Hz). LC/MS (CI): *m/z* = 217 [M+H]$^+$. Anal. Calcd. for $C_9H_{10}F_2N_2O_2$: C, 50.00; H, 4.66; N, 12.96. Found: C, 50.39; H, 4.43; N, 12.65.

1-(2,2-Difluorocyclopropyl)-4-nitro-1*H*-pyrazole (11a). HNO_3 (20 mL) was added to a solution of **10** (10.0 g, 69.4 mmol) in H_2SO_4 (96%, 150 mL) at 0 °C. The reaction mixture was stirred at 70 °C for 3 h, then cooled to rt and poured into ice, and extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were dried over Na_2SO_4 and evaporated in *vacuo*. Yield 12.1 g (92%); yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.11 (s, 1H), 4.18 (dddd, *J* = 12.5, 9.8, 5.8, 2.4 Hz, 1H), 2.33 – 2.27 (m, 1H), 2.21 (dtd, *J* = 12.5, 9.8, 6.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.4, 136.3, 129.9, 108.2 (dd, *J* = 287, 286 Hz), 39.5 (dd, *J* = 16.7, 9.6, Hz) 18.0 (t, *J* = 11.1 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –130.8 (d, *J* = 165 Hz), –142.7 (d, *J* = 165 Hz). LC/MS (CI): *m/z* = 190 [M+H]$^+$. Anal. Calcd. for $C_6H_5F_2N_3O_2$: C, 38.11; H, 2.66; N, 22.22. Found: C, 38.27; H, 2.72; N, 22.15.

4-Bromo-1-(2,2-difluorocyclopropyl)-1*H*-pyrazole (12a). A stirred solution of **10** (10.0 g, 69.4 mmol) in CH_2Cl_2 (100 mL) was cooled to 10 °C under argon atmosphere. Br_2 (16.6 g, 0.104 mol) was added over 10 min (NOTE: the temperature should not exceed 28 °C) and the resulting mixture was stirred at 25 °C for 1.5 h. Then, the solution was quenched with small portions of 10% aq Na_2SO_3 (50 mL) over 10 min, (NOTE: the temperature should not exceed 25 °C). The organic layer was separated, washed with brine (50 mL), dried over Na_2SO_4 and evaporated in *vacuo*. Yield 14.5 g (94%); brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.49 (s, 1H), 4.06 (dtd, *J* = 9.5, 6.6, 2.2 Hz, 1H), 2.19 (ddt, *J* = 14.2, 9.5, 5.6 Hz, 1H), 2.06 (dtd, *J* = 12.3, 9.9, 6.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.5, 130.2, 108.4 (dd, *J* = 288, 286 Hz), 93.6, 38.5 (dd, *J* = 16.2, 9.7 Hz), 17.3 (t, *J* = 11.1 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ –130.3 (dddd, *J* = 163, 12.3, 9.2, 5.6 Hz), –142.7 (dddd, *J* = 163, 14.2, 6.6, 2.2 Hz). GC/MS (EI): *m/z* = 222/224 [M]$^+$. Anal. Calcd. for $C_6H_5BrF_2N_2$: C, 32.31; H, 2.26; N, 12.56; Br, 35.83. Found: C, 32.44; H, 1.87; N, 12.26; Br, 35.44.

1-(2,2-Difluorocyclopropyl)-1*H*-pyrazole-4-carbaldehyde (13a). $POCl_3$ (162 mL, 266 g, 1.74 mol) was added dropwise to DMF (750 mL) at rt, the resulting mixture was stirred for 0.5 h, and pyrazole **10** (50.0 g, 0.347 mol) in DMF (500 mL) was added. The reaction mixture was stirred at 110 °C overnight, and most of DMF were evaporated in *vacuo* and the residue was poured into ice. Then aq $NaHCO_3$ was added to pH = 7–8, and the mixture was extracted $CHCl_3$ (4×250 mL). The combined organic layers were dried over Na_2SO_4 and evaporated in *vacuo*. The compound was purified by distillation in *vacuo*. Yield 34.0 g (57%), colorless liquid, bp 64–66 °C / 0.26 mmHg ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 8.05 (s, 1H), 8.01 (s, 1H), 4.22 – 4.11 (m, 1H), 2.28 – 2.14 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.7, 141.1, 134.3, 124.9, 108.6 (dd, *J* = 288, 286 Hz), 39.0 (dd, *J* = 16.3, 9.9 Hz), 18.1 (t, *J* = 11.1 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –130.6 (d, *J* = 164 Hz), –142.7 (d, *J* = 164 Hz). GC/MS (EI): *m/z* = 172 [M]$^+$. Anal. Calcd. for $C_7H_6F_2N_2O$: C, 48.84; H, 3.51; N, 16.27. Found: C, 49.00; H, 3.53; N, 15.97.

General procedure for the preparation of 14a and 14c.
To a solution of nitropyrazole **11a** or **11c** (68.5 g, 0.362 mol) in EtOH (700 mL), aqueous solution of NH_4Cl (193 g, 3.62 mol) and Fe powder (80.4 g, 1.44 mol) were added. The reaction mixture was refluxed overnight, then cooled to rt, filtered through silica gel (500 g) and washed with EtOH (100 mL). The solvent was evaporated in *vacuo*, the residue was diluted with H_2O (500 mL) and extracted with CH_2Cl_2 (3×200 mL). The combined organic layers were dried over Na_2SO_4 and evaporated in *vacuo*.

1-(2,2-Difluorocyclopropyl)-1*H*-pyrazol-4-amine (14a). The compound was purified by column chromatography on silica gel using $CHCl_3$ – MeOH (30:1) as eluent. Yield 45.5 g (79%); violet powder; mp 54–56 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 1H), 7.09 (s, 1H), 3.97 (tdd, *J* = 10.1, 5.8, 2.3 Hz, 1H), 2.82 (br s, 2H), 2.17 (ddt, *J* = 14.6, 9.4, 5.8 Hz, 1H), 2.01 (dtd, *J* = 12.8, 10.1, 6.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.6, 129.7, 118.9, 109.4 (t, *J* = 287 Hz), 38.9 (dd, *J* = 16.1, 9.7 Hz), 17.6 (t, *J* = 10.9 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –130.9 (d, *J* = 162 Hz), –143.9 (d, *J* = 162 Hz). LC/MS (CI): *m/z* = 160 [M+H]$^+$. Anal. Calcd. for $C_6H_7F_2N_3$: C, 45.28; H, 4.43; N, 26.41. Found: C, 45.27; H, 4.56; N, 26.73.

1-(2,2-Difluorocyclopropyl)-1*H*-pyrazol-3-amine (14c). The compound was purified by flash chromatography on silica gel using $CHCl_3$ – MeOH (24:1) as eluent. Yield 38.6 g (67%); brown liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 2.4 Hz, 1H), 5.64 (d, *J* = 2.4 Hz, 1H), 3.97 – 3.83 (m, 1H), 3.54 (s, 2H), 2.08 – 1.92 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.1, 132.0, 109.7 (t, *J* = 286 Hz), 94.4, 38.2 (dd, *J* = 16.1, 9.6 Hz), 18.1 (t, *J* = 10.8 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –130.5 (d, *J* = 162 Hz), –143.1 (d, *J* = 162 Hz). LC/MS (CI): *m/z* = 160 [M+H]$^+$. Anal. Calcd. for $C_6H_7F_2N_3$: C, 45.28; H, 4.43; N, 26.41. Found: C, 45.19; H, 4.78; N, 26.19.

1-(2,2-Difluorocyclopropyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (16). Bromide **12a** (1.20 g, 5.38 mmol), bis(pinacolato)diboron (1.65 g, 6.49 mmol) and KOAc (1.81 g, 18.4 mmol) were dissolved in DMSO (20 mL) under nitrogen atmosphere, and $PdCl_2(dppf)_2{\cdot}CH_2Cl_2$ (220 mg, 0.269 mmol) was added. The resulting mixture was stirred under argon atmosphere at 80 °C overnight. Then the reaction mixture was cooled to rt, filtered through a Celite pad and washed with EtOAc (3×25 mL). The filtrate was washed with H_2O (2×50 mL) and brine (50 mL), the organic layer was dried over Na_2SO_4 and evaporated in *vacuo*. The crude compound was purified by flash chromatography on silica gel using hexanes – EtOAc (3:2) as eluent. Yield 1.03 g (71%); yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.79 (s, 1H), 4.09 (tdd, *J* = 10.0, 9.8, 2.2 Hz, 1H), 2.17 (ddt, *J* = 14.3, 9.6, 5.4 Hz, 1H), 2.07 (dtd, *J* = 13.7, 9.8, 6.3 Hz, 1H), 1.30 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.2, 137.4, 109.1 (t, *J* = 287 Hz), 83.4, 38.6 (dd, *J* = 16.2, 9.7 Hz), 24.8, 24.7, 17.9 (t, *J* = 11.0 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ –130.3 (dddd, *J* = 163, 13.7, 10.0, 5.4 Hz), –142.6 (ddd, *J* = 163, 14.3, 6.3 Hz). LC/MS (CI): *m/z* = 189 [M–(HO(CH$_3$)$_2$C)$_2$+H]$^+$, 271 [M+H]$^+$. Anal. Calcd. for $C_{12}H_{17}BF_2N_2O_2$: C, 53.36; H, 6.34; N, 10.37. Found: C, 53.52; H, 6.29; N, 10.74.

1-(2,2-Difluorocyclopropyl)-1*H*-pyrazole-4-carboxylic acid (15a). Aldehyde **13a** (19.8 g, 0.115 mol) was dissolved in 1,4-dioxane (75 mL)

and a solution $KMnO_4$ (20 g, 0.126 mol, 1.1 eq.) in H_2O (15 mL) was added. The resulting mixture was stirred at rt for 5 h, then filtered and evaporated in *vacuo*. The residue was diluted with H_2O (100 mL) and acidified with 10% aq citric acid to pH 3–4. The precipitate was filtered, washed with H_2O (2×30 mL) and dried in *vacuo*. Yield 17.7 g (82%); white solid; mp 150–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.12 (s, 1H), 8.05 (s, 1H), 7.99 (s, 1H), 4.17 – 4.10 (m, 1H), 2.27 – 2.18 (m, 1H), 2.16 – 2.06 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$ + DMSO-d_6) δ 164.1, 141.7, 134.1, 116.4, 108.9 (dd, *J* = 288, 286 Hz), 39.0 (dd, *J* = 16.2, 9.7 Hz), 17.5 (t, *J* = 11.1 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –130.7 (d, *J* = 165 Hz), –142.9 (d, *J* = 165 Hz). LC/MS (CI): *m/z* = 189 [M+H]$^+$. Anal. Calcd. for $C_7H_6F_2N_2O_2$: C, 44.69; H, 3.21; N, 14.89. Found: C, 44.49; H, 2.83; N, 14.75.

5-Bromo-1-vinyl-1*H*-pyrazole (17). Diisopropylamine (8.10 g, 80.0 mmol) was dissolved in THF (70 mL) and 2.5 M solution of *n*-BuLi in hexanes (29.2 mL, 73.0 mmol) was added dropwise. The resulting solution was stirred for 20 min at –15 °C, then cooled to –40 °C, and a solution of *N*-vinylpyrazole **9a** (5.00 g, 53.1 mmol) in THF (10 mL) was added dropwise. The resulting mixture was stirred at –30 °C for 30 min, then cooled to –78 °C, and 1,2-dibromo-1,1,2,2-tetrafluoroethane (23.4 g, 9.01 mmol) was added dropwise. The mixture was stirred at –78 °C for 30 min, then warmed up to 0 °C. H_2O (100 mL) was added dropwise, and the mixture was stirred at rt for 5 min, and then diluted with EtOAc (100 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (2×70 mL). The combined organic layers were washed with 10% aq citric acid (100 mL), dried over Na_2SO_4 and evaporated in *vacuo*. The crude compound was purified by flash chromatography on silica gel using hexanes – EtOAc (14:1) as eluent. Yield 7.63 g (83%); yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 1.8 Hz, 1H), 7.15 (dd, *J* = 15.3, 8.8 Hz, 1H), 6.36 (d, *J* = 1.8 Hz, 1H), 5.81 (d, *J* = 15.3 Hz, 1H), 4.95 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.7, 129.1, 112.9, 109.6, 102.9. GC/MS (EI): *m/z* = 172/174 [M]$^+$. Anal. Calcd. for $C_5H_5BrN_2$: C, 34.71; H, 2.91; N, 16.19; Br, 46.18. Found: C, 35.09; H, 2.82; N, 15.96; Br, 46.50.

1-Vinyl-1*H*-pyrazole-5-carboxylic acid (19). *N*-vinylpyrazole (100 g, 1.06 mol) was dissolved in THF (1800 mL). 2.5 M *n*-BuLi in hexanes (468 mL, 1.17 mol) was added dropwise, and the solution was stirred at 0 °C for 30 min. Then, dry CO_2 (440 g, 10.0 mol) was added in portions at –78 °C, the mixture was stirred for 30 min and warmed up to 0 °C. Then, H_2O (600 mL) was added dropwise, most of THF was evaporated in *vacuo*, and the residue was extracted with CH_2Cl_2 (300 mL) and acidified with 10% aq citric acid to pH 3–4. The precipitate was filtered and washed with H_2O (2×100 mL). Yield 95.2 g (65%); yellowish powder; mp 135–137 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.71 (s, 1H), 7.99 (dd, *J* = 15.4, 8.8 Hz, 1H), 7.73 (d, *J* = 1.9 Hz, 1H), 6.95 (d, *J* = 1.9 Hz, 1H), 5.75 (d, *J* = 15.4 Hz, 1H), 5.01 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.9, 140.4, 133.1, 131.8, 113.1, 103.3. LC/MS (CI): *m/z* = 139 [M+H]$^+$. Anal. Calcd. for $C_6H_6N_2O_2$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.93; H, 4.66; N, 20.36.

Methyl 1-vinyl-1*H*-pyrazole-5-carboxylate (21). Cs_2CO_3 (196 g, 0.602 mol) was added to a solution of the acid **19** (83.2 g, 0.602 mol) in MeCN (850 mL) at rt. The solution was stirred for 30 min at rt and MeI (37.5 mL, 85.4 g, 0.602 mol, 1 eq.) was added dropwise and the resulting mixture was stirred at rt overnight. Then, most of MeCN was evaporated in *vacuo*, the residue was crystallized from CH_2Cl_2 (500 mL) and the precipitate was filtered off. The mother liquor was dried over Na_2SO_4 and evaporated in *vacuo*. Yield 90.1 g (99%); yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 9.5, 8.6 Hz, 1H), 7.60 (d, *J* = 0.8 Hz, 1H), 6.91 (d, *J* = 2.0 Hz, 1H), 5.90 (d, *J* = 15.4 Hz, 1H), 5.00 (d, *J* = 8.8 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9, 139.6, 131.5, 131.3, 112.6, 103.6, 52.1. LC/MS (CI): *m/z* = 153 [M+H]$^+$. Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.49; H, 4.96; N, 18.50.

General procedure for the preparation of 15b and 15c.

Ester **23** or **27** (80.0 g, 0.396 mol) was dissolved in EtOH (800 mL), and a solution of NaOH (23.8 g, 0.594 mol) in H_2O (50 mL) was added. The mixture was stirred at rt overnight, and most of EtOH was evaporated in *vacuo*. The residue was diluted with H_2O (500 mL) and the mixture was washed with CH_2Cl_2 (3×100 mL). The aqueous phase was acidified with 10% aq citric acid to pH 2–3, extracted with with EtOAc (3×250 mL). The combined organic layers were dried over Na_2SO_4 and evaporated in *vacuo*.

1-(2,2-Difluorocyclopropyl)-1*H*-pyrazole-5-carboxylic acid (15b). Yield 59.2 g (80%), yellowish crystals; mp 127–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (br s, 1H), 7.59 (d, *J* = 2.1 Hz, 1H), 7.04 (d, *J* = 2.1 Hz, 1H), 4.50 – 4.38 (m, 1H), 2.55 – 2.45 (m, 1H), 2.18 – 2.08 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.5, 139.2, 133.8, 113.7, 108.7 (dd, *J* = 288, 284 Hz), 39.9 (dd, *J* = 16.1, 9.7 Hz), 17.1 (t, *J* = 11.0 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –132.5 (d, *J* = 164 Hz), –144.8 (d, *J* = 164 Hz). LC/MS (CI): *m/z* = 189 [M+H]$^+$. Anal. Calcd. for $C_7H_6F_2N_2O_2$: C, 44.69; H, 3.21; N, 14.89. Found: C, 44.71; H, 3.45; N, 15.25.

1-(2,2-Difluorocyclopropyl)-1*H*-pyrazole-3-carboxylic acid (15c). Yield 62.9 g (85%), beige powder; mp 113–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.19 (s, 1H), 7.56 (d, *J* = 2.4 Hz, 1H), 6.89 (d, *J* = 2.5 Hz, 1H), 4.24 – 4.08 (m, 1H), 2.41 – 2.25 (m, 1H), 2.20 – 2.09 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3, 143.7, 132.5, 110.1, 108.7 (dd, *J* = 288, 287 Hz), 39.4 (dd, *J* = 16.3, 9.8 Hz), 18.2 (t, *J* = 11.1 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –130.8 (d, *J* = 164 Hz), –142.7 (d, *J* = 164 Hz). LC/MS (CI): *m/z* = 189 [M+H]$^+$. Anal. Calcd. for $C_7H_6F_2N_2O_2$: C, 44.69; H, 3.21; N, 14.89. Found: C, 44.52; H, 3.53; N, 14.67.

***tert*-Butyl (1-(2,2-difluorocyclopropyl)-1*H*-pyrazol-5-yl)carbamate (24).** The compound existed as *ca.* 5:1 mixture of rotamers. Et_3N (17.5 g, 0.173 mol) was added to a solution of carboxylic acid **15b** (19.2 g, 0.102 mol) in toluene (200 mL) at rt. DPPA (42.1 g, 0.153 mol) and *t*-BuOH (60.5 g, 0.816 mol) were added and the mixture was refluxed overnight. The solvent was evaporated in *vacuo*, and the residue was dissolved in EtOAc (500 mL). The organic phase was washed with 10% aq citric acid (150 mL), saturated aq. $NaHCO_3$ (150 mL), and brine, (150 mL), dried over Na_2SO_4, and evaporated in *vacuo*. The crude compound was purified by column chromatography on silica gel using hexanes – EtOAc (4:1) as eluent. Yield 19.6 g (74%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 2.0 Hz, 1H), 6.45 (s, 1H), 6.20 (s, 1H), 3.95 – 3.83 (m, 1H), 2.41 – 2.32 (m, 1H), 2.15 – 2.06 (m, 1H), 1.52 (s, 7.5H) and 1.43 (s, 1.5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.3, 139.7, 137.9, 109.6 (dd, *J* = 286, 284 Hz), 99.8, 82.0, 36.1 (dd, *J* = 16.1, 9.8 Hz), 28.1 and 26.9, 17.3 (t, *J* = 10.9 Hz). ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ –130.6 (d, *J* = 160 Hz), –142.8 (d, *J* = 160 Hz). LC/MS (CI): *m/z* = 260 [M+H]$^+$. Anal. Calcd. for $C_{11}H_{15}F_2N_3O_2$: C, 50.96; H, 5.83; N, 16.21. Found: C, 50.78; H, 5.70; N, 16.49.

1-(2,2-Difluorocyclopropyl)-1*H*-pyrazol-5-amine hydrochloride (14b). 3.5 M HCl in 1,4-dioxane (100 mL) was added to a solution of *N*-Boc-amine **24** (45.0 mmol) in Et_2O (100 mL), and the reaction mixture was stirred overnight at rt. The precipitate was filtered, washed with Et_2O (3×50 mL) and dried in *vacuo*. Yield 8.71 g (99%); beige solid; mp 140–142 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, *J* = 2.8 Hz, 1H), 6.29 (s, 3H), 5.67 (d, *J* = 2.8 Hz, 1H), 4.27 (dddd, *J* = 10.4, 8.5, 6.1, 2.8 Hz, 1H), 2.49 – 2.32 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 151.6 (d, *J* = 34.4 Hz), 137.4, 110.4 (dd, *J* = 288, 283 Hz), 91.22, 34.45 (dd, *J* = 16.6, 9.2 Hz), 17.76 (t, *J* = 10.6 Hz). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –130.5 (d, *J* = 159 Hz), –142.1 (d, *J* = 159 Hz). LC/MS (CI): *m/z* = 160 [M-HCl+H]$^+$. Anal. Calcd. for $C_6H_8ClF_2N_3$: C, 36.84; H, 4.12; N, 21.48; Cl, 18.12. Found: C, 37.13; H, 4.27; N, 21.63; Cl, 17.89.

1-Vinyl-1*H*-pyrazole-5-carbaldehyde (18). Diisopropylamine (116 g, 1.14 mol) was dissolved in THF (1000 mL), and 2.5 M *n*-BuLi in hexanes (414 mL, 1.04 mol) was added dropwise. The resulting solution was stirred for 20 min at –15 °C, then cooled to –30 °C, and a solution of *N*-vinylpyrazole **9a** (71.4 g, 0.757 mol) in THF (150 mL) was added

dropwise. The resulting mixture was stirred at –30 °C for 30 min, and then cooled to –78 °C. DMF (111 g, 1.52 mol) was added dropwise, and the mixture was stirred at –78 °C for 30 min. Then, the mixture was warmed up to 0 °C, H_2O (700 mL) was added dropwise. The mixture stirred for 15 min at rt, and diluted with EtOAc (500 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (2×500 mL). The combined organic layers were washed with aq citric acid (10%, 750 mL), dried over Na_2SO_4 and evaporated in *vacuo*. The crude compound was purified by distillation in *vacuo*. Yield 66.6 g (72%); yellowish oil; bp 77–79 °C / 13 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.89 (dd, *J* = 15.4, 8.7 Hz, 1H), 7.63 (d, *J* = 2.2 Hz, 1H), 6.94 (d, *J* = 1.9 Hz, 1H), 5.89 (d, *J* = 15.4 Hz, 1H), 5.01 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.6, 140.3, 137.9, 131.4, 116.6, 104.4. GC/MS (EI): *m/z* = 122 [M]$^+$. Anal. Calcd. for $C_6H_6N_2O$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.36; H, 5.20; N, 23.14.

5-(Dimethoxymethyl)-1-vinyl-1*H*-pyrazole (20). Aldehyde **18** (64.9 g, 0.513 mol) was dissolved in MeOH (900 mL), and trimethyl orthoformate (65.3 g, 0.616 mol) and *p*-toluenesulfonic acid monohydrate (5.44 g, 2.86 mmol) were added to the solution. The reaction mixture was stirred at rt for 20 h. Then, H_2O (500 mL) and 10% aq $NaHCO_3$ were added to pH 9–10, and most of MeOH was evaporated in *vacuo*. The resulting mixture was extracted with CH_2Cl_2 (3×300 mL), dried over Na_2SO_4, and evaporated in *vacuo*. The crude compound was purified by distillation in *vacuo*. Yield 74.2 g (86%); yellowish oil; bp 70–72 °C / 0.27 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 2.2 Hz, 1H), 7.17 (dd, *J* = 9.6, 8.9 Hz, 1H), 6.35 (d, *J* = 1.7 Hz, 1H), 5.71 (d, *J* = 15.3 Hz, 1H), 5.47 (s, 1H), 4.81 (d, *J* = 8.8 Hz, 1H), 3.26 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.8, 138.7, 130.4, 107.8, 101.4, 97.1, 52.8. GC/MS (EI): *m/z* = 168 [M]$^+$. Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.44; H, 7.59; N, 17.03.

1-(2,2-Difluorocyclopropyl)-1*H*-pyrazole-5-carbaldehyde (13b). Acetal **22** (57.0 g, 0.261 mol) was dissolved in THF (285 mL), and 1 M aq HCl (285 mL) was added. The reaction mixture was stirred at rt overnight. Then most of THF was evaporated in *vacuo*, the residue was diluted with H_2O (200 mL) and neutralized with 10% $NaHCO_3$ to pH = 7. The mixture was extracted with CH_2Cl_2 (3×200 mL), dried over Na_2SO_4 and evaporated in *vacuo*. The crude compound was purified by distillation in *vacuo*. Yield 41.8 g (93%); yellowish liquid; bp 77–79 °C / 0.27 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.60 (d, *J* = 2.0 Hz, 1H), 6.96 (d, *J* = 2.0 Hz, 1H), 4.47 (tdd, *J* = 10.1, 6.8, 2.0 Hz, 1H), 2.53 – 2.44 (m, 1H), 2.12 (dtd, *J* = 12.3, 10.1, 6.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.2, 140.7, 139.5, 115.2, 108.7 (dd, *J* = 289, 285 Hz), 39.6 (dd, *J* = 15.9, 9.7 Hz), 16.7 (t, *J* = 11.1 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –132.0 (d, *J* = 163 Hz), –145.1 (d, *J* = 163 Hz). GC/MS (EI): *m/z* = 172 [M]$^+$. Anal. Calcd. for $C_7H_6F_2N_2O$: C, 48.84; H, 3.51; N, 16.27. Found: C, 49.19; H, 3.55; N, 15.87.

3-Nitro-1-vinyl-1*H*-pyrazole (25). To a solution of 3-nitropyrazole (88.5 g, 0.783 mol) in $(CH_2Cl)_2$ (1200 mL), $Bu_4N^+Br^-$ (12.6 g, 39.1 mmol) was added, followed by a solution of KOH (350 g, 6.24 mol) in H_2O (600 mL). The reaction mixture was refluxed overnight, then cooled to rt, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×300 mL), the combined organic layers were washed with 10% aq citric acid (300 mL), dried over Na_2SO_4 and evaporated in *vacuo*. The crude compound was purified by column chromatography on silica gel using hexanes – EtOAc (gradient 8:1 to 4:1) as eluent. Yield 68.6 g (63%); yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 2.6 Hz, 1H), 7.08 (dd, *J* = 15.6, 8.8 Hz, 1H), 7.00 (d, *J* = 2.7 Hz, 1H), 5.80 (dd, *J* = 15.7, 2.1 Hz, 1H), 5.18 (dd, *J* = 8.8, 2.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6, 132.5, 129.7, 105.3, , 103.9. LC/MS (CI): *m/z* = 140 [M+H]$^+$. Anal. Calcd. for $C_5H_5N_3O_2$: C, 43.17; H, 3.62; N, 30.21. Found: C, 43.31; H, 3.85; N, 29.90.

3-Bromo-1-(2,2-difluorocyclopropyl)-1*H*-pyrazole (12c). A solution of $NaNO_2$ (8.67 g, 126 mmol) in H_2O (10 mL) was added dropwise to a solution of amine **14c** (10.0 g; 62.8 mmol) in 40% aq HBr (40 mL) at 0 °C, the reaction mixture was warmed up to 30 °C and stirred for 1 h. Then CuBr (4.50 g; 31.4 mmol) was added in portions at 0 °C. After the completion of intensive gas evolution, the reaction mixture was warmed up to 35 °C and stirred for 40 min. H_2O (120 mL) was added, and the resulting mixture was washed with CH_2Cl_2 (3×50 mL), combined organic layers were washed with 10% aq Na_2CO_3 (50 mL), dried over Na_2SO_4, filtered through silica gel and evaporated in *vacuo*. Yield 11.5 g (82%); yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 2.6 Hz, 1H), 6.30 (d, *J* = 2.4 Hz, 1H), 4.04 (tdd, *J* = 9.7, 5.8, 2.5 Hz, 1H), 2.19 (ddt, *J* = 14.4, 9.7, 5.8 Hz, 1H), 2.12 – 2.04 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.8, 126.8, 109.6, 109.0 (t, *J* = 287 Hz), 38.9 (dd, *J* = 16.4, 9.7 Hz), 18.1 (t, *J* = 11.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –130.7 (d, *J* = 164 Hz), –142.8 (d, *J* = 164 Hz). LC/MS (CI): *m/z* = 223/225 [M+H]$^+$. Anal. Calcd. for $C_6H_5BrF_2N_2$: C, 32.31; H, 2.26; N, 12.56; Br, 35.83. Found: C, 31.92; H, 2.15; N, 12.22; Br, 35.66.

Ethyl 1-(2-hydroxyethyl)-1*H*-pyrazole-3-carboxylate (31). NaH (60%, 18.8 g, 0.470 mol) was suspended in THF (900 mL) at 0 °C and ethyl-1*H*-pyrazole-3-carboxylate (60.0 g; 0.428 mol) was added in portions at 0 °C. After addition, the reaction mixture was warmed up to 35 °C and stirred for 1.5 h, then cooled to 5 °C, and 2-bromoethanol (62.2 g; 0.514 mol) was added at 5 - 10 °C. The mixture was stirred overnight at 38 °C, then cooled to 5 °C, and H_2O (450 mL) was added dropwise. Most of THF was evaporated in *vacuo*, and the residue was washed with CH_2Cl_2 (3×450 mL). The combined organic layers were washed with H_2O (300 mL), dried over Na_2SO_4 and evaporated in *vacuo*. The residue was purified by flash chromatography on silica gel using $CHCl_3$ – MeOH (40:1) as eluent. Yield 53.6 g (68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 2.2 Hz, 1H), 6.78 (d, *J* = 2.2 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 4.31 (t, *J* = 5.1 Hz, 2H), 4.02 (t, *J* = 5.1 Hz, 2H), 2.71 (s, 1H), 1.38 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.3, 143.9, 131.7, 108.8, 61.3, 60.9, 54.9, 14.3. LC/MS (CI): *m/z* = 185 [M+H]$^+$. Anal. Calcd. for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 52.40; H, 6.85; N, 14.86.

Ethyl 1-(2-((methylsulfonyl)oxy)ethyl)-1*H*-pyrazole-3-carboxylate (32). MsCl (24.6 g, 0.215 mol) was added to a solution of alcohol **31** (36.0 g, 0.195 mol) in CH_2Cl_2 (250 mL) at rt. The reaction mixture was cooled to 5 °C and Et_3N (32.8 mL, 0.235 mol) was added at 5 °C. After addition, the mixture was stirred at rt overnight, then washed with 10% aq citric acid (150 mL), dried over Na_2SO_4 and evaporated in *vacuo*. The residue was diluted with hexanes - EtOAc (10:1, v/v, 200 mL) and the precipitate was filtered. Yield 47.1 g (92%), yellowish solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 2.3 Hz, 1H), 6.81 (d, *J* = 2.3 Hz, 1H), 4.61 (t, *J* = 4.5 Hz, 2H), 4.52 (t, *J* = 4.9 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.88 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.0, 144.8, 132.1, 109.2, 67.5, 61.1, 51.8, 37.4, 14.4. LC/MS (CI): *m/z* = 263 [M+H]$^+$. Anal. Calcd. for $C_9H_{14}N_2O_5S$: C, 41.22; H, 5.38; N, 10.68; S, 12.22. Found: C, 41.26; H, 5.72; N, 10.98; S, 12.44.

Ethyl 1-vinyl-1*H*-pyrazole-3-carboxylate (26). DBU (178 g, 1.29 mol) was added to a solution of mesylate **32** (169 g, 0.644 mol) in THF (1500 mL), and the mixture was heated 48 h. Then, the reaction mixture was cooled to rt and most of THF was evaporated in *vacuo*. The residue was dissolved in CH_2Cl_2 (1000 mL), the solution was washed with 10% aq citric acid (2×600 mL), dried over Na_2SO_4 and evaporated in *vacuo*. The crude compound was purified by column chromatography on silica gel using hexanes – EtOAc (8:1 to 4:1) as eluent. Yield 67.4 g (63%). For phisical and spectral data, see ref.[41]

(1-(2,2-Difluorocyclopropyl)-1*H*-pyrazol-3-yl)methanol (28). The crude compound was purified by flash chromatography on silica gel using hexanes – EtOAc (4:1) as eluent. A suspension of ester **28** (43.0 g, 0.199 mol) and $LiBH_4$ (6.53 g; 0.300 mol) in THF (1300 mL) was refluxed overnight. Then, the reaction mixture was cooled to 0 °C and quenched with 1N aq HCl to pH = 6. The resulting mixture was diluted with EtOAc (3×500 mL) and washed with saturated aq $NaHCO_3$ (2×400 mL), the combined organic layers were dried over Na_2SO_4 and evaporated in *vacuo*. Yield 25.8 g (74%); yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.42 (d, *J* = 2.4 Hz, 1H), 6.26 (d, *J* = 2.4 Hz, 1H), 4.64 (s, 2H), 4.01 (tdd, *J* = 9.7, 5.8, 2.3 Hz, 1H), 2.62 (s, 1H), 2.17 – 2.08 (m, 1H), 2.03 (ddt, *J* = 12.6, 9.7, 5.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.8, 129.2, 106.7 (dd, *J* = 287, 286 Hz), 102.5, 56.2, 35.9 (dd, *J* = 16.0, 9.6 Hz), 15.5 (t, *J* = 11.0 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –130.7 (d, *J* = 163 Hz), –143.0 (d, *J* = 163 Hz). LC/MS (CI): *m/z* = 157 [M-F+H]$^+$. Anal. Calcd. for $C_7H_6F_2N_2O$: C, 48.28; H, 4.63; N, 16.09. Found: C, 48.21, H, 4.62; N, 15.93.

1-(2,2-Difluorocyclopropyl)-1*H*-pyrazole-3-carbaldehyde (13c). MnO_2 (50.0 g, 0.575 mol) was added to a solution of alcohol **28** (10.0 g, 57.4 mmol) in EtOAc (200 mL) and reaction mixture was refluxed overnight. Then, the mixture was cooled to rt, filtered through silica gel (50 mL) and evaporated in *vacuo*. The crude compound was purified by column chromatography on silica gel using hexanes – EtOAc (6:1) as eluent. Yield 7.51 g (76%); yellowish crystals; mp 127–129 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.58 (d, *J* = 2.3 Hz, 1H), 6.85 (d, *J* = 1.6 Hz, 1H), 4.20 (dddd, *J* = 10.5, 8.2, 5.9, 2.1 Hz, 1H), 2.35 (ddt, *J* = 15.1, 8.2, 5.9 Hz, 1H), 2.22 – 2.16 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.1, 152.0, 132.7, 108.6 (dd, *J* = 288, 286 Hz), 106.5, 39.3 (dd, *J* = 16.1, 9.9 Hz), 17.8 (t, *J* = 11.2 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –130.8 (d, *J* = 164 Hz), –143.3 (d, *J* = 164 Hz). LC/MS (CI): *m/z* = 173 [M+H]$^+$. Anal. Calcd. for $C_7H_6F_2N_2O$: C, 48.84; H, 3.51; N, 16.27. Found: C, 48.69; H, 3.58; N, 16.01.

General procedure for the preparation of 29a–c.
The corresponding bromide **12** (250 mg, 1.12 mmol), phenylboronic acid (164 mg, 1.35 mmol) and K_2CO_3 (387 mg, 2.80 mmol) were dissolved in $(CH_2OMe)_2$ - H_2O (3:1, v/v, 12 mL) under argon atmosphere at rt. The resulting solution was heated at 40 °C for 20 min, and $Pd(PPh_3)_4$ (64.7 mg, 56.0 μmol) was added under argon flow. The reaction mixture was stirred at 85 °C overnight, then cooled to rt and diluted with EtOAc (25 mL) and H_2O (10 mL). The organic layer was separated, filtered through silica gel and washed with EtOAc (25 mL). The mother liquor was dried over Na_2SO_4 and evaporated in *vacuo*. The compound was purified by column chromatography on silica gel using hexanes – EtOAc (6:1) as eluent.

1-(2,2-Difluorocyclopropyl)-4-phenyl-1*H*-pyrazole (29a). The compound was purified by column chromatography on silica gel using hexanes – EtOAc (6:1) as eluent. Yield 185 mg (75%), white solid; mp 68–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.73 (s, 1H), 7.48 – 7.44 (m, 2H), 7.38 – 7.33 (m, 2H), 7.28 – 7.20 (m, 1H), 4.11 – 4.03 (m, 1H), 2.27 – 2.21 (m, 1H), 2.13 – 2.06 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.0, 131.9, 128.9, 127.3, 126.8, 125.7, 124.0, 109.2 (t, *J* = 287 Hz), 38.9 (dd, *J* = 16.2, 9.7 Hz), 18.0 (t, *J* = 11.0 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ –124.5 – –132.9 (m), –142.6 (ddd, *J* = 163, 14.5, 6.2 Hz). LC/MS (CI): *m/z* = 221 [M+H]$^+$. Anal. Calcd. for $C_{12}H_{10}F_2N_2$: C, 65.45; H, 4.58; N, 12.72. Found: C, 65.58; H, 4.80; N, 12.86.

1-(2,2-Difluorocyclopropyl)-5-phenyl-1*H*-pyrazole (29b). The compound was purified by column chromatography on silica gel using hexanes – EtOAc (6:1) as eluent. Yield 160 mg (65%), yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 1.8 Hz, 1H), 7.53 – 7.50 (m, 2H), 7.50 – 7.47 (m, 2H), 7.46 – 7.42 (m, 1H), 6.41 (d, *J* = 1.8 Hz, 1H), 4.03 (tdd, *J* = 9.6, 6.9, 2.1 Hz, 1H), 2.47 (ddt, *J* = 14.4, 9.6, 5.8 Hz, 1H), 2.02 (dtd, *J* = 13.1, 9.6, 6.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.2, 139.4, 129.8, 128.8, 128.8, 128.4, 110.0 (dd, *J* = 288, 286 Hz), 107.0, 38.5 (dd, *J* = 15.7, 9.8 Hz), 17.0 (t, *J* = 11.1 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ –131.5 (ddt, *J* = 161, 13.1, 6.9 Hz), –143.8 (ddd, *J* = 161, 14.4, 6.9 Hz). LC/MS (CI): *m/z* = 221 [M+H]$^+$. Anal. Calcd. for $C_{12}H_{10}F_2N_2$: C, 65.45; H, 4.58; N, 12.72. Found: C, 65.53; H, 4.28; N, 12.64.

1-(2,2-Difluorocyclopropyl)-3-phenyl-1*H*-pyrazole (29c). The compound was purified by column chromatography on silica gel using hexanes – EtOAc (6:1) as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.79 (m, 1H), 7.78 (s, 1H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 6.58 (d, *J* = 2.5 Hz, 1H), 4.12 (tdd, *J* = 10.1, 6.3, 2.4 Hz, 1H), 2.25 (ddt, *J* = 14.5, 10.1, 5.6 Hz, 1H), 2.11 (dtd, *J* = 12.9, 9.8, 6.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 133.0, 131.9, 128.64, 128.0, 125.8, 109.4 (t, *J* = 289 Hz), 103.8, 38.9 (dd, *J* = 16.1, 9.7 Hz), 18.20 (t, *J* = 10.9 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ –130.0 (dddd, *J* = 163, 12.9, 9.8, 5.6 Hz), –142.4 (ddd, *J* = 163, 14.5, 6.3 Hz). LC/MS (CI): *m/z* = 221 [M+H]$^+$. Anal. Calcd. for $C_{12}H_{10}F_2N_2$: C, 65.45; H, 4.58; N, 12.72. Found: C, 65.73, H, 4.89; N, 12.73.

General procedure for the preparation of 30a–c.
The corresponding bromide **12** (250 mg, 1.12 mmol) was dissolved in DMF (2 mL), Et_3N (339 mg, 0.468 mL, 3.36 mmol) and phenylacetylene (172 mg, 0.185 mL, 1.68 mmol) were added under argon atmosphere. Then, $Pd(OAc)_2$ (7.63 mg, 34.0 μmol), PPh_3 (17.6 mg, 67.0 μmol) and CuI (21.3 mg, 112 μmol) were added in argon flow. The resulting mixture was stirred at 85 °C overnight, then cooled to rt and diluted with EtOAc (25 mL) and H_2O (10 mL). Organic layer was separated, dried over Na_2SO_4 and evaporated in *vacuo*.

1-(2,2-Difluorocyclopropyl)-4-(phenylethynyl)-1*H*-pyrazole (30a). The compound was purified by column chromatography on silica gel using hexanes – EtOAc (9:1) as eluent. Yield 210 mg (78%); yellowish solid; mp 61–63 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.68 (s, 1H), 7.49 – 7.45 (m, 2H), 7.34 – 7.29 (m, 3H), 4.12 – 4.04 (m, 1H), 2.26 – 2.16 (m, 1H), 2.14 – 2.03 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.8, 133.1, 131.4, 128.4, 128.2, 123.2, 108.9 (t, *J* = 287 Hz), 104.5, 90.5, 79.8, 38.8 (dd, *J* = 16.2, 9.7 Hz), 17.9 (t, *J* = 11.1 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –130.7 (d, *J* = 163 Hz), –143.1 (d, *J* = 163 Hz). LC/MS (CI): *m/z* = 245 [M+H]$^+$. Anal. Calcd. for $C_{14}H_{10}F_2N_2$: C, 68.85; H, 4.13; N, 11.47. Found: C, 68.77; H, 3.98; N, 11.26.

1-(2,2-Difluorocyclopropyl)-5-(phenylethynyl)-1*H*-pyrazole (30b). The compound was purified by column chromatography on silica gel using hexanes – EtOAc (9:1) as eluent. Yield 195 mg (72%); yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.51 (d, *J* = 1.8 Hz, 1H), 7.38 – 7.34 (m, 3H), 6.52 (d, *J* = 1.9 Hz, 1H), 4.17 – 4.06 (m, 1H), 2.49 – 2.40 (m, 1H), 2.18 – 2.07 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.6, 131.53, 129.2, 128.5, 127.5, 121.9, 110.8, 109.2 (t, *J* = 287 Hz), 97.5, 38.0 (dd, *J* = 16.2, 9.7 Hz), 17.2 (t, *J* = 11.2 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –131.6 (d, *J* = 162 Hz), –143.5 (d, *J* = 162 Hz). Anal. Calcd. for $C_{14}H_{10}F_2N_2$: C, 68.85; H, 4.13; N, 11.47. Found: C, 68.86; H, 3.75; N, 11.52.

1-(2,2-Difluorocyclopropyl)-3-(phenylethynyl)-1*H*-pyrazole (30c). The compound was purified by column chromatography on silica gel using hexanes – EtOAc (9:1) as eluent. Yield 120 mg (44%), white solid; mp 75–77 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 2H), 7.48 (s, 1H), 7.35 – 7.28 (m, 3H), 6.48 (s, 1H), 4.15 – 3.98 (m, 1H), 2.31 – 2.21 (m, 1H), 2.13 – 2.04 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.0, 131.7, 131.3, 128.6, 128.3, 122.6, 110.5, 109.0 (t, *J* = 287 Hz), 90.1, 81.6, 38.96 (dd, *J* = 16.3, 9.7 Hz), 18.0 (t, *J* = 10.9 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ –130.2 (ddd, *J* = 163, 14.4, 7.0 Hz), –142.5 (ddd, *J* = 163, 14.2, 6.4 Hz). LC/MS (CI): *m/z* = 245 [M+H]$^+$. Anal. Calcd. for $C_{14}H_{10}F_2N_2$: C, 68.85; H, 4.13; N, 11.47. Found: C, 68.65, H, 4.31; N, 11.25.

Acknowledgements

The work was funded by Enamine Ltd. The authors thank Mr. Bohdan V. Vashchenko for his invaluable help with manuscript preparation, and Prof. Andrey A. Tolmachev for his encouragement and support.

Keywords: organofluorine compounds • cycloalkanes • Ruppert – Prakash reagent • azoles • building blocks

References

[1] T. Itoh, in *Fluor. Med. Chem. Chem. Biol.*, John Wiley & Sons, Ltd, **2009**, pp. 313–334.

[2] A. D. Dilman, V. V. Levin, *Acc. Chem. Res.* **2018**, *51*, 1272–1280.

[3] O. O. O. Grygorenko, O. S. O. S. Artamonov, I. V. I. V. Komarov, P. K. P. K. Mykhailiuk, *Tetrahedron* **2011**, *67*, 803–823.

[4] T. Taguchi, M. Okada, *J. Fluor. Chem.* **2000**, *105*, 279–283.

[5] E. David, G. Milanole, P. Ivashkin, S. Couve-Bonnaire, P. Jubault, X. Pannecoucke, *Chem. Eur. J.* **2012**, *18*, 14904–14917.

[6] X. Song, C. Xu, M. Wang, *Tetrahedron Lett.* **2017**, *58*, 1806–1816.

[7] C. Ni, J. Hu, *Synthesis* **2014**, *46*, 842–863.

[8] M. Bos, T. Poisson, X. Pannecoucke, A. B. Charette, P. Jubault, *Chem. Eur. J.* **2017**, *23*, 4950–4961.

[9] D. Munemori, K. Narita, T. Nokami, T. Itoh, *Org. Lett.* **2014**, *16*, 2638–2641.

[10] A. Poris, T. Poisson, X. Pannecoucke, A. Charette, P. Jubault, *Synthesis* **2016**, *48*, 4060–4071.

[11] L. R. Marcin, M. A. Higgins, J. J. Bronson, F. C. Zusi, J. E. Macor, M. Ding, WO 2015/042243, **2015**.

[12] R. Giovannini, B. Bertani, M. Ferrara, I. Lingard, R. Mazzaferro, H. Rosenbrock, WO2013/17657, **2013**.

[13] J. Lim, E. H. Kelley, L. Methot, Joey, H. Zhou, A. Petrocchi, U. F. Mansoor, C. Fischer, M. O'boyle, Brendan, D. J. Guerin, E. Bienstock, Corey, W. Boyce, Christopher, H. Daniels, Matthew, D. Falcone, I. Ferguson, Ronald, D., S. Fevrier, X. Huang, K. A. Lipford, L. Sloman, David, K. Wison, W. Zhou, D. Witter, M. Malebc, Milana, P. Siliphaivanh, WO 2013/063214, **2013**.

[14] K. Dilger, Andrew, R. Corte, James, I. De Lucca, T. Fang, W. Yang, Y. Wang, K. B. Pabbisetty, R. Ewing, William, Y. Zhu, R. Wexler, Ruth, J. P. Pinto, Donald, J. Orwat, Michael, M. Smith II, Leon, WO 2015/116882, **2015**.

[15] F. Wang, T. Luo, J. Hu, Y. Wang, H. S. Krishnan, P. V Jog, S. K. Ganesh, G. K. S. Prakash, G. A. Olah, *Angew. Chemie Int. Ed.* **2011**, *50*, 7153–7157.

[16] P. Rullière, P. Cyr, A. B. Charette, *Org. Lett.* **2016**, *18*, 1988–1991.

[17] R. M. Bychek, V. V. Levterov, I. V. Sadkova, A. A. Tolmachev, P. K. Mykhailiuk, *Chem. Eur. J.* **2018**, *24*, 12291–12297.

[18] P. S. Nosik, S. V. Ryabukhin, O. O. Grygorenko, D. M. Volochnyuk, *Adv. Synth. Catal.* **2018**, *360*, 4104–4114.

[19] P. S. Nosik, A. O. Gerasov, R. O. Boiko, E. Rusanov, S. V. Ryabukhin, O. O. Grygorenko, D. M. Volochnyuk, *Adv. Synth. Catal.* **2017**, *359*, 3126–3136.

[20] P. S. Nosik, S. V. Ryabukhin, M. O. Pashko, G. P. Grabchuk, O. O. Grygorenko, D. M. Volochnyuk, *J. Fluor. Chem.* **2019**, *217*, 80–89.

[21] M. Goswami, B. de Bruin, W. I. Dzik, *Chem. Commun.* **2017**, *53*, 4382–4385.

[22] S. M. Banik, K. M. Mennie, E. N. Jacobsen, *J. Am. Chem. Soc.* **2017**, *139*, 9152–9155.

[23] D. Gill, N. McLay, M. Waring, C. Wilkinson, J. Sweeney, *Synlett* **2014**, *25*, 1756–1758.

[24] M. Hu, C. Ni, L. Li, Y. Han, J. Hu, *J. Am. Chem. Soc.* **2015**, *137*, 14496–14501.

[25] H. Takenaka, Y. Masuhara, K. Narita, T. Nokami, T. Itoh, *Org. Biomol. Chem.* **2018**, *16*, 6106–6114.

[26] J. Xu, E.-A. Ahmed, B. Xiao, Q.-Q. Lu, Y.-L. Wang, C.-G. Yu, Y. Fu, *Angew. Chemie Int. Ed.* **2015**, *54*, 8231–8235.

[27] T.-P. Yang, Q. Li, J.-H. Lin, J.-C. Xiao, *Chem. Commun.* **2014**, *50*, 1077–1079.

[28] D. Munemori, K. Narita, T. Nokami, T. Itoh, *Org. Lett.* **2014**, *16*, 2638–2641.

[29] T. Aono, H. Sasagawa, K. Fuchibe, J. Ichikawa, *Org. Lett.* **2015**, *17*, 5736–5739.

[30] K. R. Gassen, B. Baasner, *J. Fluor. Chem.* **1990**, *49*, 127–139.

[31] W. R. Dolbier, F. Tian, J.-X. Duan, A.-R. Li, S. Ait-Mohand, O. Bautista, S. Buathong, J. Marshall Baker, J. Crawford, P. Anselme, X. H. Cai, A. Modzelewska, H. Koroniak, M. A. Battiste, Q.-Y. Chen, *J. Fluor. Chem.* **2004**, *125*, 459–469.

[32] D. K. Tosh, K. Phan, Z.-G. Gao, A. A. Gakh, F. Xu, F. Deflorian, R. Abagyan, R. C. Stevens, K. A. Jacobson, V. Katritch, *J. Med. Chem.* **2012**, *55*, 4297–4308.

[33] J. Defaux, M. Antoine, M. Le Borgne, T. Schuster, I. Seipelt, B. Aicher, M. Teifel, E. Günther, M. Gerlach, P. Marchand, *ChemMedChem* **2014**, *9*, 217–232.

[34] V. Kubyshkin, Y. Kheylik, P. K. Mykhailiuk, *J. Fluor. Chem.* **2015**, *175*, 73–83.

[35] W.-P. Gu, J.-H. Lin, J.-C. Xiao, *Chinese Chem. Lett.* **2014**, *25*, 24–28.

[36] J. B. Liu, X. H. Xu, F. L. Qing, *Org. Lett.* **2015**, *17*, 5048–5051.

[37] D. G. Twigg, N. Kondo, S. L. Mitchell, W. R. J. D. J. D. Galloway, H. F. Sore, A. Madin, D. R. Spring, *Angew. Chemie Int. Ed.* **2016**, *55*, 12479–12483.

[38] J. Wenz, C. A. Rettenmeier, H. Wadepohl, L. H. Gade, *Chem. Commun.* **2016**, *52*, 202–205.

[39] V. N. Kizhnyaev, F. A. Pokatilov, N. A. Tsypina, G. V. Ratovskii, L. I. Vereshchagin, A. I. Smirnov, *Russ. J. Org. Chem.* **2002**, *38*, 1056–1059.

[40] I. I. Grandberg, G. I. Sharova, *Chem. Heterocycl. Compd.* **1971**, *4*, 797–798.

[41] V. I. Rstakyan, A. E. Akopyan, A. A. Saakyan, O. S. Attaryan, G. V. Asratyan, *Russ. J. Gen. Chem.* **2014**, *84*, 1945–1949.

[42] D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson, A. Wood, *Nat. Chem.* **2018**, *10*, 383–394.

[43] F. W. Goldberg, J. G. Kettle, T. Kogej, M. W. D. Perry, N. P. Tomkinson, *Drug Discov. Today* **2015**, *20*, 11–17.

[44] W. L. F. Armarego, C. Chai, *Purification of Laboratory Chemicals*, Elsevier: Oxford, **2003**.

Fluorine-containing sp^3-Enriched Building Blocks for the Multigram Synthesis of Fluorinated Pyrazoles and Pyrimidines with (Hetero)aliphatic Substituents

Anastasiya Fedinchyk,[a,b] Maksym Herasymchuk,[a,b] Vladyslav O. Smirnov,[a,b] Kostiantyn P. Melnykov,[a,b] Dmytro V. Yarmoliuk,[a] Andrii A. Kyrylchuk,[a,c] and Oleksandr O. Grygorenko*[a,b]

Dedicated to all the people in Ukraine that made finalizing this publication possible

[a] A. Fedinchyk, M. Herasymchuk, V. O. Smirnov, Dr. K. P. Melnykov, D. V. Yarmoliuk, Dr. A. A. Kyrylchuk, Prof. Dr. O. O. Grygorenko
Enamine Ltd. (www.enamine.net),
Chervonotkatska Street 78, Kyiv 02094, Ukraine
[b] A. Fedinchyk, M. Herasymchuk, V. O. Smirnov, Dr. K. P. Melnykov, Prof. Dr. O. O. Grygorenko
Taras Shevchenko National University of Kyiv
Volodymyrska Street 60, Kyiv 01601, Ukraine
E-mail: gregor@univ.kiev.ua
[c] Dr. A. A. Kyrylchuk
Institute of Organic Chemistry, National Academy of Sciences of Ukraine
Murmanska Street 5, Kyiv 02094, Ukraine

Supporting information for this article is given via a link at the end of the document.

Abstract: Efficient approaches to the gram-scale synthesis of fluorinated pyrazoles and pyrimidines bearing saturated (hetero)cyclic substituents are described. The methods rely on the heterocyclizations of sp^3-enriched β-bromo-α,α-difluoroketones and fluorinated enaminones (in turn prepared from saturated heterocyclic α-fluoroketones), respectively; these compounds themselves are useful synthetic intermediates that have been prepared on multigram scale for the first time. Log*P* and aqueous solubility measurements, as well as lead-likeness assessment using the Nelson's LLAMA tool show that the 19 synthesized sp^3-enriched fluorinated building blocks meet the lead-oriented synthesis criteria.

Introduction

Fluorinated heterocyclic cores are among the most attractive scaffolds in drug discovery.[1–6] They represent the key moieties of the various drugs developed to date. An antifungal medication Voriconazole and anticancer agents Abemaciclib and Pralsetinib can serve as prominent examples (Figure 1). The latter compound was approved by U.S. Food and Drug Administration very recently.[7] The ongoing search for new drug molecules makes the development of robust and versatile pathways to fluorinated heterocycles an essential challenge that organic and medicinal chemistry face.

An important trend observed in early drug discovery over the last two decades is special attention to sp^3-enriched molecules.[8–11] In this regard, the development of new approaches to biologically relevant heterocycles bearing cyclic (hetero)aliphatic substituents seems to be an important objective – a design concept leading to privileged structural motifs sometimes referred to as "biocores".[12,13] Thus, augmenting fluorinated pyrazole or piperidine scaffold with moieties like piperidine, pyrrolidine, azetidine, or cyclohexanone affords very promising chemotypes for drug discovery (Figure 2). In fact, piperidines are known to have superior developability in drug discovery compared to other saturated heterocycles.[14] On the other hand, structural motifs obtained by a combination of six-membered to and six- or five-membered rings connected through a single bond are among the top ten privileged Bemis-Murcko scaffolds in medicinal chemistry.[15]

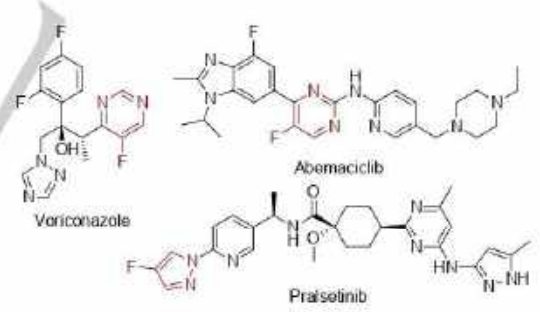


Figure 1. Selected drugs featuring fluorinated pyrimidine and pyrazole moieties

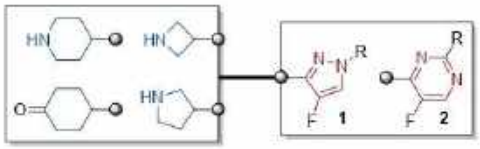
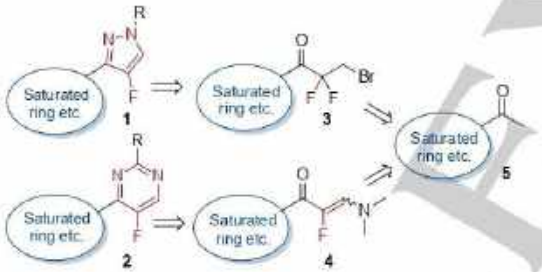


Figure 2. Design of the target molecules of this study

The most straightforward approach to the synthesis of fluorinated heterocycles – direct fluorination – is often a difficult

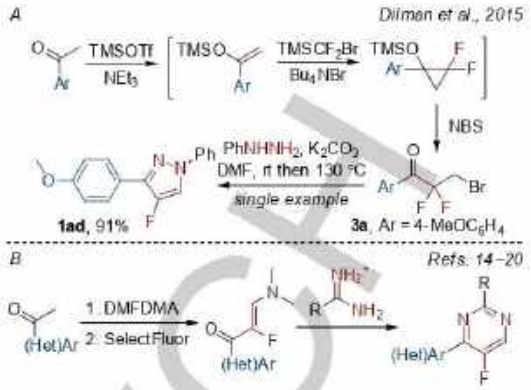
task because of the high reactivity of starting compounds toward fluorinating reagents and the high oxidative properties of the electrophilic fluorinating reagents. The use of precursors that already include fluorine atoms at the target positions offers an alternative promising route to a wide range of fluorinated compounds. We have considered this approach for the synthesis of target molecules **1** and **2** shown in Figure 2.

Thus, cyclization of the hydrazines with fluorine-containing building blocks **3** (in turn prepared from ketones **5**) may serve as the easy and scalable method for the synthesis of corresponding pyrazole derivatives **1** (Scheme 1). Recently, Dilman and co-workers have developed an approach to β-bromo-α,α-difluoroketones of type **3** *via* the "difluorohomologation" of the corresponding ketones, mostly acetophenones (Scheme 2, *A*).[16] Furthermore, a single example of 1,3-diaryl-4-fluoropyrazole (**1ad**) was obtained in 91 % yield by the reaction of corresponding product **3a** with phenyl hydrazine in the presence of K_2CO_3 in DMF. We have also noted that ketones **5** can give access to corresponding enaminones **4** (Scheme 1). Compounds of this type can be useful building blocks for the synthesis of 5-fluoropyrimidines like **2** (Scheme 2, *B*). Again, this approach was more or less well-studied for the fluorinated enaminones with aromatic and heteroaromatic substituents;[17–23] only a few simplest representatives of their aliphatic counterparts have been known to date.[24,25] In principle, building blocks of type **4** can also provide access to 4-fluorinated pyrazoles.[26]



Scheme 1. Retrosynthetic disconnection of the target fluorinated heterocycles

In this work, our primary goal was to develop an efficient multigram approach to fluorinated building blocks **3** and **4** bearing protected versions of the heteroaliphatic substituents listed in Figure 2. In addition to that, the corresponding 4-methoxyphenyl derivatives were also obtained as model compounds to correlate our results with the literature data. Furthermore, heterocyclizations of **3** and **4** with a series of simple *N*,*N*-dinucleophiles were performed to demonstrate their synthetic potential towards the preparation of fluorinated heterocycles **1** and **2** bearing sp^3-enriched substituents (Figure 3). Finally, the lead-likeness of the synthesized scaffolds was assessed using Nelson's LLAMA tool,[27] together with experimental measurements of the Log*P* values for the selected representatives and the corresponding non-fluorinated analogs.



Scheme 2. Some known syntheses of fluorinated pyrazoles and pyrimidines

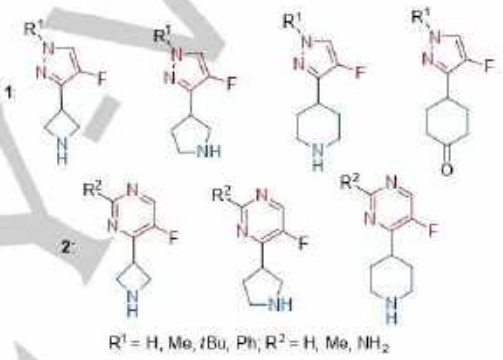
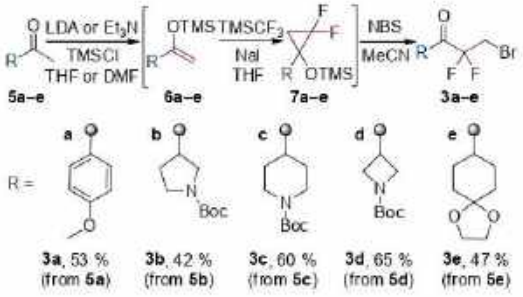


Figure 3. Target fluorinated heterocyclic scaffolds **1** and **2** studied in this work

Results and Discussion

Synthesis of fluorinated pyrazoles. Our work commenced with the preparation of building blocks **3** using a modified procedure of Dilman and co-workers.[16] Thus, commercially available ketones **5** were transformed to silyl enolates **6** that were not isolated in pure form but treated with a difluorocarbene source to give cyclopropanes **7** (Scheme 3). We have employed the Ruppert – Prakash reagent[28] as the difluorocarbene source instead of $TMSCF_2Br$ – Bu_4NBr used by the previous authors[16] because of substantially lower cost of $TMSCF_3$. The cyclopropanations proceeded smoothly and produced compounds **7** in 80–95 % yields (according to ^1H NMR spectra). In the case of pyrrolidine-substituted ketone **5b**, obtained silyl enolate **6b** contained ca. 20 % of the starting compound, which was possibly a result of partial hydrolysis during isolation. Intriguingly, this impurity disappeared after 2 days of the reaction of **6b** with the $TMSCF_3$ – NaI system. Taking into account to results obtained by Lloyd-Jones and co-authors,[29] we assumed that the starting ketone **5b** (in the enol form) is also capable of forming cyclopropane **7b** under the reaction conditions. Indeed, the direct reaction of **5b** with the $TMSCF_3$ – NaI system proceeded and gave **7b**, albeit with modest purity.



Scheme 3. Synthesis of building blocks **3a–e**

Notably, albeit intermediates of type **7** were observed by the previous authors,[29] they underwent further ring opening and fluoride elimination to give fluorinated enones under the nucleophilic conditions used ($TMSCF_3$ – $Bu_4N[Ph_3SiF_2]$). Since the $TMSCF_3$ – NaI system has been shown to give a much lower steady state concentration of highly nucleophilic species,[30] isolation of cyclopropanes **7** was possible in our case. This is one more illustration of how 'special' the $TMSCF_3$ – NaI reaction conditions are.

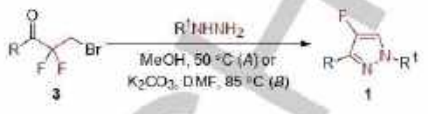
Due to their limited stability, cyclopropanes **7** were not isolated in pure form but subjected to the ring-opening reaction with *N*-bromosuccinimide according to the protocol of Dilman and co-workers[16] giving target fluorinated building blocks **3** in 42–65 % overall yield on up to 70 g scale. These yields are somewhat lower as compared to those obtained by the original authors (56–96 %).[16] Nevertheless, the previously described substrate scope included only aromatic ketones and simple cycloalkanones lacking additional functional groups, more expensive Me_3SiCF_2Br was used instead of the Ruppert – Prakash reagent, and the corresponding products were obtained on less than 1 g scale.

Having in hands significant quantities of compounds **3a–e**, we proceeded to the synthesis of 4-fluoropyrazoles **1** by reaction of these electrophilic intermediates with hydrazines (Table 1). It was found that the reaction of **3a–e** with hydrazine hydrate proceeded smoothly in refluxing MeOH, providing the corresponding products in 58–96 % yield. With *N*-substituted hydrazines (R^1 = Me, *t*Bu, or Ph), however, the yield of the target pyrazoles were modest at these conditions. These results correlate with the data obtained by Dilman and co-workers for the synthesis of compound **1ad** (see Scheme 2, *A*).[16] Therefore, we adopted the literature conditions for the preparation of all *N*-substituted fluorinated pyrazoles (K_2CO_3, DMF, rt, then 130 °C). We have found that it was better to perform the reaction at lower temperature (85 °C), especially with azetidine-derived starting compounds having modest stability. In all cases, the corresponding products were obtained in 42–82 % yield.

The regioselectivity of the pyrazole formation was confirmed by NOESY experiments performed with compounds **1cb**, **1db**, and **1dd** (Figure 4).

Selected examples of the resulting fluorinated pyrazoles bearing the *N*-Boc and ketal moieties were then successfully deprotected to yield corresponding derivatives **8** (Schemes 4 and 5). In both cases, the products were obtained in high yields on up to 16 g scale. CF_3COOH was used in the case of azetidines **1da–1dd** since in our experience, this heterocycle can be susceptible to nucleophilic ring opening with HCl.

Table 1. Synthesis of fluorinated pyrazoles **1**



#	Starting compound	R	R^1	Method [a]	Pyrazole	Yield, %
1	**3a**		H	*A*	**1aa**	92
2			Me	*B*	**1ab**	75
3	**3b**		H	*A*	**1ba**	78
4			Me	*B*	**1bb**	43
5			*t*Bu	*B*	**1bc**	47
6			Ph	*B*	**1bd**	78
7	**3c**		H	*A*	**1ca**	58
8			Me	*B*	**1cb**	50
9			Ph	*B*	**1cd**	82
10	**3d**		H	*A*	**1da**	96
11			Me	*B*	**1db**	70
12			Ph	*B*	**1dd**	62
13	**3e**		H	*A*	**1ea**	76

[a] Conditions, *A*: $N_2H_4 \cdot xH_2O$ (3 eq), MeOH, 50 °C; *B*: R^1NHNH_2 (1.5 eq), K_2CO_3 (3 eq), DMF, 85 °C

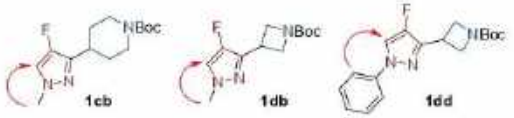
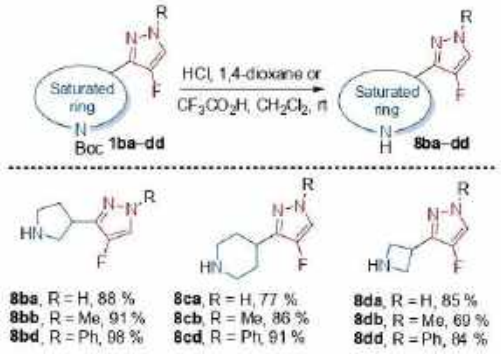


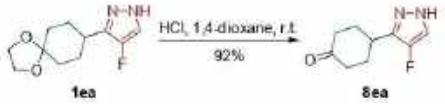
Figure 4. Correlations in NOE spectra of compounds **1cb**, **1db**, and **1dd**

Synthesis of fluorinated pyrimidines. Since building blocks **3** can also be potential 1,3-dielectrophilic precursors for the synthesis of fluorinated pyrimidines **2**, we tested reaction of **3a** with guanidinium chloride. Unfortunately, a complex mixture of products was formed, presumably containing 5,5-difluoro-1,4,5,6-tetrahydropyrimidine **9** as a major component instead of the target pyrimidine according to ^1H and $^{19}F\{^1H\}$ NMR spectra

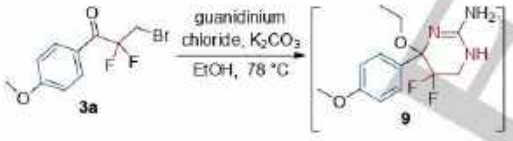
(Scheme 6). Our attempts to convert this product to aromatic pyrimidine by treatment with a base were unsuccessful. Variation of the solvent and the temperature used for the heterocyclization also did not lead to the desired result.



Scheme 4. Synthesis of building blocks **8ba – 8dd** (the compounds were obtained as HCl or TFA salts, not shown)

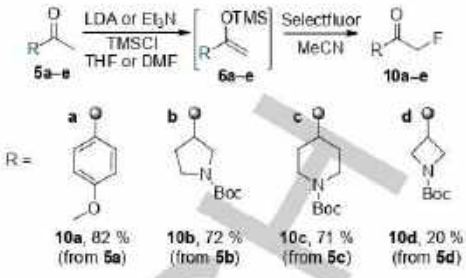


Scheme 5. Synthesis of ketone **8ea**



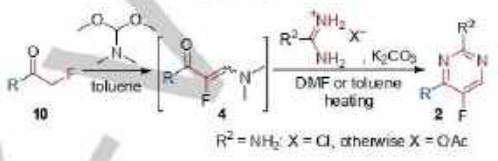
Scheme 6. Reaction of ketone **3a** with guanidinium chloride

Therefore, we have switched to enaminones **4** as the key intermediates in the synthesis of 5-fluorinated pyrimidines **2**. Formation of these precursors can be achieved by reaction of α-fluoroketones **10** with dimethylformamide dimethyl acetal.[26,31] In turn, synthesis of **10** can be performed by electrophilic fluorination of silyl enolates **6** (Scheme 7).[17-23] We have found that fluorination of silyl enolates **6a–d** pre-formed from the corresponding ketones **5a–d** with SelectFluor® in acetonitrile proceeded smoothly, and the products **10a–d** were obtained in 20–82 % yield on up to 70 g scale. Modest yield of azetidine-containing compound **10d** can be addressed to limited stability of this product at r.t. It should be noted that sp^3-enriched heterocyclic α-fluoroketones **10b–d** are very promising novel fluorinated building blocks for medicinal chemistry, and since they are now accessible on multigram scale, they should find their application in early drug discovery in the nearest future.



Scheme 7. Synthesis of α-fluoroketones **10**

Table 2. Synthesis of fluorinated pyrimidines **2**



#	Starting compound	R	R^2	Pyrimidine	Yield, %[b]
1	**10a**		H	**2aa**	40[c]
2			NH_2	**2ab**	68[c]
3	**10b**		H	**2ba**	27
4			NH_2	**2bb**	36
5			Me	**2bc**	51
7	**10c**		H	**2ca**	20[c] (42[c,d])
8			NH_2	**2cb**	61[c]
9			Me	**2cc**	68[c]
10	**10d**		H	**2da**	12
11			NH_2	**2db**	36
12			Me	**2dc**	30

[a] Conditions: amidine (3 eq), K_2CO_3 (5 eq), DMF, 80–100 °C (unless noted otherwise). Unless noted otherwise, overall yields for two steps are given

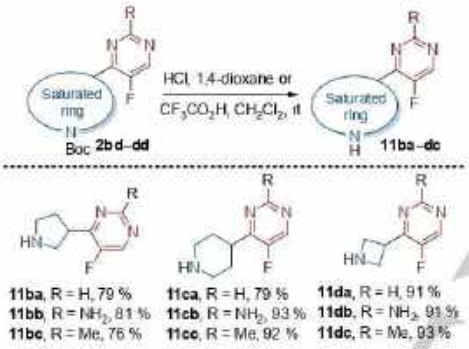
[b] Yields are given starting from **4a** or **4c** (in turn obtained in 85 % and 94 % yield from **10a** and **10c**, respectively)

[c] Yield in parentheses correspond to the gram-scale synthesis performed in toluene under reflux

Reaction of **10a** and **10c** with dimethylformamide dimethyl acetal proceeded in an expected manner with high efficiency (85 % and 94 % yield, respectively) (Table 2). In the case of **10b** and **10d**, the products could not be isolated in pure form due to limited stability (*ca.* 60 % and 40 % conversion into **4b** and **4d**, respectively, was observed); hence they were used in the next

step without characterization. At ca. 0.2–0.3 g scale, the reaction of **4a–d** and amidine or guanidine salts was performed in the presence of K_2CO_3 in DMF at 100 °C, and the corresponding pyrimidines were formed in ca. 40–70 % yield (starting from **4**). For products **2ca–2cc**, we also checked if multigram-scale synthesis of the products is possible. While **2cb** and **2cc** were obtained with nearly retained efficiency (10.5 g, 61 % and 12.0 g, 68 %, respectively), in the case of **2ca**, the yield diminished significantly under the typical conditions upon scale-up. Nevertheless, we have found that replacing DMF with less polar toluene allowed performing the gram-scale synthesis of **2ca** with reasonable efficiency (13.8 g, 42 % yield).

As in the case of pyrazoles **1**, selected examples of pyrimidines **2** were deprotected upon acidic conditions to give sp^3-enriched fluorinated building blocks **11** (Scheme 8). Again, azetidine-containing products were obtained as trifluoroacetates due to the potential lability of this heterocycle towards HCl.



Scheme 8. Synthesis of building blocks **11ba – 11dc** (the compounds were obtained as HCl or TFA salts, not shown)

Lead-likeness assessment. Since we anticipated application of the synthesized fluorinated heterocycles as building blocks for early drug discovery, we evaluated their physicochemical properties (Log*P* and aqueous solubility, S_w), as well as propensity to generate lead-like compound libraries. In order to evaluate the effect of a fluorine atom on Log*P* and S_w of the obtained heterocycles, benzoylated derivatives **12–15** were prepared from fluorine-containing pyrazole **8cb**, pyrimidine **11ca**, and their non-fluorinated counterparts (Figure 5, see the Experimental Section for more details). As it follows from the obtained results, the fluorine atom slightly increased lipophilicity of the corresponding derivatives (by 0.56 and 0.32 Log*P* units for the pyrazole and pyrimidine series, respectively). The effect of the fluorination on aqueous solubility was less unambiguous: slight increase for the pyrazole derivatives and almost 2.5-fold decrease – for the pyrimidines was observed.

To assess the suitability of the synthesized sp^3-enriched fluorinated heterocyclic derivatives for producing lead-like compound libraries, we applied LLAMA tool developed by Nelson and co-authors.[27] The key parameter evaluated by this tool is lead-likeness penalty (LLP), a combined measure of the compound compliance with a modified Churcher's definition of lead-likeness (MW = 200…350, LogP = –1…3)[10] based on the calculated physicochemical properties (heavy atom count, ALog*P*, number of aromatic rings, and undesirable functional group increment). The LLP parameter value equals zero for the compounds perfectly fitting the lead-like chemical space and increases as the compound goes away from it.

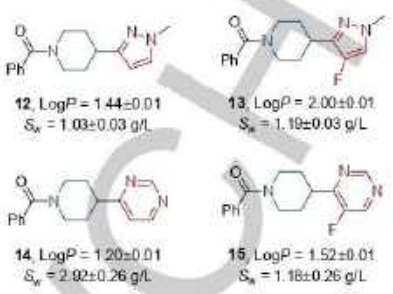


Figure 5. Log*P* and S_w values for model benzoylated derivatives **12–15** measured at 22 °C

All the 19 building blocks obtained in this work were used to generate the virtual library using default settings of the LLAMA tool; only the molecules that have been decorated once were considered as the products. It was found that 89 % of the pyrimidine-derived library members had LLP = 0; the value was somewhat lower for the pyrazole series (70 %) due to the presence of phenyl group in the molecules of **8bd**, **8cd**, and **8dd** (Figure 6, *A*). Only four library members do not fall under less stringent definition of lead-likeness according to "rule-of-four" (MW < 400, Log*P* < 4; see Figure 6, *B*).[8] These results show that the sp^3-enriched fluorinated chemotypes proposed in this work are indeed suitable for the preparation of lead-like compound libraries.

Conclusions

Over the last decade, sp^3-enriched molecules have attracted special attention in medicinal chemistry. Incorporation of such structural motifs into biologically relevant molecule (e.g. fluorinated heterocycles) is an important design concept in early drug discovery. Nevertheless, this strategy is often hampered by additional synthetic issues arising when the known synthetic methods are extended to the compounds bearing (functionalized) saturated moieties.[32] In this work, a convenient approach to fluorinated pyrazoles and pyrimidines bearing saturated (hetero)cyclic substituents is described allowing for the preparation of gram quantities of the target products. In both cases, heterocyclizations of the appropriate fluorinated sp^3-enriched precursors is used at the key step. The corresponding synthetic intermediates (β-bromo-α,α-difluoro- and α-fluoroketones, respectively) have been prepared on multigram scale for the first time; they are also promising building blocks for organic synthesis and medicinal chemistry. Log*P* and aqueous solubility measurements showed that these physicochemical properties are not affected dramatically by the fluorination; in particular, only slight increase of liphophilicity (by 0.3–0.5 units) is observed. Finally, lead-likeness assessment of the 19 fluorinated sp^3-enriched building blocks obtained showed that they comply well with the requirement of lead-oriented synthesis.

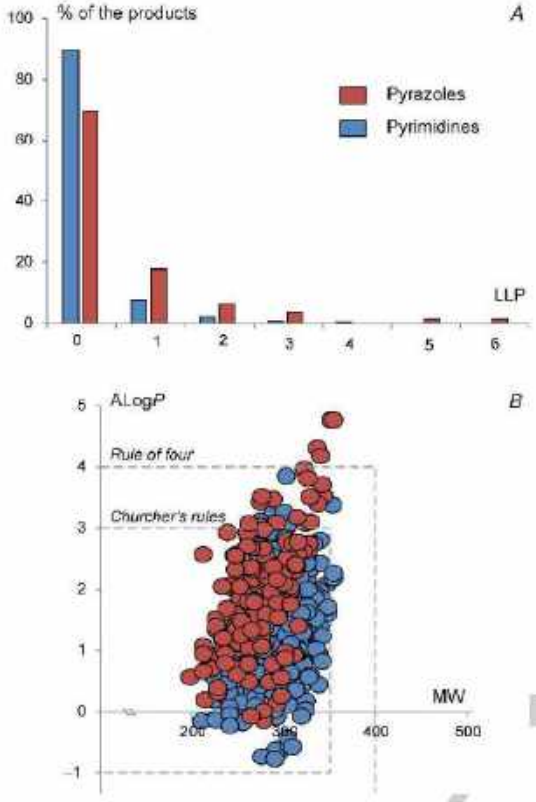


Figure 6. Lead-likeness penalty (LLP) (*A*) and Log*P* – molecular weight (MW) (*B*) distributions of virtual compound libraries generated from building blocks **8** and **11** using LLAMA tool.

Experimental Section

4-(1-Methyl-1*H*-pyrazol-3-yl)piperidine and 4-(piperidin-4-yl)pyrimidine[20] were provided by courtesy of Enamine Ltd. All other starting materials were purchased from commercial sources. Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230- 400 mesh) as the stationary phase. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C{^{1}H} NMR, and 470 MHz for ^{19}F{^{1}H} NMR), Agilent ProPulse 600 spectrometer (at 600 MHz for ^{1}H NMR and 151 MHz for ^{13}C{^{1}H} NMR), and Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C{^{1}H} NMR, and 376 MHz for ^{19}F{^{1}H} NMR). NMR chemical shifts are reported in ppm downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C{^{1}H} in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C{^{1}H} in DMSO-d_6. ^{19}F{^{1}H} NMR chemical shifts are relative to hexafluorobenzene at δ = –164.9 ppm (internal reference). Coupling constants (*J*) are shown in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)). Preparative reverse-phase HPLC purifications were performed on an Agilent 1100 instrument using Chromatorex C18 column (100×19 mm, 5 µm particle size) and gradient MeCN – H_2O or MeOH – H_2O as eluent.

3-Bromo-2,2-difluoro-1-(4-methoxyphenyl)propan-1-one (3a). NEt_3 (8.62 mL, 0.0619 mol) and TMSCl (3.80 mL, 0.030 mol) were added to a solution of *p*-metoxyacetophenone **5a** (3.75 g, 0.025 mol) in DMF (10 mL). The reaction mixture was stirred overnight at 80 °C. Then it was allowed to cool to r.t. and poured into an ice/water mixture (20 mL) and extracted with hexanes (2×20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to give crude **6a** (*ca.* 0.022 mol) used in the next step without characterization.
$TMSCF_3$ (6.67 mL, 0.045 mol) and NaI (0.68 g, 0.004 mol) were added to the solution of crude **6a** in THF (70 mL). The reaction mixture was stirred for 1 h at r.t and overnight at 50 °C. Then it was evaporated, diluted with *t*BuOMe (30 mL), filtered off and the filtrate was evaporated to give crude **7a** (*ca.* 0.018 mol) used in the next step without characterization.
NBS (4.29 g, 0.024 mol) was added to the solution of crude **7a** in MeOH (70 mL). The reaction mixture was stirred at r.t for 1 h6 and water (200 mL) was added. The mixture was extracted with hexane (2×200 mL), combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (gradient hexanes – *t*BuOMe (95:5 to 0:100) as eluent). Yield 3.70 g (53 %). All spectral and physical data correspond to those reported in the literature.[18]

***tert*-Butyl 3-(3-bromo-2,2-difluoropropanoyl)pyrrolidine-1-carboxylate (3b).** A solution of *n*BuLi (2.5 M in hexane, 142 mL, 0.356 mol) was added dropwise to a solution of diisopropylamine (52.6 mL, 0.373 mol) in THF (1300 mL) cooled to 0 °C under argon atmosphere. The reaction mixture was stirred at −78 °C for 1 h, and a solution of **5b** (72.3 g, 0.339 mol) in THF (100 mL) was added dropwise. Then a solution of TMSCl (47.3 mL, 0.373 mol) in THF (50 mL) was slowly added dropwise at −78 °C, and the mixture was allowed to warm up to r.t. Reaction progress was monitored by TLC (*t*BuOMe – hexanes (1:1) as eluent). The reaction mixture was diluted with *t*BuOMe (600 mL) and washed with 10% aq NH_4Cl (2×400 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (*t*BuOMe – hexanes (1:5) as eluent).
The crude product was dissolved in THF (1400 mL), and NaI (12.8 g, 85.8 mmol) was added. The mixture was heated to intense boiling and then the solution of $TMSCF_3$ (72.5 mL, 0.490 mol) in THF (70 mL) was slowly added dropwise. After 5 minutes, the reaction mixture was cooled, diluted with *t*BuOMe (700 mL), filtered through silica gel pad, and evaporated.
The residue was dissolved in dry acetonitrile (1100 mL). The solution was cooled to 0 °C, and NBS (54.5 g, 0.306 mol) was added. The mixture was stirred overnight at r.t., then water (800 mL) was added. The mixture was extracted with *t*BuOMe (3×300 mL), organic phase was dried over Na_2SO_4 and evaporated. The product was purified by flash chromatography (*t*BuOMe – hexanes (1:5) as eluent). Yield 48.0 g (42 %). Brownish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (t, *J* = 13.3 Hz, 2H), 3.64 – 3.52 (m, 3H), 3.48 (br s, 1H), 3.42 – 3.34 (m, 1H), 2.26 – 2.06 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.5 (t, *J* = 30.8 Hz), 154.1, 114.1, 79.7, 46.8, 45.1, 45.1, 44.2, 28.4, 27.2 (t, *J* = 29.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –105.3, –105.6. MS (APCI): *m/z* = 364/366 [M+Na]$^+$, 286/288 [M– $CH_2C(CH_3)_2$+H]$^+$. The compound had limited stability and did not give satisfactory elemental analysis.

***tert*-Butyl 4-(3-bromo-2,2-difluoropropanoyl)piperidine-1-carboxylate (3c)** was synthesized analogously to **3b** starting from 74.2 g of **5d**. Yield 70.2 g (60 %). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 – 4.05 (m, 2H), 3.69 (t, *J* = 13.4 Hz, 2H), 3.06 (tt, *J* = 11.3, 3.8 Hz, 1H), 2.83 (t, *J* = 12.6 Hz, 2H), 1.92 – 1.82 (m, 2H), 1.64 – 1.52 (m, 2H), 1.44 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 200.8 (t, *J* = 29.7 Hz), 154.6, 114.5 (t, *J* = 256.2 Hz), 79.9, 43.4, 42.9, 28.5, 27.6 (t, *J* = 29.4 Hz), 27.1. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –105.7. MS (EI): *m/z* = 355/357 [M]$^+$, 282/284 [M–$OC(CH_3)_3$]$^+$. Anal. Calcd. for $C_{13}H_{20}BrF_2NO_3$: C 43.83; H 5.66; N 3.93; Br 22.43. Found: C 43.63; H 5.74; N 3.95; Br 22.82.

***tert*-Butyl 3-(3-bromo-2,2-difluoropropanoyl)azetidine-1-carboxylate (3d)** was synthesized analogously to **3b** starting from 62.4 g of **5d**. Yield 51.4 g (65 %). Brownish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.18 – 4.06 (m, 4H), 3.92 – 3.82 (m, 1H), 3.69 (t, *J* = 13.3 Hz, 2H), 1.41 (s, 9H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 196.7 (t, *J* = 31.2 Hz), 156.0, 114.3 (t, *J* = 255.2 Hz), 80.2, 34.4, 34.2, 28.3, 26.8 (t, *J* = 29.2 Hz). ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ –105.1. The compound had limited stability and did not give satisfactory elemental analysis.

3-Bromo-1-(1,4-dioxaspiro[4.5]decan-8-yl)-2,2-difluoropropan-1-one (3e) was synthesized analogously to **3b** starting from 8.60 g of **5e**.Yield 6.90 g (47 %). Brownish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 4H), 3.68 (t, *J* = 13.5 Hz, 2H), 2.93 (tt, *J* = 11.2, 3.6 Hz, 1H), 1.98 – 1.90 (m, 2H), 1.86 – 1.72 (m, 4H), 1.68 – 1.57 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 201.6 (t, *J* = 29.5 Hz), 114.5 (t, *J* = 256.2 Hz), 107.7, 64.5, 64.5, 43.7, 33.8, 27.8 (t, *J* = 29.3 Hz), 25.6. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –105.9. MS (APCI): *m/z* = 313/315 [M+H]$^+$. Anal. Calcd for $C_{11}H_{15}BrF_2O_3$: C 42.19; H 4.83; Br 25.52. Found: C 41.81; H 4.86; Br 25.46.

Synthesis of 4-fluorinated pyrazoles 1.

Method A. Hydrazine hydrate (253 mmol) was added to the solution of compound **3** (84.2 mmol) in methanol (450 mL). The mixture was stirred overnight at 50 °C, then evaporated, the residue was dissolved in water (600 mL) and extracted with *t*BuOMe (2×150 mL). Combined organic phases were washed with water (100 mL), dried over Na_2SO_4 and evaporated.

Method B. Substituted hydrazine or its salt (43.8 mmol) and K_2CO_3 (18.1 g, 0.131 mol) were added to a solution of compound **3** (29.2 mmol) in DMF (150 mL) at rt. The mixture was stirred overnight at 85 °C. Then water (600 mL) was added, and the obtained mixture was extracted with *t*BuOMe (2×150 mL). Combined organic phases were washed with water (3×150 mL), dried over Na_2SO_4, and evaporated. Flash chromatography (hexane – *t*BuOMe (2:1) as eluent) was used for the purification of the crude product unless noted otherwise.

4-Fluoro-3-(4-methoxyphenyl)-1*H*-pyrazole (1aa). Obtained according to method A starting from 1.00 g of **3a**. Yield 0.63 g (92 %). Yellowish crystals. M.p. 122–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.07 (br.s, 1H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 4.5 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 2H), 3.85 (s, 3H). ^{13}H NMR (126 MHz, $CDCl_3$) δ 159.1, 146.3 (d, *J* = 246.8 Hz), 126.8 (d, *J* = 3.6 Hz),121.2, 120.8 (br s, 2C), 113.8, 54.8. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): –178.8. MS (APCI): *m/z* = 193 [M+H]$^+$. Anal. Calcd for $C_{10}H_9FN_2O$: C 62.49; H 4.72; N 14.58. Found: C 62.28; H 4.54; N 14.62.

4-Fluoro-3-(4-methoxyphenyl)-1-methyl-1*H*-pyrazole (1ab).[34] Obtained according to method B starting from methyl hydrazine and 1.00 g of **3a**. Yield 690 mg (75 %). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.6 Hz, 2H), 7.27 (d, *J* = 4.8 Hz, 1H), 7.07 (d, *J* = 8.6 Hz, 2H), 3.89 (s, 3H), 3.84 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.3, 146.8 (d, *J* = 248.3 Hz), 136.8 (d, *J* = 6.5 Hz), 127.3, 127.3, 124.0 (d, *J* = 4.1 Hz), 117.4 (d, *J* = 28.5 Hz), 114.1 (2C), 55.3, 39.9. ^{19}F NMR (470 MHz, $CDCl_3$) δ –175.6 (d, *J* = 4.8 Hz). MS (APCI): *m/z* = 207 [M+H]$^+$. Anal. Calcd for $C_{11}H_{11}FN_2O$: C 64.07; H 5.38; N 13.58. Found: C 63.85; H 5.10; N 13.46.

***tert*-Butyl 3-(4-fluoro-1*H*-pyrazol-3-yl)pyrrolidine-1-carboxylate (1ba).** Obtained according to method A starting from 10.0 g of **3b**. Yield 5.80 g (78 %). Reddish oil. The compound existed as a mixture of rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 4.5 Hz, 1H), 3.83–3.71 (m, 1H), 3.61–3.34 (m, 4H), 2.29–2.20 (m, 1H), 2.17–2.07 (m, 1H), 1.45 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.8, 147.6 (d, *J* = 243.9 Hz), 135.0, 118.9, 79.7, 50.3, 49.8 and 45.8 and 45.5, 35.2 and 34.5, 31.1 and 30.3, 28.6. ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ –180.36 and –180.39. MS (APCI): m/z = 254 [M–H]$^-$. Anal. Calcd for $C_{12}H_{18}FN_3O_2$: C 56.46; H 7.11; N 16.46. Found: C 56.36; H 7.48; N 16.12.

***tert*-Butyl 3-(4-fluoro-1-methyl-1*H*-pyrazol-3-yl)pyrrolidine-1-carboxylate (1bb).** Obtained according to method B starting from methyl hydrazine sulfate and 12.0 g of **3b**. Yield 4.07 g (43 %). Yellowish oil. The compound existed as a mixture of rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 – 7.14 (m, 1H), 3.74 (s, 3H), 3.60 – 3.69 (m, 1H), 3.60 – 3.50 (m, 1H), 3.44 – 3.29 (m, 3H), 2.24 – 2.18 (m, 1H), 2.15 – 2.06 (m, 1H), 1.44 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.7, 147.2 (d, *J* = 245.6 Hz), 137.8, 116.7 (d, *J* = 27.6 Hz), 79.3, 50.4 and 50.1, 45.9 and 45.6, 39.7, 35.8 and 35.1, 31.1 and 30.5, 28.6. ^{19}F NMR (470 MHz, $CDCl_3$) δ –177.7 (d, *J* = 4.8 Hz) and –177.8 (d, *J* = 3.9 Hz). MS (APCI): *m/z* = 214 [M–$CH_2C(CH_3)_2$+H]$^+$. Anal. Calcd for $C_{13}H_{20}FN_3O_2$: C 57.98; H 7.49; N 15.60. Found: C 58.23; H 7.73; N 15.21.

***tert*-Butyl 3-(1-*tert*-butyl-4-fluoro-1*H*-pyrazol-3-yl)pyrrolidine-1-carboxylate (1bc).** Obtained according to method B starting from *tert*-butyl hydrazine hydrochloride and 1.00 g of **3b**. Yield 430 mg (47 %). Brownish oil. The compound existed as a mixture of rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 4.8 Hz, 1H), 3.78 – 3.67 (m, 1H), 3.59 – 3.30 (m, 4H), 2.22 – 2.10 (m, 2H), 1.48 (s, 9H), 1.45 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.73 and 154.67, 146.9 (d, *J* = 245.0 Hz), 136.8 (d, *J* = 8.2 Hz) and 136.7 (d, *J* = 9.2 Hz), 112.5 (d, *J* = 28.2 Hz), 79.1 and 79.0, 58.7, 50.5 and 50.0, 46.0 and 45.6, 36.2 and 35.3, 31.3 and 30.4, 29.5, 28.7. ^{19}F NMR (470 MHz, $CDCl_3$) δ –178.7 (d, *J* = 4.8 Hz) and –178.8 (d, *J* = 4.8 Hz). MS (APCI): m/z = 256 [M–$CH_2C(CH_3)_2$+H]$^+$. Anal. Calcd for $C_{16}H_{26}FN_3O_2$: C 61.71; H 8.42; N 13.49. Found: C 61.89; H 8.34; N 13.22.

***tert*-Butyl 3-(4-fluoro-1-phenyl-1*H*-pyrazol-3-yl)pyrrolidine-1-carboxylate (1bd).** Obtained according to method B starting from phenyl hydrazine and 18.0 g of **3b**. Brownish crystals. Mp = 109–110 °C. The compound existed as a mixture of rotamers. Yield 13.7 g (78 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 4.7 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.26 – 7.22 (m, 1H), 3.88 – 3.75 (m, 1H), 3.69 – 3.47 (m, 3H), 3.44 – 3.33 (m, 1H), 2.32 – 2.16 (m, 2H), 1.46 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.7, 149.0 (d, *J* = 249.3 Hz), 140.6, 140.1, 129.6, 126.5, 118.5, 113.5 (d, *J* = 29.0 Hz), 79.3, 50.3 and 49.9, 45.9 and 45.6, 35.9 and 35.1, 31.1 and 30.4, 28.7. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –175.8 and –175.9. MS (APCI): m/z = 276 [M–$CH_2C(CH_3)_2$+H]$^+$. Anal. Calcd for $C_{16}H_{22}FN_3O_2$: C 65.24; H 6.69; N 12.68. Found: C 64.99; H 6.7; N 12.51.

***tert*-Butyl 4-(4-fluoro-1*H*-pyrazol-3-yl)piperidine-1-carboxylate (1ca).** Obtained according to method A starting from 30.0 g of **3c**. Yield 13.1 g (58 %). Brownish crystals. Mp = 129–131 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.40 (br s, 1H), 7.33 (d, *J* = 4.5 Hz, 1H), 4.24 – 4.08 (m, 2H), 2.88 (tt, *J* = 12.0, 3.8 Hz, 1H), 2.85 – 2.75 (m, 2H), 1.90 (d, *J* = 12.4 Hz, 2H), 1.72 (qd, *J* = 12.4, 4.3 Hz, 2H), 1.45 (s, 9H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 155.0, 147.2 (d, *J* = 243.5 Hz), 137.3, 119.9, 79.8, 43.9, 33.1, 30.6, 28.6. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –180.9. MS (APCI): m/z = 268 [M–H]$^-$. Anal. Calcd for $C_{13}H_{20}FN_3O_2$: C 57.98; H 7.49; N 15.6. Found: C 57.82; H 7.70; N 15.97.

***tert*-Butyl 4-(4-fluoro-1-methyl-1*H*-pyrazol-3-yl)piperidine-1-carboxylate (1cb).** Obtained according to method B starting from methyl hydrazine sulfate and 30.0 g of **3c**. Yield 12.0 g (50 %). Yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 4.8 Hz, 1H), 4.25 – 4.05 (m, 2H), 3.74 (s, 3H), 2.90 – 2.71 (m, 3H), 1.91 – 1.81 (m, 2H), 1.72 (qd, *J* = 12.2, 4.2 Hz, 2H), 1.45 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.9, 147.0 (d, *J* = 245.0 Hz), 141.3 (d, *J* = 9.2 Hz), 116.6 (d, *J* = 27.8 Hz), 79.4, 43.9, 39.6, 33.9, 30.8, 28.6. ^{19}F NMR (470 MHz, $CDCl_3$) δ –178.0 (d, *J* = 4.8 Hz). MS (APCI): m/z = 228 [M–$CH_2C(CH_3)_2$+H]$^+$. Anal. Calcd for $C_{14}H_{22}FN_3O_2$: C 59.35; H 7.83; N 14.83. Found: C 59.57; H 7.9; N 14.97.

***tert*-Butyl 4-(4-fluoro-1-phenyl-1*H*-pyrazol-3-yl)piperidine-1-carboxylate (1cd).** Obtained according to method B starting from phenyl hydrazine and 1.00 g of **3c**. Yield 0.80 g (82 %). Yellowish oil. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.25 (d, *J* = 4.8 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.94 (t, *J* = 7.8 Hz, 2H), 6.77 (t, *J* = 7.2 Hz, 1H), 3.78 – 3.61 (m, 2H), 2.53

– 2.37 (m, 3H), 1.49 (d, *J* = 11.9 Hz, 2H), 1.36 (qd, *J* = 11.9, 4.2 Hz, 2H), 1.01 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 154.9, 148.9 (d, *J* = 249.0 Hz), 143.8 (d, *J* = 9.4 Hz), 140.2, 129.5, 126.3, 118.4, 113.3 (d, *J* = 28.9 Hz), 79.5, 43.7, 34.0 (d, *J* = 3.3 Hz), 30.5, 28.6. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –175.9. MS (APCI): *m/z* = 290 [M–$CH_2C(CH_3)_2$+H]$^+$. Anal. Calcd for $C_{15}H_{20}FN_3O_2$: C 66.07; H 7.00; N 12.17. Found: C 66.03; H 7.30; N 12.19.

***tert*-Butyl 3-(4-fluoro-1*H*-pyrazol-3-yl)azetidine-1-carboxylate (1da).** Obtained according to method A starting from 26.0 g of **3d**. The product was purified by flash chromatography (*t*BuOMe as eluent). Yield 18.3 g (96 %). Brownish liquid. ^1H NMR (500 MHz, $CDCl_3$) δ 10.11 (s, 1H), 7.39 – 7.34 (m, 1H), 4.29 – 4.22 (m, 2H), 4.18 – 4.10 (m, 2H), 3.86 – 3.78 (m, 1H), 1.42 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 156.0, 147.0 (d, *J* = 247.5 Hz), 135.8, 117.4 (d, *J* = 14.9 Hz), 79.4, 54.1, 27.9, 23.8 (d, *J* = 2.9 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –181.1. LC/MS (API-ES): *m/z* = 264 [MNa]$^+$. Anal. Calcd for $C_{11}H_{16}FN_3O_2$: C 54.76; H 6.68; N 17.42. Found: C 54.57; H 6.89; N 17.33.

***tert*-Butyl 3-(4-fluoro-1-methyl-1*H*-pyrazol-3-yl)azetidine-1-carboxylate (1db).** Obtained according to method B starting from methyl hydrazine sulfate and 24.0 g of **3d**. Yield 13.1 g (70 %). Brownish oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.21 (t, *J* = 8.6 Hz, 2H), 4.12 (t, *J* = 7.3 Hz, 2H), 3.76 (s, 3H), 1.40 (d, *J* = 5.8 Hz, 11H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 156.3, 147.1 (d, *J* = 245.5 Hz), 138.0 (d, *J* = 9.1 Hz), 116.8 (d, *J* = 27.2 Hz), 79.4, 54.4, 39.7, 28.4, 24.7 (d, *J* = 3.6 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –178.5. LC/MS (API-ES): *m/z* = 256 [M+H]$^+$. Anal. Calcd for $C_{12}H_{18}FN_3O_2$: C 56.46; H 7.11; N 16.46. Found: C 56.08; H 7.23; N 16.27.

***tert*-Butyl 3-(4-fluoro-1-phenyl-1*H*-pyrazol-3-yl)azetidine-1-carboxylate (1dd).** Obtained according to method B starting from phenyl hydrazine and 10.0 g of **3d**. The compound was purified by flash chromatography (hexane – *t*BuOMe (1:1) as eluent). Yield 6.00 g (62 %). Brownish oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 4.8 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 2H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 1H), 4.33 – 4.20 (m, 4H), 3.95 – 3.83 (m, 1H), 1.44 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 158.4, 148.8 (d, *J* = 249.9 Hz), 140.6 (d, *J* = 10.0 Hz), 139.9, 129.5, 126.5, 118.4, 113.6 (d, *J* = 28.3 Hz), 79.5, 54.2, 28.4, 24.9 (d, *J* = 3.3 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –176.1. LC/MS (API-ES): *m/z* = 318 [M+H]$^+$. Anal. Calcd for $C_{17}H_{20}FN_3O_2$: C 64.34; H 6.35; N 13.24. Found: C 64.64; H 6.08; N 12.84.

3-(1,4-Dioxaspiro[4.5]decan-8-yl)-4-fluoro-1*H*-pyrazole (1ea). Obtained according to method B starting from 1.00 g of **3e**. Yield 0.55 g (76 %). Yellowish oil. ^1H NMR (600 MHz, $CDCl_3$) δ 10.56 (br s, 1H), 7.48 (d, *J* = 4.5 Hz, 1H), 3.98 (s, 4H), 2.82 (tt, *J* = 11.8, 3.8 Hz, 1H), 2.01 – 1.95 (m, 2H), 1.94 – 1.87 (m, 2H), 1.87 – 1.82 (m, 2H), 1.68 (td, *J* = 13.2, 4.3 Hz, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 146.9 (d, *J* = 242.3 Hz), 136.6, 121.7, 108.3, 64.5, 64.4, 34.7, 33.0, 29.2. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –181.4. MS (APCI): *m/z* = 227 [M+H]$^+$. Anal. Calcd for $C_{11}H_{15}FN_2O_2$: C 58.4; H 6.68; N 12.38. Found: C 58.28; H 6.34; N 12.48.

2-Fluoro-1-(4-methoxyphenyl)ethan-1-one (10a). Silyl enolate **6a** was obtained from 2.16 g (0.0144 mol) of **5a** following the procedure for the first (silylation) step in the preparation of **3a** and was used without purification. Selectfluor (4.91 g, 0.014 mol) was added to a solution of **6a** in MeCN (40 mL) at 0 °C. The reaction mixture was stirred overnight at r.t., then it was evaporated, water (50 mL) was added, and the mixture was extracted by ethyl acetate (2x50 mL). Combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (gradient *t*BuOMe – hexanes as eluent). Yield 1.74 g (82 %). Colorless solid. Mp 79–82 °C (lit.[35] 82–84 °C). Other spectral and physical data were in accordance with those reported in the literature.[35,36]

***tert*-Butyl 3-(2-fluoroacetyl)pyrrolidine-1-carboxylate (10b).** Silyl enolate **6b** was obtained from 72.3 g (0.340 mol) of **5b** following the procedure for the first (silylation) step in the preparation of **3b** and was used without purification. The fluorination step was performed as described for **10a**. The product was purified by column chromatography (*t*BuOMe – hexanes (1:5) as eluent). Yield 70.0 g (72 %). Yellowish oil. ^1H NMR (500 MHz, $CDCl_3$) δ 4.88 (d, *J* = 47.5 Hz, 2H), 3.60 – 3.50 (m, 2H), 3.47 – 3.32 (m, 3H), 2.13 – 2.09 (m, 2H), 1.44 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 206.0 (d, *J* = 23.1 Hz), 154.4, 84.6 (d, *J* = 185.5 Hz), 79.7, 46.5, 46.5, 45.2, 28.6, 27.2. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –228.8. MS(EI): *m/z* = 231 [M]$^+$, 174/176 [M–*t*Bu]$^+$. Anal. Calcd for $C_{11}H_{18}FNO_3$: C 57.13; H 7.85; N 6.06. Found: C 57.42; H 7.61; N 5.78.

***tert*-Butyl 4-(2-fluoroacetyl)piperidine-1-carboxylate (10c).** Starting compound **6c** was obtained from 12.8 g of **5c** following the procedure for the first (silylation) step in the preparation of **3c** and was used without purification. Fluorination was performed as described for **10a**. The product was purified by column chromatography (*t*BuOMe – hexanes (1:2) as eluent). Yield 9.80 g (71 %). White crystals. ^1H NMR (400 MHz, $CDCl_3$) δ 4.90 (d, *J* = 47.6 Hz, 2H), 4.13 (d, *J* = 13.3 Hz, 2H), 2.90 – 2.76 (m, 3H), 1.83 (d, *J* = 13.3 Hz, 2H), 1.64 – 1.51 (m, 2H), 1.46 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 207.4 (d, *J* = 18.5 Hz), 154.1, 83.7 (d, *J* = 185.5 Hz), 79.2, 43.8, 27.9, 26.2. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –229.5. MS(EI): *m/z* = 245 [M]$^+$, 189/188 [M–*t*Bu]$^+$. Anal. Calcd for $C_{12}H_{20}FNO_3$: C 58.76; H 8.22; N 5.71. Found: C 58.43; H 8.62; N 5.31.

***tert*-Butyl 3-(2-fluoroacetyl)azetidine-1-carboxylate (10d)** was obtained analogously to **10b** starting from 62.4 g of **5d**. The product was purified by column chromatography (*t*BuOMe – hexanes (1:1) as eluent). Yield 13.6 g (29 %). White crystals. ^1H NMR (400 MHz, $CDCl_3$) δ 4.89 (d, *J* = 47.4 Hz, 2H), 4.16 – 4.05 (m, 4H), 3.76 – 3.64 (m, 1H), 1.42 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 204.8 (d, *J* = 22.0 Hz), 156.2, 84.6 (d, *J* = 183.9 Hz), 80.1, 49.9, 35.8, 28.4. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –228.8. MS (EI): *m/z* = 217 [M]$^+$, 162/161 [M–*t*Bu]$^+$. Anal. Calcd for $C_{10}H_{16}FNO_3$: C 55.29; H 7.42; N 6.45. Found: C 55.18; H 7.52; N 6.80.

Synthesis of 5-fluorinated pyrimidines 2. *N,N*-Dimethylformamide dimethyl acetal (64.6 mL, 0.484 mol) was added to a solution of **10** (0.119 mol) in toluene (150 mL). The mixture was stirred overnight at 145 °C and then evaporated. Water (150 mL) was added and the mixture was extracted with dichloromethane (2×150 mL). Combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and evaporated to give crude product **4**. In the case of compounds **4a** and **4c**, purification was performed by flash chromatography (gradient *t*BuOMe – hexanes as eluent). Fluorinated enaminones **4b** and (especially) **4d** had limited stability and were used further without purification.

The corresponding guanidine or amidine salt (0.173 mol) and K_2CO_3 (39.8 g, 0.288 mol) were added to a solution of compound **4** (57.6 mmol) in DMF (110 mL). The mixture was stirred overnight at 100 °C. Then water (500 mL) was added, and the obtained mixture was extracted with *t*BuOMe (3×150 mL). The combined organic phases were washed with water (3×150 mL), dried over Na_2SO_4, and evaporated.

3-(Dimethylamino)-2-fluoro-1-(4-methoxyphenyl)prop-2-en-1-one (4a) was obtained from 20.0 g of **10a**. Yield 22.5 g (85 %). Brownish solid. Mp 109–112 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.2 Hz, 2H), 6.89 (d, *J* = 8.2 Hz, 2H), 6.73 (d, *J* = 27.9 Hz, 1H), 3.83 (s, 3H), 3.08 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 184.4, 161.9, 140.5 (d, *J* = 229.9 Hz), 135.9, 131.1, 130.8, 130.7, 113.4 (2C), 55.5, 42.9 (2C). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –166.5. MS (APCI): *m/z* = 224 [M+H]$^+$. Anal. Calcd for $C_{12}H_{14}FNO_2$: C 64.56; H 6.32; N 6.27. Found: C 64.22; H 6.54; N 6.50.

***tert*-Butyl 4-[3-(dimethylamino)-2-fluoroprop-2-enoyl]piperidine-1-carboxylate (4c)** was obtained from 15.0 g of **10c**. Yield 17.3 g (94 %). Yellowish crystals. Mp 158–159 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, *J* = 28.9 Hz, 1H), 4.10 (br s, 2H), 3.03 (s, 6H), 2.75 (br s, 3H), 1.73 – 1.52 (m, 4H), 1.42 (s, 9H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 154.7, 139.0 (d, *J* = 230.0 Hz), 138.3, 130.8, 79.3, 43.6, 43.2, 42.4, 41.9 (2C), 28.4 (3C), 27.7 (2C). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –173.9. Anal. Calcd for $C_{15}H_{25}FN_2O_3$: C 59.98; H 8.39; N 9.33. Found: C 59.78; H 8.58; N 9.07.

5-Fluoro-4-(4-methoxyphenyl)pyrimidine (2aa) was obtained from formamidine acetate and compound **4a** (1.00 g, 4.90 mmol). The crude product was purified by reverse-phase HPLC (gradient MeCN – H_2O (25:75 to 50:50) as eluent). Yield 0.360 g (40 %). Yellowish solid. Mp 124–126 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 9.01 (d, J = 3.3 Hz, 1H), 8.81 (d, J = 4.1 Hz, 1H), 8.03 (d, J = 8.6 Hz, 2H), 7.07 (d, J = 8.6 Hz, 2H), 3.82 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 161.7, 155.1 (d, J = 266.3 Hz), 154.4 (d, J = 7.7 Hz), 150.2 (d, J = 7.0 Hz), 146.1 (d, J = 23.8 Hz), 130.6 (d, J = 7.0 Hz), 124.6 (d, J = 5.6 Hz), 114.3, 55.4. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ –135.6. MS (APCI): m/z = 205 $[M+H]^+$. Anal. Calcd for $C_{11}H_9FN_2O$: C 64.7; H 4.44; N 13.72. Found: C 64.71; H 4.48; N 13.58.

5-Fluoro-4-(4-methoxyphenyl)pyrimidin-2-amine (2ab) was obtained from guanidine hydrochloride and compound **4a** (3.70 g, 0.016 mol). The crude product was triturated with tBuOMe (3×5 mL). Yield 2.47 g (68 %). Brownish solid. Mp 205–208 °C. ^1H NMR (600 MHz, DMSO-d_6) δ 8.29 (d, J = 3.9 Hz, 1H), 7.96 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 8.7 Hz, 2H), 6.62 (s, 2H), 3.82 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 161.1, 160.4 (d, J = 2.6 Hz), 150.4 (d, J = 6.6 Hz), 149.3 (d, J = 247.3 Hz), 146.9 (d, J = 25.6 Hz), 130.2 (d, J = 6.8 Hz), 125.7 (d, J = 5.5 Hz), 114.0, 55.3. $^{19}F\{^1H\}$ NMR (376 MHz, CDCl3) δ –153.0. MS (APCI): m/z = 220 $[M+H]^+$. Anal. Calcd for C11H10FN3O: C 60.27; H 4.60; N 19.17. Found: C 60.12; H 5; N 19.28.

***tert*-Butyl 3-(5-fluoropyrimidin-4-yl)pyrrolidine-1-carboxylate (2ba)** was synthesized from formamidine acetate and 0.412 g of **10b**. The crude product was purified by reverse-phase HPLC (gradient MeOH – H_2O (45:55 to 70:30) as eluent). Yield 38.7 mg (27 %). Colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 8.98 – 8.92 (m, 1H), 8.52 – 8.47 (m, 1H), 3.78 (s, 2H), 3.65 – 3.60 (m, 2H), 3.47 – 3.43 (m, 1H), 2.29 – 2.23 (m, 2H), 1.47 (s, 9H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 157.0, 156.3 (d, J = 265.4 Hz), 154.4 (d, J = 7.9 Hz), 154.4, 144.0 (d, J = 21.5 Hz), 79.4, 49.4, 45.6, 38.5, 30.1, 28.5. $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ –140.16. LC/MS (API-ES): m/z = 268 $[M+H]^+$. Anal. Calcd for $C_{13}H_{18}FN_3O_2$: C 58.41; H 6.79; N 15.72. Found: C 58.18; H 6.62; N 15.56.

***tert*-Butyl 3-(2-amino-5-fluoropyrimidin-4-yl)pyrrolidine-1-carboxylate (2bb)** was synthesized from guanidine hydrochloride and 0.275 g of **10b**. The crude product was purified by reverse-phase HPLC (gradient MeCN – H_2O (30:70 to 45:55) as eluent). Yield 103 mg (36 %). Colorless crystals. Mp 134–135 °C. The product existed as a mixture of two rotamers. ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 4.92 (s, 2H), 3.74 – 3.45 (m, 4H), 3.43 – 3.34 (m, 1H), 2.19 – 2.11 (m, 2H), 1.45 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.1, 157.3, 154.0, 150.5 (d, J = 248.8 Hz), 144.4 (d, J = 23.8 Hz), 78.8, 49.0 and 48.6, 45.3 and 45.1, 38.3 and 37.6, 29.9 and 29.2, 28.1. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –158.46 and –158.57. LC/MS (API-ES): m/z = 283 $[M+H]^+$. Anal. Calcd for $C_{13}H_{19}FN_4O_2$: C 55.31; H 6.78; N 19.85. Found: C 55.27; H 6.99; N 20.22.

***tert*-Butyl 3-(5-fluoro-2-methylpyrimidin-4-yl)pyrrolidine-1-carboxylate (2bc)** was synthesized from acetamidine hydrochloride and 0.275 g of **10b**. The crude product was purified by reverse-phase HPLC (gradient MeOH – H_2O (50:50 to 100:0) as eluent). Yield 146 mg (51 %). Yellowish oil. The product existed as a mixture of two rotamers. ^1H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 3.82 – 3.54 (m, 4H), 3.46 – 3.37 (m, 1H), 2.66 (s, 3H), 2.24 – 2.20 (m, 2H), 1.46 (s, 9H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 163.9, 156.5, 154.8 (d, J = 261.2 Hz), 154.4, 143.8 (d, J = 21.9 Hz), 79.3, 49.6 and 49.3, 45.8 and 45.54 38.8 and 38.0, 30.5 and 29.8, 28.5, 25.2. $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ –147.5. LC/MS (API-ES): m/z = 282 $[M+H]^+$. Anal. Calcd for $C_{14}H_{20}FN_3O_2$: C 59.77; H 7.17; N 14.94. Found: C 59.7; H 6.84; N 15.26.

***tert*-Butyl 4-(5-fluoropyrimidin-4-yl)piperidine-1-carboxylate (2ca)** was obtained from formamidine acetate and 35.0 g of **4c**, using toluene at reflux as a solvent instead of DMF at the cyclization step. The crude product was purified by flash chromatography (tBuOMe – hexanes (1:3) as eluent) and then by column chromatography ($CHCl_3$ – MeOH (50:1) as eluent). Yield 13.8 g (42 %). Beige crystals. Mp 94–97 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.93 (d, J = 2.3 Hz, 1H), 8.47 (d, J = 2.3 Hz, 1H), 4.27 – 4.23 (m, 2H), 3.22 – 3.14 (m, 1H), 2.87 – 2.83 (m, 2H), 1.91 – 1.75 (m, 4H), 1.46 (d, J = 1.6 Hz, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 160.0 (d, J = 11.8 Hz), 155.9 (d, J = 264.8 Hz), 154.4 (d, J = 7.8 Hz), 144.0, 143.9, 79.6, 37.3, 29.4, 28.4. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –141.3. LC/MS (API-ES): m/z = 282 $[M+H]^+$. Anal. Calcd for $C_{14}H_{20}FN_3O_2$: C 59.77; H 7.17; N 14.94. Found: C 59.76; H 7.08; N 14.67.

***tert*-Butyl 4-(2-amino-5-fluoropyrimidin-4-yl)piperidine-1-carboxylate (2cb)** was obtained from guanidine hydrochloride and 17.3 g of **4c**. Yield 10.5 g (61 %). Yellowish crystals. Mp 153–155 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 2.1 Hz, 1H), 4.95 – 4.91 (m, 2H), 4.24 – 4.20 (m, 2H), 3.04 – 2.96 (m, 1H), 2.83 – 2.79 (m, 3H), 1.83 – 1.71 (m, 2H), 1.46 (s, 9H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 160.8 (d, J = 13.6 Hz), 159.5 (d, J = 3.0 Hz), 154.7, 150.6 (d, J = 247.7 Hz), 144.7 (d, J = 24.3 Hz), 79.5, 44.2 amd 43.2, 37.3 (d, J = 2.2 Hz), 29.3, 28.4. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –159.3. LC/MS (API-ES): m/z = 297 $[M+H]^+$. Anal. Calcd for $C_{14}H_{21}FN_4O_2$: C 56.74; H 7.14; N 18.91. Found: C 56.59; H 7.1; N 18.66.

***tert*-Butyl 4-(5-fluoro-2-methylpyrimidin-4-yl)piperidine-1-carboxylate (2cc)** was obtained from acetamidine hydrochloride and 18.0 g of **4c**. The product was purified by flash chromatography (tBuOMe – hexanes (1:2) as eluent). Yield 12.0 g (68 %). Beige crystals. Mp 120–123 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, J = 2.1 Hz, 1H), 4.26 – 4.22 (m, 2H), 3.11 (t, J = 12.4, 4.0 Hz, 1H), 2.85 – 2.81 (m, 2H), 2.66 (s, 3H), 1.85 (qd, J = 12.4, 4.0 Hz, 2H), 1.76 (d, J = 12.4 Hz, 2H), 1.47 (s, 9H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 163.8 (d, J = 7.2 Hz), 159.6 (d, J = 11.8 Hz), 154.6, 154.4 (d, J = 260.5 Hz), 143.6 (d, J = 22.2 Hz), 79.5, 43.2 37.5 (d, J = 2.3 Hz), 29.4, 28.4, 25.2 (d, J = 2.1 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –148.4. LC/MS (API-ES): m/z = 296 $[M+H]^+$. Anal. Calcd for $C_{15}H_{22}FN_3O_2$: C 61; H 7.51; N 14.23. Found: C 60.82; H 7.59; N 14.56.

***tert*-Butyl 3-(5-fluoropyrimidin-4-yl)azetidine-1-carboxylate (2da)** was synthesized from formamidine acetate and 2.60 g of **10d**. Compound **2da** compound **4d**. The product was purified by flash chromatography (tBuOMe – hexanes (1:1) as eluent). Yield 360 mg (12 %). ^1H NMR (500 MHz, $CDCl_3$) δ 9.03 (d, J = 2.8 Hz, 1H), 8.51 (s, 1H), 4.33 – 4.22 (m, 4H), 4.17 – 4.08 (m, 1H), 1.45 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 156.5 (d, J = 12.4 Hz), 156.1 (d, J = 267.1 Hz), 156.3, 154.6 (d, J = 7.9 Hz), 144.1 (d, J = 20.8 Hz), 79.8, 53.0 (2C), 29.7, 28.4 (3C). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –137.6. LC/MS (API-ES): m/z = 254 $[M+H]^+$. Anal. Calcd for $C_{12}H_{16}FN_3O_2$: C 56.91; H 6.37; N 16.59. Found: C 57.23; H 6.37; N 16.73.

***tert*-Butyl 3-(2-amino-5-fluoropyrimidin-4-yl)azetidine-1-carboxylate (2db)** was synthesized from guanidine hydrochloride and 0.800 g of **10d**. Yield 375 mg (36 %). Yellowish crystals. Mp 152–154 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 2.0 Hz, 1H), 5.15 – 5.11 (m, 2H), 4.24 – 4.14 (m, 4H), 3.94 (tt, J = 13.2, 3.9 Hz, 1H), 1.44 (s, 9H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 159.7 (d, J = 3.1 Hz), 157.2 (d, J = 14.3 Hz), 156.3, 150.6 (d, J = 248.4 Hz), 144.8 (d, J = 23.4 Hz), 79.6, 50.3 (2C), 29.7, 28.3 (3C). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –156.3. LC/MS (API-ES): m/z = 269 $[M+H]^+$. Anal. Calcd for $C_{12}H_{17}FN_4O_2$: C 53.72; H 6.39; N 20.88. Found: C 53.89; H 6.59; N 21.11.

***tert*-Butyl 3-(5-fluoro-2-methylpyrimidin-4-yl)azetidine-1-carboxylate (2dc)** was synthesized from acetamidine hydrochloride and 0.800 g of **10d**. The crude product was purified by flash chromatography (tBuOMe as eluent). Yield 315 mg (30 %). Yellowish oil. ^1H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, J = 1.8 Hz, 1H), 4.25 (d, J = 7.5 Hz, 4H), 4.05 (p, J = 7.5 Hz, 1H), 2.70 (s, 3H), 1.44 (s, 9H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 164.2 (d, J = 7.5 Hz), 156.3, 155.9 (d, J = 12.3 Hz), 154.6 (d, J = 261.4 Hz), 143.8 (d, J = 21.1 Hz), 79.8, 52.9, 28.6, 28.6, 25.2. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –144.9. LC/MS (API-ES): m/z = 268 $[M+H]^+$. Anal. Calcd for $C_{13}H_{18}FN_3O_2$: C 58.41; H 6.79; N 15.72. Found: C 58.51; H 6.68; N 15.50.

Synthesis of pyrazoles 8 and pyrimidines 11.

Method A. Compound 1 (50 mmol) was added to 4 M HCl in 1,4-dioxane (130 mL). The mixture was stirred at r.t. overnight and then evaporated. The residue was triturated with CCl_4 (130 mL) and re-evaporated; this step was repeated one more time. The resulting solid was washed with MeCN (2×50 mL) and dried in vacuo.

Method B. TFA (11.6 mL, 152 mmol) was added to the solution of 1 (75.8 mmol) in CH_2Cl_2 (270 mL). The mixture was stirred overnight at r.t. and evaporated. The product was triturated with $CHCl_3$ (200 mL) and re-evaporated. The latter step was repeated 2–3 times until the product solidified; then it was dried in vacuo.

4-Fluoro-3-(pyrrolidin-3-yl)-1*H*-pyrazole hydrochloride (8ba·HCl) was obtained according to method A starting from 5.80 g of **1ba**. Yield 3.83 g (88 %). Brownish solid. Mp 141–144 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.23 (s, 1H, partially exchanged with HDO), 9.72 (s, 1H), 9.66 (s, 1H), 7.71 (d, J = 4.6 Hz, 1H), 3.53 – 3.37 (m, 1H), 3.29 – 3.03 (m, 3H), 2.29 – 2.18 (m, 1H), 1.98 – 1.84 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 147.0 (d, J = 241.3 Hz), 133.8 (d, J = 12.9 Hz), 118.1 (d, J = 24.5 Hz), 48.1, 44.6, 33.9 (d, J = 3.6 Hz), 30.1. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −181.7. LC/MS (API-ES): m/z = 156 [M−Cl]$^+$. Anal. Calcd for $C_7H_{11}ClFN_3$: C 43.87; H 5.79; N 21.93; Cl 18.50. Found: C 43.79; H 5.43; N 22.24; Cl 18.84.

4-Fluoro-1-methyl-3-(pyrrolidin-3-yl)-1*H*-pyrazole hydrochloride (8bb·HCl), obtained according to method A starting from 4.00 g of **1bb**. Yield 2.77 g (91 %). Brownish amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.72 (s, 1H), 9.67 (s, 1H), 7.81 (d, J = 4.6 Hz, 1H), 3.69 (s, 3H), 3.52 – 3.39 (m, 2H), 3.30 – 3.22 (m, 1H), 3.22 – 3.14 (m, 1H), 3.17 – 3.07 (m, 1H), 2.29 – 2.20 (m, 1H), 1.97 – 1.86 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 146.5 (d, J = 242.2 Hz), 135.4 (d, J = 9.5 Hz), 118.5 (d, J = 27.7 Hz), 48.1, 44.7, 39.8, 34.2 (d, J = 3.6 Hz), 30.2. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −179.4. LC/MS (API-ES): m/z = 170 [M−Cl]$^+$. Anal. Calcd for $C_8H_{13}ClFN_3$: C 46.72; H 6.37; N 20.43; Cl 17.24. Found: C 47.06; H 6.43; N 20.25; Cl 16.93.

4-Fluoro-1-phenyl-3-(pyrrolidin-3-yl)-1*H*-pyrazole hydrochloride (8bd·HCl) was obtained according to method A starting from 13.7 g of **1bd**. Yield 10.9 g (98 %). Greenish crystals. M.p. 161–164 °C (dec.). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.71 (s, 1H), 9.56 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.49 (t, J = 7.8 Hz, 2H), 7.31 (t, J = 7.4 Hz, 1H), 3.69 – 3.56 (m, 2H), 3.36 – 3.25 (m, 3H), 2.43 – 2.30 (m, 1H), 2.15 – 2.02 (m, 1H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 148.1 (d, J = 246.7 Hz), 139.3, 138.6 (d, J = 10.3 Hz), 129.5, 126.4, 117.8, 115.3 (d, J = 28.9 Hz), 47.7, 44.3, 33.9 (d, J = 3.2 Hz), 29.6. ^{19}F{^{1}H} NMR (376 MHz, D_2O) δ −175.8. MS (APCI): m/z = 232 [M−Cl]$^+$. Anal. Calcd for $C_9H_{13}ClFN_3$: C 46.72; H 6.37; N 20.43; Cl 17.24. Found: C 46.52; H 6.38; N 20.09; Cl 17.54.

4-(4-Fluoro-1*H*-pyrazol-3-yl)piperidine dihydrochloride (8ca·2HCl) was obtained according to method A starting from 13.1 g of **1ca**. Yield 9.10 g (77 %). Brownish crystals. M.p. > 190 °C (dec.). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.32 (s, 1H), 9.06 (s, 1H), 7.60 (d, J = 4.5 Hz, 1H), 3.27 (d, J = 11.3 Hz, 2H), 3.09 – 2.89 (m, 3H), 2.09 – 1.88 (m, 4H), 2H are exchanged with HDO. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 146.3 (d, J = 240.9 Hz), 136.0 (d, J = 13.6 Hz), 117.6 (d, J = 24.8 Hz), 42.4, 29.7, 26.6. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −182.1. MS (APCI): m/z = 170 [M−Cl−HCl]$^+$. Anal. Calcd for $C_8H_{14}Cl_2FN_3$: C 39.69; H 5.83; N 17.36; Cl 29.28. Found: C 39.85; H 5.95; N 17.24; Cl 29.36.

4-(4-Fluoro-1-methyl-1*H*-pyrazol-3-yl)piperidine hydrochloride (8cb·HCl) was obtained according to method A starting from 12.0 g of **1cb**. Yield 7.98 g (86 %). Colorless crystals. M.p. > 200 °C (dec.). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.34 (s, 1H), 9.14 (s, 1H), 7.76 (d, J = 4.3 Hz, 1H), 3.70 (s, 3H), 3.24 (d, J = 12.0 Hz, 2H), 3.00 – 2.92 (m, 3H), 1.96 (d, J = 13.5 Hz, 2H), 1.92–1.85 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 145.9 (d, J = 242.2 Hz), 138.8 (d, J = 9.2 Hz), 117.6 (d, J = 28.0 Hz), 42.7, 39.3, 30.2 (d, J = 3.2 Hz), 27.1. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −179.5. MS (APCI): m/z = 184 [M−Cl]$^+$. Anal. Calcd for $C_8H_{13}ClFN_3$: C 49.21; H 6.88; N 19.13; Cl 16.14. Found: C 49.38; H 6.76; N 19.20; Cl 15.81.

4-(4-Fluoro-1-phenyl-1*H*-pyrazol-3-yl)piperidine hydrochloride (8cd·HCl) was obtained according to method A starting from 0.200 g of **1cd**. Yield 0.150 g (91 %). Beige crystals. Mp 246–249 °C (dec). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.34 (s, 1H), 9.07 (s, 1H), 8.65 (d, J = 4.4 Hz, 1H), 7.75 (d, J = 7.9 Hz, 2H), 7.48 (t, J = 7.9 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 3.31 (d, J = 12.7 Hz, 2H), 3.17 – 3.08 (m, 1H), 3.02 (q, J = 11.6 Hz, 2H), 2.17 – 2.03 (m, 2H), 2.03 – 1.91 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 148.0 (d, J = 246.6 Hz), 141.9 (d, J = 9.8 Hz), 139.4, 129.5, 126.2, 117.6, 115.0 (d, J = 29.3 Hz), 42.6, 30.3, 26.8. ^{19}F{^{1}H} NMR (470 MHz, DMSO-d_6) δ −175.7. MS (APCI): m/z = 246 [M−Cl]$^+$. Anal. Calcd for $C_{14}H_{17}ClFN_3$: C 59.68; H 6.08; N 14.91; Cl 12.58. Found: C 59.77; H 5.77; N 14.69; Cl 12.46.

3-(Azetidin-3-yl)-4-fluoro-1*H*-pyrazole trifluoroacetate (8da·TFA) was obtained according to method B starting from 18.3 g of **1da**; *t*BuOMe was used instead of $CHCl_3$ at the last steps. Yield 16.5 g (85 %). Brownish solid. Mp 92–94 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.21 (br s, 1H), 8.89 (br s, 2H), 7.78 (d, J = 4.7 Hz, 1H), 4.30 – 4.17 (m, 2H), 4.17 – 4.07 (m, 3H), 1H is exchanged with HDO. ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 159.1 (q, J = 33.6 Hz), 147.2 (d, J = 241.9 Hz), 134.3, 117.6, 117.0 (q, J = 296.4 Hz), 50.8, 27.2 (d, J = 3.4 Hz). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −74.6, −182.3. LC/MS (API-ES): m/z = 142 [M−CF_3CO_2]$^+$. Anal. Calcd for $C_8H_9F_4N_3O_2$: C 37.66; H 3.56; N 16.47. Found: C 37.37; H 3.19; N 16.74.

3-(Azetidin-3-yl)-4-fluoro-1-methyl-1*H*-pyrazole bis(trifluoroacetate) (8db·2TFA) was obtained according to method B starting from 13.1 g of **1db**; $CHCl_3$ was used instead of *t*BuOMe at the last steps. The product did not solidify after three re-evaporation cycles. The residue was redissolved twice in fresh portions of CCl_4 and reevaporated. Yield 13.5 g (69 %). Brownish oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.15 (br s, 1H), 9.01 (br s, 1H), 8.85 (br s, 2H), 7.81 (d, J = 4.7 Hz, 1H), 4.26 – 4.16 (m, 2H), 4.14 – 4.04 (m, 3H), 3.75 (s, 3H); 1H is exchanged with HDO. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 158.5 (q, J = 36.3 Hz), 146.0 (d, J = 243.3 Hz), 134.8 (d, J = 9.7 Hz), 118.2 (d, J = 27.4 Hz), 115.7 (q, J = 291.4 Hz), 50.5, 50.4, 26.8 (d, J = 3.4 Hz). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −75.4, −179.4. LC/MS (API-ES): m/z = 156 [M−TFA−CF_3CO_2]$^+$. Anal. Calcd for $C_{11}H_{12}F_7N_3O_4$: C 34.48; H 3.16; N 10.97. Found: C 34.38; H 3.37; N 10.97.

3-(Azetidin-3-yl)-4-fluoro-1-phenyl-1*H*-pyrazole bis(trifluoroacetate) (8dd·2TFA) was obtained according to method B starting from 6.00 g of **1dd**. Yield 7.07 g (84 %). Greenish crystals. M.p. 86–88 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.26 (br s, 1H), 8.98 (br s, 2H), 8.70 (d, J = 4.5 Hz, 1H), 7.79 (d, J = 7.9 Hz, 2H), 7.49 (t, J = 7.9 Hz, 2H), 7.31 (t, J = 7.9 Hz, 1H), 4.35 – 4.25 (m, 2H), 4.27 – 4.18 (m, 3H); 1H is exchanged with HDO. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 158.5 (q, J = 35.9 Hz), 148.0 (d, J = 247.1 Hz), 139.4, 138.1 (d, J = 10.4 Hz), 129.5, 126.6, 117.9, 115.9 (q, J = 292.7 Hz), 115.5 (d, J = 28.5 Hz), 50.2, 27.0 (d, J = 2.9 Hz). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −75.2, −176.3. LC/MS (API-ES): m/z = 218 [M−TFA−CF_3CO_2]$^+$. Anal. Calcd for $C_{18}H_{14}F_7N_3O_4$: C 43.16; H 3.17; N 9.44. Found: C 43.44; H 3.01; N 9.09.

4-(4-Fluoro-1*H*-pyrazol-3-yl)cyclohexan-1-one (8ea) was obtained according to method A starting from 100 mg of **1ea**. After the evaporation, the product was triturated with 10% aq $NaHCO_3$ (5 mL) and extracted with EtOAc (3×2 mL). The combined extracts were washed with brine (2 mL), dried over Na_2SO_4, and evaporated in vacuo. Yield 74.0 mg (92 %). Brownish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 4.6 Hz, 1H), 6.98 (br s, 1H), 3.24 (tt, J = 11.0, 3.6 Hz, 1H), 2.57 – 2.40 (m, 4H), 2.36 – 2.24 (m, 2H), 2.14 – 2.02 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 211.0, 147.5 (d, J = 241.6 Hz), 138.4 (d, J = 10.9 Hz), 118.2 (d, J = 26.5 Hz),

40.7, 33.1, 31.2. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −180.1. MS (APCI): *m/z* = 183 $[M+H]^+$.

5-Fluoro-4-(pyrrolidin-3-yl)pyrimidine hydrochloride (11ba·HCl) was obtained according to method A starting from 25.8 mg of **2ba**. Yield 15.5 mg (79 %). Brownish crystals. Mp 132–135 °C (dec.). ^1H NMR (500 MHz, DMSO-d_6) δ 9.75 (br s, 1H), 9.57 (br s, 1H), 9.01 (d, *J* = 3.0 Hz, 1H), 8.84 (d, *J* = 2.1 Hz, 1H), 3.91 (quint, *J* = 8.0 Hz, 1H), 3.59 – 3.50 (m, 1H), 3.49 – 3.34 (m, 1H), 3.34 – 3.23 (m, 2H), 2.40 – 2.30 (m, 1H), 2.11 – 2.00 (m, 1H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 156.4 (d, *J* = 263.8 Hz), 156.0 (d, *J* = 12.4 Hz), 154.7 (d, *J* = 7.9 Hz), 145.2 (d, *J* = 21.1 Hz), 47.5, 45.0, 37.7 (d, *J* = 1.8 Hz), 30.0. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ −137.1. LC/MS (API-ES): *m/z* = 168 $[M-Cl]^+$. Anal. Calcd for $C_8H_{11}ClFN_3$: C 47.18; H 5.44; N 20.63; Cl 17.41. Found: C 47.32; H 5.16; N 20.57; Cl 17.63.

5-Fluoro-4-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride (11bb·HCl) was obtained according to method A starting from 69.0 mg of **2bb**. Yield 43.3 mg (81 %). Yellowish crystals. Mp 158–162 °C (dec.). ^1H NMR (400 MHz, DMSO-d_6) δ 9.62 (br s, 1H), 9.51 (br s, 1H), 8.28 (d, *J* = 2.2 Hz, 1H), 3.69 (quint, *J* = 7.8 Hz, 1H), 3.50 – 3.40 (m, 1H), 3.40 – 3.21 (m, 3H), 2.35 – 2.23 (m, 1H), 2.06 – 1.92 (m, 1H). 2H are exchanged with HDO. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 160.1, 156.9 (d, *J* = 14.2 Hz), 149.7 (d, *J* = 244.6 Hz), 144.7 (d, *J* = 23.8 Hz), 47.6, 44.7, 37.8, 29.6. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ −158.2. LC/MS (API-ES): *m/z* = 183 $[M-Cl-HCl]^+$. Anal. Calcd for $C_8H_{12}ClFN_4$: C 43.94; H 5.53; N 25.62; Cl 16.21. Found: C 44.26; H 5.21; N 25.82; Cl 16.43.

5-Fluoro-2-methyl-4-(pyrrolidin-3-yl)pyrimidine hydrochloride (11bc·HCl) was obtained according to method A starting from 97.2 mg of **2bc**. Yield 57.2 mg (76 %). Yellowish crystals. Mp > 200 °C (dec.). ^1H NMR (500 MHz, DMSO-d_6) δ 9.84 (br s, 1H), 9.62 (br s, 1H), 8.68 (d, *J* = 2.0 Hz, 1H), 3.84 (quint, *J* = 8.0 Hz, 1H), 3.56 – 3.46 (m, 1H), 3.44 – 3.35 (m, 1H), 3.37 – 3.20 (m, 2H), 2.59 (s, 3H), 2.37 – 2.27 (m, 1H), 2.08 – 1.97 (m, 1H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 163.6 (d, *J* = 7.3 Hz), 155.4 (d, *J* = 12.7 Hz), 155.0 (d, *J* = 260.4 Hz), 145.0 (d, *J* = 21.6 Hz), 47.5, 44.9, 37.7 (d, *J* = 1.7 Hz), 29.9, 25.4 (d, *J* = 2.2 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ −144.0. LC/MS (API-ES): *m/z* = 182 $[M-Cl]^+$. Anal. Calcd for $C_9H_{13}ClFN_3$: C 49.66; H 6.02; N 19.30; Cl 16.29. Found: C 49.84; H 6.32; N 19.18; Cl 16.30.

5-Fluoro-4-(piperidin-4-yl)pyrimidine dihydrochloride (11ca·2HCl) was obtained according to method A starting from 13.8 g of **2ca**. Yield 9.90 g (79 %). Colorless crystals. Mp > 205 °C (dec.). ^1H NMR (500 MHz, DMSO-d_6) δ 9.15 (br s, 1H), 9.00 (d, *J* = 2.6 Hz, 1H), 8.88 (br s, 1H), 8.80 (d, *J* = 2.6 Hz, 1H), 3.42 – 3.30 (m, 3H), 3.04 (q, *J* = 12.0 Hz, 2H), 2.05 – 1.85 (m, 4H); 1H is exchanged with HDO. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 158.9 (d, *J* = 11.9 Hz), 156.1 (d, *J* = 263.4 Hz), 154.9 (d, *J* = 7.9 Hz), 145.1 (d, *J* = 21.4 Hz), 42.9, 34.2, 26.4. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ −138.4. LC/MS (API-ES): *m/z* = 182 $[M-Cl-HCl]^+$. Anal. Calcd for $C_9H_{14}Cl_2FN_3$: C 42.54; H 5.55; N 16.54; Cl 27.90. Found: C 42.40; H 5.88; N 16.22; Cl 28.24.

5-Fluoro-4-(piperidin-4-yl)pyrimidin-2-amine hydrochloride (11cb·HCl) was obtained according to method A starting from 10.5 g of **2cb**. Yield 7.67 g (93 %). Yellowish crystals. Mp > 215 °C (dec.). ^1H NMR (500 MHz, DMSO-d_6) δ 9.25 (br s, 1H), 9.04 (br s, 1H), 8.26 (d, *J* = 2.6 Hz, 1H), 3.30 (d, *J* = 12.6 Hz, 2H), 3.21 – 3.11 (m, 1H), 2.98 (q, *J* = 12.6 Hz, 2H), 1.98 – 1.82 (m, 4H); 2H are exchanged with HDO. ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.7, 159.0, 148.9 (d, *J* = 243.5 Hz), 142.8 (d, *J* = 25.8 Hz), 42.5, 34.2, 25.8. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ −157.9. LC/MS (API-ES): *m/z* = 197 $[M-Cl-HCl]^+$. Anal. Calcd for $C_9H_{14}ClFN_4$: C 46.46; H 6.06; N 24.08; Cl 15.23. Found: C 46.58; H 6.32; N 23.74; Cl 15.57.

5-Fluoro-2-methyl-4-(piperidin-4-yl)pyrimidine hydrochloride (11cc·HCl) was obtained according to method A starting from 12.0 g of **2cc**. *t*BuOMe was used instead of MeCN at the last step. Yield 8.67 g (92 %). Colorless crystals. Mp > 190 °C (dec.). ^1H NMR (500 MHz, DMSO-d_6) δ 9.39 (br s, 1H), 9.02 (br s, 1H), 8.64 (s, 1H), 3.31 (d, *J* = 11.6 Hz, 3H), 3.01 (q, *J* = 11.6 Hz, 2H), 2.58 (s, 3H), 1.99 (q, *J* = 13.4 Hz, 2H), 1.89 (d, *J* = 13.4 Hz, 2H). 1H is exchanged with HDO. $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 163.6 (d, *J* = 7.2 Hz), 156.4 (d, *J* = 12.3 Hz), 154.6 (d, *J* = 259.4 Hz), 144.8 (d, *J* = 21.9 Hz), 42.9, 34.2, 26.4, 25.4. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ −145.1. LC/MS (API-ES): *m/z* = 196 $[M-Cl]^+$. Anal. Calcd for $C_{10}H_{15}ClFN_3$: C 51.84; H 6.53; N 18.14; Cl 15.30. Found: C 52.09; H 6.13; N 17.74; Cl 15.52.

3-(5-Fluoropyrimidin-4-yl)azetidine trifluoroacetate (11da·TFA) was obtained according to method B starting from 240 mg of **2da**; CCl_4 was used instead of $CHCl_3$ at the last steps, and the product did not solidify after three re-evaporation cycles. Yield 228 mg (91 %). Yellowish oil. ^1H NMR (400 MHz, DMSO-d_6) δ 9.16 (s, 1H), 9.12 (d, *J* = 2.5 Hz, 1H), 8.93 (s, 1H), 8.85 (d, *J* = 2.5 Hz, 1H), 4.53 – 4.42 (m, 1H), 4.32 – 4.22 (m, 4H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 158.5 (q, *J* = 36.4 Hz), 155.6 (d, *J* = 264.4 Hz), 154.4 (d, *J* = 7.9 Hz), 154.2 (d, *J* = 13.0 Hz), 144.7 (d, *J* = 20.6 Hz), 115.7 (q, *J* = 291.0 Hz), 48.8, 30.7. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ −75.2, −137.5. LC/MS (API-ES): *m/z* = 154 $[M-CF_3CO_2]^+$. Anal. Calcd for $C_9H_8F_4N_3O_2$: C 40.46; H 3.40; N 15.73. Found: C 40.32; H 3.15; N 15.53.

3-(2-Amino-5-fluoropyrimidin-4-yl)azetidine trifluoroacetate (11db·TFA) was obtained according to method B starting from 250 mg of **2db**; CCl_4 was used instead of $CHCl_3$ at the last steps. Yield 240 mg (91 %). Orangish crystals. Mp 124–127 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 9.77 (br s, 2H), 9.06 (br s, 1H), 8.72 (br s, 1H), 8.24 (d, *J* = 2.0 Hz, 1H), 4.30 – 4.14 (m, 5H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 160.2 (d, *J* = 2.6 Hz), 158.5 (q, *J* = 37.2 Hz), 154.2 (d, *J* = 14.4 Hz), 149.3 (d, *J* = 244.4 Hz), 145.1 (d, *J* = 22.5 Hz), 115.4 (q, *J* = 290.2 Hz), 48.5 (d, *J* = 2.1 Hz), 31.0 (d, *J* = 2.0 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ −75.4, −158.7. LC/MS (API-ES): *m/z* = 169 $[M-CF_3CO_2]^+$. Anal. Calcd for $C_9H_{10}F_4N_4O_2$: C 38.31; H 3.57; N 19.85. Found: C 38.47; H 3.59; N 19.46.

3-(5-Fluoro-2-methylpyrimidin-4-yl)azetidine trifluoroacetate (11dc·TFA) was obtained according to method B starting from 210 mg of **2dc**; the product did not solidify after three re-evaporation cycles. The residue was redissolved twice in fresh portions of CCl_4 and reevaporated. Yield 205 mg (93 %). Orangish oil. ^1H NMR (400 MHz, DMSO-d_6) δ 9.03 (s, 1H), 8.78 (s, 1H), 8.71 (d, *J* = 1.8 Hz, 1H), 4.42 (quint, *J* = 8.4 Hz, 1H), 4.26 (dd, *J* = 8.4, 4.7 Hz, 4H), 2.66 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 163.3 (d, *J* = 7.4 Hz), 158.5 (q, *J* = 37.1 Hz), 154.2 (d, *J* = 260.3 Hz), 153.6 (d, *J* = 13.2 Hz), 144.6 (d, *J* = 20.9 Hz), 115.5 (q, *J* = 290.1 Hz), 48.8, 30.7 (d, *J* = 1.5 Hz), 24.8 (d, *J* = 2.0 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ −75.3, −144.3. LC/MS (API-ES): *m/z* = 168 $[M-CF_3CO_2]^+$. Anal. Calcd for $C_{10}H_{11}F_4N_3O_2$: C 42.71; H 3.94; N 14.94. Found: C 42.43; H 3.59; N 14.76.

1-Benzoyl-4-(1-methyl-1*H*-pyrazol-3-yl)piperidine (12). Triethylamine (0.240 mL, 1.80 mmol) was slowly added to a solution of 4-(1-methyl-1*H*-pyrazol-3-yl)piperidine (248 mg, 1.50 mmol) in CH_2Cl_2 (5 mL). Then benzoyl chloride (0.170 mL, 1.50 mmol) was added dropwise upon cooling with ice bath. The mixture was stirred at r.t. overnight, then washed with water (75 mL) and extracted with dichloromethane (3×5 mL). Organic phase was dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (*t*BuOMe as eluent). Yield 251 mg (62 %). Brownish oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.35 (m, 5H), 7.27 (d, *J* = 2.2 Hz, 1H), 6.05 (d, *J* = 2.2 Hz, 1H), 4.94 – 4.67 (m, 1H), 3.86 (s, 3H), 3.83 – 3.78 (m, 1H), 3.13 – 3.09 (m, 1H), 2.99 – 2.88 (m, 2H), 2.10 – 1.85 (m, 2H), 1.77 – 1.57 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 170.3, 155.7, 136.3, 130.7, 129.4, 128.4, 126.8, 102.5, 48.0, 42.4, 38.6, 35.8, 32.7, 32.6. LC/MS (API-ES): *m/z* = 270 $[M+H]^+$. Anal. Calcd for $C_{16}H_{19}N_3O$: C 71.35; H 7.11; N 15.60. Found: C 71.60; H 7.34; N 15.78.

1-Benzoyl-4-(4-fluoro-1-methyl-1*H*-pyrazol-3-yl)piperidine (13). Triethylamine (0.390 mL, 2.80 mmol) was added slowly to a solution of compound **8cb**·HCl (241 mg, 1.10 mmol) in CH_2Cl_2 (5 mL). Then benzoyl

chloride (0.130 mL, 1.10 mmol) was added dropwise under cooling with ice. The mixture was stirred overnight at r.t., then washed with water (75 mL) and extracted with dichloromethane (3×5 mL). Organic phase was dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (tBuOMe as eluent). Yield 181 mg (57 %). Brownish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.34 (m, 5H), 7.16 (d, *J* = 4.8 Hz, 1H), 4.72 (br s, 1H), 3.85 – 3.79 (m, 1H), 3.74 (s, 3H), 3.22 – 2.82 (m, 3H), 2.02 (br s, 1H), 1.84 (br s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 170.3, 146.8 (d, *J* = 245.1 Hz), 140.6 (d, *J* = 9.3 Hz), 136.3, 129.4, 128.4, 126.8, 116.6 (d, *J* = 27.8 Hz), 47.9, 42.2, 39.5, 33.6 (d, *J* = 3.3 Hz), 31.1, 30.7. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –178.4. LC/MS (API-ES): *m/z* = 288 [M+H]$^+$. Anal. Calcd for $C_{16}H_{18}FN_3O$: C 66.88, H 6.31, N 14.62. Found: C 66.87, H 6.23, N 14.42.

4-(1-Benzoylpiperidin-4-yl)pyrimidine (14) was obtained analogously to the compound **12** starting from 250 mg of 4-(piperidin-4-yl)pyrimidine. Yield 236 mg (59 %). Brownish crystals. Mp 111–113 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.66 (d, *J* = 5.2 Hz, 1H), 7.45 – 7.37 (m, 5H), 7.21 (d, *J* = 5.2 Hz, 1H), 4.89 – 4.85 (m, 1H), 3.94 – 3.90 (m, 1H), 3.15 – 3.11 (m, 1H), 3.00 – 2.90 (m, 2H), 2.12 – 1.71 (m, 4H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 172.1, 170.5, 158.5, 157.1, 136.0, 129.7, 128.5, 126.9, 118.9, 47.7, 43.9, 42.2, 31.1. LC/MS (API-ES): *m/z* = 268 [M+H]$^+$. Anal. Calcd for $C_{16}H_{17}N3O$: C 71.89, H 6.41, N 15.72. Found: C 72.19, H 6.16, N 15.78.

4-(1-Benzoylpiperidin-4-yl)-5-fluoropyrimidine (15) was obtained analogously to compound **13** starting from 350 mg of **11ca**·2HCl using 0.670 mL of triethylamine. Yield 188 mg (54 %). Colorless crystals. Mp 158–159 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.99 (d, *J* = 3.1 Hz, 1H), 8.78 (d, *J* = 2.3 Hz, 1H), 7.47 – 7.42 (m, 3H), 7.40 – 7.37 (m, 2H), 4.58 (br s, 1H), 3.67 (br s, 1H), 3.41 – 3.32 (m, 1H), 3.22 (s, 1H), 2.95 (br s, 1H), 1.88 (br s, 1H), 1.73 (br s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.5, 159.5 (d, *J* = 11.8 Hz), 156.0 (d, *J* = 263.2 Hz), 154.8 (d, *J* = 7.9 Hz), 144.9 (d, *J* = 21.6 Hz), 136.7, 129.8, 128.9, 127.1, 47.3, 41.7, 36.6, 30.2, 29.5, 27.3. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –138.7. LC/MS (API-ES): *m/z* = 286 [M+H]$^+$.

Acknowledgements

The work was funded by Enamine Ltd. and Ministry of Education and Science of Ukraine (Grants No. 0121U100387 (21BF037-01M) and 0122U001962 (22BF037-02)). The authors thank Mr. Artem Skreminskiy for Log*P* measurements, Ms. Olga Kovalenko and Ms. Margarita Bolgova for pK_a titrations, Ms. Yulia Kuchkovska for her help with manuscript preparation, Prof. Andrey A. Tolmachev for his encouragement and support, Mr. Andrii Yakymenko for the cover picture photo, Mr. Bohdan Vashchenko and Ms. Vladyslava Prykhodko for their help with the cover preparation, and all the brave people in Ukraine that made finalizing this publication possible.

Keywords: heterocycles • sp^3-enriched compounds • fluorine • pyrazoles • pyrimidines

[1] N. A. Meanwell, K. J. Eastman, E. P. Gillis, in *Fluorine in Heterocyclic Chemistry Volume 1*, Springer International Publishing, Cham, **2014**, pp. 1–54.

[2] J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506.

[3] H. Mei, J. Han, S. Fustero, M. Medio-Simon, D. M. Sedgwick, C. Santi, R. Ruzziconi, V. A. Soloshonok, *Chem. Eur. J.* **2019**, *25*, 11797–11819.

[4] P. K. Mykhailiuk, *Chem. Rev.* **2021**, *121*, 1670–1715.

[5] P. K. Mykhailiuk, R. M. Koenigs, *Chem. – A Eur. J.* **2019**, *25*, 6053–6063.

[6] L. Mertens, R. M. Koenigs, *Org. Biomol. Chem.* **2016**, *14*, 10547–10556.

[7] A. Markham, *Drugs* **2020**, *80*, 1865–1870.

[8] O. O. Grygorenko, D. M. Volochnyuk, S. V. Ryabukhin, D. B. Judd, *Chem. Eur. J.* **2020**, *26*, 1196–1237.

[9] R. Doveston, S. Marsden, A. Nelson, *Drug Discov. Today* **2014**, *19*, 813–819.

[10] A. Nadin, C. Hattotuwagama, I. Churcher, *Angew. Chem. Int. Ed.* **2012**, *51*, 1114–1122.

[11] F. Lovering, *Med. Chem. Commun.* **2013**, *4*, 515–519.

[12] R. Kombarov, A. Altieri, D. Genis, M. Kirpichenok, V. Kochubey, N. Rakitina, Z. Titarenko, *Mol. Divers.* **2009**, *14*, 193–200.

[13] N. I. Vasilevich, R. V. Kombarov, D. V. Genis, M. A. Kirpichenok, *J. Med. Chem.* **2012**, *55*, 7003–7009.

[14] T. J. Ritchie, S. J. F. Macdonald, S. Peace, S. D. Pickett, C. N. Luscombe, *MedChemComm* **2012**, *3*, 1062.

[15] G. W. Bemis, M. A. Murcko, *J. Med. Chem.* **1996**, *39*, 2887–2893.

[16] O. V. Fedorov, M. D. Kosobokov, V. V. Levin, M. I. Struchkova, A. D. Dilman, *J. Org. Chem.* **2015**, *80*, 5870–5876.

[17] L. Andersson, E. Arzel, S. Berg, J. Burrows, S. Hellberg, F. Huerta, T. Pedersen, T. Rein, D. Rotticci, K. Staaf, D. Turek, WO2007040440, **2007**.

[18] H. Shao, S. Shi, D. W. Foley, F. Lam, A. Y. Abbas, X. Liu, S. Huang, X. Jiang, N. Baharin, P. M. Fischer, S. Wang, *Eur. J. Med. Chem.* **2013**, *70*, 447–455.

[19] S. Tadesse, M. Yu, L. B. Mekonnen, F. Lam, S. Islam, K. Tomusange, M. H. Rahaman, B. Noll, S. K. C. Basnet, T. Teo, H. Albrecht, R. Milne, S. Wang, *J. Med. Chem.* **2017**, *60*, 1892–1915.

[20] H. Shao, S. Shi, S. Huang, A. J. Hole, A. Y. Abbas, S. Baumli, X. Liu, F. Lam, D. W. Foley, P. M. Fischer, M. Noble, J. A. Endicott, C. Pepper, S. Wang, *J. Med. Chem.* **2013**, *56*, 640–659.

[21] A. Scribner, R. Dennis, J. Hong, S. Lee, D. McIntyre, D. Perrey, D. Feng, M. Fisher, M. Wyvratt, P. Leavitt, P. Liberator, A. Gurnett, C. Brown, J. Mathew, D. Thompson, D. Schmatz, T. Biftu, *Eur. J. Med. Chem.* **2007**, *42*, 1334–1357.

[22] S. Tadesse, L. Banbe, K. Tomusange, M. Yu, S. Islam, N. Bykovska, B. Noll, G. Zhu, P. Li, F. Lam, M. Kumarasiri, R. Milne, S. Wang, *Br. J. Pharmacol.* **2018**, *175*, 2399–2413.

[23] M. R. V. Finlay, D. G. Acton, D. M. Andrews, A. J. Barker, M. Dennis, E. Fisher, M. A. Graham, C. P. Green, D. W. Heaton, G. Karoutchi, S. A. Loddick, R. Morgentin, A. Roberts, J. A. Tucker, H. M. Weir, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4442–4446.

[24] I. I. Gerus, Y. I. Zhuk, L. M. Kacharova, G. V. Röschenthaler, E. N. Shaitanova, A. E. Sorochinski, S. I. Vdovenko, J. Wojcik, *J. Fluorine Chem.* **2020**, *229*, 109413.

[25] K. Funabiki, T. Kurita, M. Matsui, K. Shibata, *Chem. Lett.* **1997**, *26*, 739–740.

[26] T. D. Penning, J. J. Talley, S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Docter, M. J. Graneto, L. F. Lee, J. W. Malecha, J. M. Miyashiro, R. S. Rogers, D. J. Rogier, S. S. Yu, G. D. Anderson, E. G. Burton, J. N. Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert, A. W. Veenhuizen, Y. Y. Zhang, P. C. Isakson, *J. Med. Chem.* **1997**, *40*, 1347–1365.

[27] I. Colomer, C. J. Empson, P. Craven, Z. Owen, R. G. Doveston, I. Churcher, S. P. Marsden, A. Nelson, *Chem. Commun.* **2016**, *52*,

7209–7212.
[28] F. Wang, T. Luo, J. Hu, Y. Wang, H. S. Krishnan, P. V Jog, S. K. Ganesh, G. K. S. Prakash, G. A. Olah, *Angew. Chem. Int. Ed.* **2011**, *50*, 7153–7157.
[29] C. P. Johnston, T. H. West, R. E. Dooley, M. Reid, A. B. Jones, E. J. King, A. G. Leach, G. C. Lloyd-Jones, *J. Am. Chem. Soc.* **2018**, *140*, 11112–11124.
[30] A. García-Domínguez, T. H. West, J. J. Primozic, K. M. Grant, C. P. Johnston, G. G. Cumming, A. G. Leach, G. C. Lloyd-Jones, *J. Am. Chem. Soc.* **2020**, *142*, 14649–14663.
[31] S. Abele, G. Schmidt, M. J. Fleming, H. Steiner, *Org. Process Res. Dev.* **2014**, *18*, 993–1001.
[32] D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson, A. Wood, *Nat. Chem.* **2018**, *10*, 383–394.
[33] A. Pasternak, S. D. Goble, P. P. Vicario, J. Di Salvo, J. M. Ayala, M. Struthers, J. A. DeMartino, S. G. Mills, L. Yang, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 994–998.
[34] F. Kazumasa, O. Tetsuya, I. Takashi, Y. Hiroki, *Chem. Lett.* **1995**, *24*, 239–240.
[35] J. Li, Y. L. Li, N. Jin, A. L. Ma, Y. N. Huang, J. Deng, *Adv. Synth. Catal.* **2015**, *357*, 2474–2478.
[36] A. J. Jordan, P. K. Thompson, J. P. Sadighi, *Org. Lett.* **2018**, *20*, 5242–5246.

WILEY-VCH

УДК 547.544.31+546.16
DOI: https://doi.org/10.17721/1728-2209.2024.1(59).1

Костянтин МЕЛЬНИКОВ[1,2], канд. хім. наук
ORCID ID: 0009-0003-6522-681X
e-mail: kostiantyn.melnykov@knu.ua

Олексій ПІДВИШЕННИЙ[1,2], студ.
ORCID ID: 0009-0004-0396-1269
e-mail: o.pidvyshennyi@enamine.net

Олег СМИРНОВ[1,2], асп.
ORCID ID: 0009-0001-4863-1456
e-mail: ol.smyrnov@enamine.net

Олександр ГРИГОРЕНКО[1,2], д-р хім. наук, проф.
ORCID ID: 0000-0002-6036-5859
e-mail: gregor@univ.kiev.ua

[1]Київський національний університет імені Тараса Шевченка, Київ, Україна
[2]ТОВ "НВП "Єнамін", Київ, Україна

ФЛУОРОВАНІ СУЛЬФОКСІМІНИ ЖИРНОАРОМАТИЧНОГО РЯДУ: МАСШТАБОВАНИЙ СИНТЕЗ І ВПЛИВ СТРУКТУРНИХ ЕЛЕМЕНТІВ НА ЛІПОФІЛЬНІСТЬ

Вступ. *Сульфоксиміни нещодавно привернули значну увагу дослідників як біоізостерні аналоги сульфонового, амідного, сульфонамідного й інших споріднених структурних фрагментів. З іншого боку, введення атомів Флуору є відомим прийомом у медичній хімії, що дозволяє поліпшувати фармакокінетичні та фізико-хімічні параметри біологічно активних речовин. Отже, розробка ефективних методів синтезу флуоровмісних сульфоксимінів, зокрема з додатковими функціональними групами, а також визначення впливу їхньої структури на основні фізико-хімічні властивості, є актуальним завданням. Мета цієї роботи – розробка масштабованих протоколів синтезу 1-бромо-4-(S-(флуороалкіл)сульфонімідоїл)бензенів і встановлення впливу атомів Флуору та сульфоксимінового фрагменту на ліпофільність (порівняно з нефлуорованими аналогами та відповідними сульфонами).*

Методи. *Багатограмовий органічний синтез флуорованих сульфоксимінів жирноароматичного ряду; доведення будови та характеристика синтезованих речовин за допомогою спектроскопії ЯМР на ядрах ^1H, ^{19}F, ^{13}C і хроматомас-спектрометрії; вимірювання ліпофільності методом рідинної екстракції в поєднанні з ВЕРХ.*

Результати. *На основі відомого підходу до синтезу сульфоксимінів, що передбачає введення імінового фрагменту шляхом окиснення відповідного жирноароматичного сульфіду за участі фенілйодозодіацетату у присутності карбамату амонію, розроблено масштабовані протоколи синтезу 1-бромо-4-(S-(флуороалкіл)сульфонімідоїл)бензенів (флуороалкіл – CH_2F, CHF_2, CF_3). Методом рідинної екстракції в поєднанні з ВЕРХ (протокол "shake-flask") визначено ліпофільність одержаних сполук (а саме, логарифм коефіцієнту розподілу у системі 1-октанол – вода, LogP) і порівняно її зі значеннями для нефлуорованих аналогів, а також відповідних сульфонів.*

Висновки. *Показано, що підхід до синтезу сульфоксимінів, що передбачає окиснення відповідного жирноароматичного сульфіду за участі фенілйодозодіацетату у присутності карбамату амонію, є ефективним для одержання флуорованих жирноароматичних похідних у багатограмових кількостях. Виявлено, що флуорування 1-бромо-4-(S-метилсульфонімідоїл)бензену за метильною групою поетапно підвищує ліпофільність молекули (у середньому приблизно на 0.6 одиниць LogP на кожен атом Флуору), тоді як перехід від сульфонів до сульфоксимінів у досліджуваній серії сполук знижує її приблизно на 0.7 одиниць LogP.*

Ключові слова: *сульфурорганічні сполуки, флуороорганічні сполуки, сульфоксиміни, сульфони, ліпофільність, коефіцієнт розподілу.*

Вступ

Донедавна сульфоксиміни були доволі екзотичним класом сульфурорганічних сполук, який нечасто привертав увагу дослідників у галузі створення лікарських засобів. Ситуація різко змінилася в останнє десятиліття, коли було показано, що сульфоксиміновий фрагмент є перспективним для біоізостерних замін сульфонів, сульфонамідів, амідів та інших споріднених угрупувань (Mäder, & Kattner, 2020), (Frings et al., 2017) (рис. 1). Найбільш успішними прикладами втілення цієї концепції є розробка експериментальних протиракових препаратів Атувециклібу (BAY 1143572), Енітоциклібу (BAY 1251152) і Цераласертібу (AZD6738), що досягли стадії клінічних досліджень (Han et al., 2021).

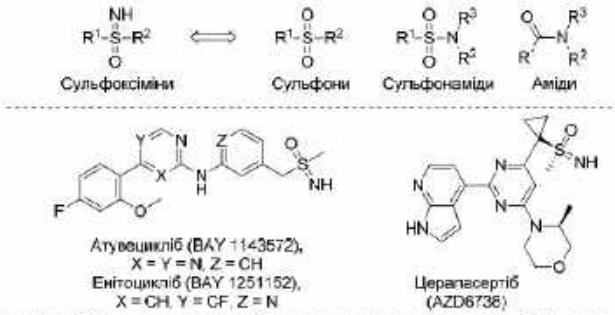
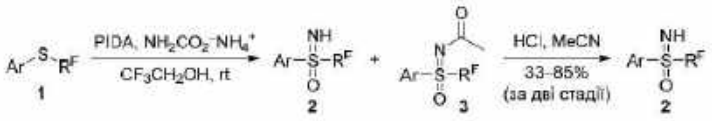


Рис. 1. Сульфоксиміни – перспективний клас сполук для проведення біоізостерних замін

© Мельников Костянтин, Підвишенний Олексій, Смирнов Олег, Григоренко Олександр, 2024

Не дивно, що підвищений інтерес до сульфоксимінів із боку фармацевтичної індустрії спонукав хіміків-органіків до розробки ефективних методів їхнього синтезу, а також вивчення фізико-хімічних і фармакокінетичних властивостей. Основним підходом до синтезу сульфоксимінів є імінування сульфоксидів із використанням як метал-каталізованих (Miao, Richards, & Ge, 2014), (Yu, Li, & Bolm, 2018), так і безметальних методів (Wang et al., 2017), (Zenzola et al., 2016), (Bull, Degennaro, & Luisi, 2017). Так само, сульфоксиди можуть одержуватись із відповідних сульфідів шляхом контрольованого окиснення, зокрема в однореакторному варіанті. Так, у 2018 р. групою вчених на чолі з Маньє та Ребулом було повідомлено про одностадійне окиснення флуорованих жирноароматичних сульфідів **1** до сульфоксимінів дією фенілйодозоацетату (PIDA) і карбамату амонію ($NH_2CO_2^-NH_4^+$) у трифторетанолі (Chaabouni et al., 2018). Спочатку утворювалась суміш цільових сульфоксимінів **2** та *N*-ацильних похідних **3**, яку було переведено в чисті продукти **2** шляхом кислотного гідролізу.



Ar = Ph, 4-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$ та ін.; R^F = CF_3, CHF_2, CH_2F та ін.

Схема 1. Синтез флуорованих жирноароматичних сульфоксимінів за Маньє–Ребулом

У межах цього дослідження ми звернули увагу на вищезгаданий метод з погляду його використання для одержання багатограмових кількостей флуорованих сульфоксимінів жирноароматичного ряду, зокрема, бромопохідних **2a–c**, що могли б потенційно використовуватись як будівельні блоки в реакціях метал-каталізованого крос-сполучення. Варто зазначити, що в роботі попередніх авторів повідомлялося про одержання сполуки **2a** (R^F = CF_3) у кількості 78 мг; на увагу заслуговує неповна конверсія вихідної речовини в умовах реакції (76 %), що спостерігалася й для інших похідних з 4-бромофенільним замісником. Сполука **2b** (R^F = CHF_2) також була відома в літературі, однак її одержували іншими методами (Pégot et al., 2015). У цій роботі ми оптимізували методику Маньє та Ребула для одержання речовин **2a–c** у кількостях десятків грам, а також виміряли ліпофільність (а саме, коефіцієнт розподілу в системі 1-октанол – вода, Log*P*) для цих сульфоксимінів, нефлуорованого аналога **2d**, а також відповідних сульфонів **4a–d** (рис. 2).

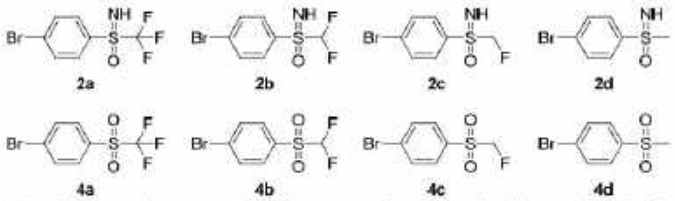


Рис. 2. Ключові сполуки цієї роботи – сульфоксиміни 2a–d і сульфони 4a–d

Методи

Усі вихідні сполуки, реактиви й розчинники було одержано від ТОВ "НВП "УкрОргСинтез". ^{1}H, ^{13}C і ^{19}F ЯМР спектри було зареєстровано на спектрометрах Agilent ProPulse 600 (за 600 МГц для ^{1}H ЯМР, 151 МГц для ^{13}C ЯМР), Bruker 170 Avance 500 (за 500 МГц для ^{1}H ЯМР, 126 МГц для ^{13}C ЯМР і 470 МГц для ^{19}F ЯМР) або Varian Unity Plus 400 (за 400 МГц для ^{1}H ЯМР, 101 МГц для ^{13}C ЯМР і 376 МГц для ^{19}F ЯМР). Хімічні зсуви (δ) наведено у м.ч.; як внутрішній стандарт використовували залишкові сигнали розчинника. Дані хроматомас-спектрометрії отримано на високоефективному рідинному хроматографі Agilent 1100 Series, обладнаному діодною матрицею з мас-селективним детектором Agilent LC\MSD SL, метод іонізації – хімічна іонізація за атмосферного тиску (APCI). Температури плавлення визначені на автоматичній установці MPA100 OptiMelt. Вимірювання ліпофільності (*LogP*) сульфоксимінів **2a–d** і сульфонів **4a–d** проводилося за описаною в літературі методикою (Holovach et al., 2022).

Загальна методика одержання сульфідів ***1.*** До розчину вихідного 4-бромотіофенолу (0.266 моль) у ДМФА (200 мл) під час охолодження до 0 °C додавали порціями гідрид натрію (0.320 моль, 60 % суспензія в мінеральному маслі). Після цього реакційну суміш перемішували впродовж 30 хв за кімнатної температури. Потім суміш охолоджували до 0 °C і краплинами додавали розчин флуоровмісного алкілгалогеніду (0.400 моль) у ДМФ (100 мл) упродовж 20 хв. Далі реакційну суміш залишали перемішуватися на ніч за кімнатної температури. Після проходження реакції реакційну суміш розбавляли водою (300 мл) і екстрагували *t*-BuOMe (700 мл). Органічну фазу промивали промивали водою (4×200 мл), сушили над Na_2SO_4, концентрували на роторному випаровувачі. Унаслідок чого отримували маслянисті речовини жовтуватого кольору.

Загальна методика одержання сульфоксимінів **2.** До розчину сульфану **1** (0.330 моль) у CF_3CH_2OH (500 мл) за 0 °C додали карбамат амонію (51.5 г, 0.660 моль), після чого порціями додавали діацетоксийодобензен (212 г, 0.660 моль). Реакційну суміш перемішували за кімнатної температури протягом 8 год, після чого знову додавали діацетоксийодобензен (53.1 г, 0.165 моль) і карбамату амонію (25.7 г, 0.330 моль). Уведення вказаних додаткових кількостей реагентів повторювали 2–3 рази кожні 8 год до досягнення максимальної конверсії (близько 70 %). Після цього реакційну суміш концентрували на роторному випаровувачі, затирали ацетонітрилом, маточний розчин конентрували у вакуумі. Після цього залишок фільтрували через шар SiO_2, елюювали спочатку гексаном (1 л), потім сумішшю *t*-BuOMe – гексан (1:1) (800 мл) і, нарешті, *t*-BuOMe (1 л), надалі фракцію

ISSN 1728-3817

t-BuOMe концентрували на роторному випаровувачі. Унаслідок чого отримували маслянисті суміші світло-жовтого кольору, що містили *N*-ацильовані похідні **3** та цільові сульфоксіміни **2**. До утвореної суміші (близько 0.200 моль) додавали 6 М соляну кислоту (200 мл). Після цього реакційну суміш перемішували за 60 °С протягом 3 год. Після проходження реакції суміш концентрували у вакуумі, твердий залишок висушували за зниженого тиску. Унаслідок отримували безбарвні або жовтуваті тверді речовини.

Результати

Із використанням викладених у попередньому розділі методик було синтезовано багато сульфурорганічних похідних, характеристики яких наведено нижче.

(4-Бромофеніл)(трифторометил)сульфід ***(1a)***. Вихід 105.6 г, 81%. Жовтувате масло. Усі фізичні та спектральні характеристики відповідали літературним даним (Harsányi et al., 2011).

(4-Бромофеніл)(дифторометил)сульфід ***(1b)***. Вихід 28.3 г, 87 %. Жовтувате масло. Усі фізичні та спектральні характеристики відповідали літературним даним (Bayarmagnai et al., 2015).

(4-Бромофеніл)(фторометил)сульфід ***(1c)***. Вихід 38.7 г, 90 %. Жовтувате масло. Усі фізичні та спектральні характеристики відповідали літературним даним (Webb et al., 2020).

(4-Бромофеніл)(трифторометил)(іміно)-λ^6-сульфанон ***(2a)***. Вихід 60.4 г, 51%. Жовтуваті кристали. Т. плавл. 94–96 °С (літ. 92–93 °С). Усі інші фізичні та спектральні характеристики відповідали літературним даним (Zenzola et al., 2016).

(4-Бромофеніл)(дифторометил)(іміно)-λ^6-сульфанон ***(2b)***. Вихід 17.9 г, 56%. Жовтуваті кристали. Т. плавл. 67–69 °С (літ. – масло). Усі інші фізичні та спектральні характеристики відповідали літературним даним (Pégot et al., 2015).

(4-Бромофеніл)(фторометил)(іміно)-λ^6-сульфанон ***(2c)***. Вихід 27.4 г, 62 %. Безбарвний порошок. Т. плавл. 55–56 °С. ^{1}H ЯМР (400 МГц, DMSO-d_6), δ 7.96 (d, *J* = 8.5 Гц, 2H, 3-C$\underline{H}_{аром}$), 7.86 (d, *J* = 8.3 Гц, 2H, 2-C$\underline{H}_{аром}$), 5.76 (d, *J* = 45.7 Гц, 2H, C$\underline{H}_2$F). ^{19}F{^{1}H} ЯМР (376 МГц, DMSO-d_6), δ –204.3. МС (APCI, *m*/*z*): 252/254 [M + H]$^+$.

Дані щодо ліпофільності (*LogP*) сульфоксімінів **2a–d** і сульфонів **4a–d** наведено в табл. 1.

Таблиця 1

Коефіцієнт розподілу в системі 1-октанол – вода (Log*P*) сполук 2a–d і 4a–d за 22 °С

№ п/п	R^F	Сульфоксімін	Log*P*	Сульфон	Log*P*
1	CF_3	**2a**	2.72±0.02	**4a**	3.28±0.08
2	CHF_2	**2b**	1.72±0.01	**4b**	2.48±0.02
3	CH_2F	**2c**	1.14±0.02	**4c**	1.94±0.01
4	CH_3	**2d**	0.82±0.01	**4d**	1.41±0.01

Дискусія і висновки

Синтез цільових сполук **2a–c** розпочинався алкілуванням 4-бромотіофенолу CF_3I, CHF_2Cl або CH_2FI у присутності гідриду натрію у ДМФА за кімнатної температури. Одержані флуоровані жирноароматичні сульфіди **1a–c** (вихід 81–90 %) було введено в реакцію з діацетоксийодобензеном (PIDA) і карбаматом амонію у трифлуороетанолі за способом Маньє та Ребула (Схема 1) [10]. Під час масштабування вищезгаданої методики було виявлено багато проблем, зокрема неповна конверсія на стадії окиснення. За звичайних умов реакції (кімнатна температура, 24 год) конверсія сягала 40–50 %. Підвищення температури до 40 °С не сприяло суттєвому зростанню конверсії, а за більш інтенсивного нагрівання (70 °С, 6–18 год) спостерігалася поступова деструкція продукту та проходження побічних процесів. У ході подальших досліджень було з'ясовано, що додаткове дво- або трикратне введення обох реагентів (PIDA – по 0.5 екв, карбамат амонію – по 1 екв) кожні 8 год сприяло підвищенню конверсії на 20–30 %. Водночас кількість утворених у реакції нецільових сольових продуктів також збільшувалася, проте це не впливало на чистоту продукту, оскільки вони кількісно відділялися під час обробки реакційної суміші. Після проведення стадії гідролізу цільові продукти було одержано в кількостях 17,92–60,4 г із виходом 51–62 %.

Визначення ліпофільності одержаних сульфоксімінів **2a–c**, нефлуорованого аналогу **2d**, а також сульфонів **4a–d** показало, що в серії сульфоксімінів флуорування приводило до підвищення значення Log*P* на 0.32±0.03, 0.58±0.03 і 1.00±0.03 одиниці для першого, другого та третього атома Флуору, відповідно (середнє значення 0.63±0.34) (рис. 3). У випадку сульфонів підвищення ліпофільності складало 0.53±0.02, 0.54±0.03 і 0.80±0.10 одиниці Log*P*, відповідно (середнє значення 0.62±0.15). Можна констатувати, що монофлуоровані похідні є дещо більш гідрофільними, ніж можна очікувати на основі середнього інкременту Log*P*, а CF_3-заміщені – дещо більш ліпофільними, що можна пояснити частковою компенсацією дипольних моментів відповідних зв'язків. З іншого боку, середній інкремент атома Флуору є майже однаковим для сульфонів і сульфоксімінів.

Порівняння значень Log*P* для серії сульфоксімінів **2a–d** та сульфонів **4a–d** показує, що відповідні сульфоксіміни є більш гідрофільними – на 0.59±0.02 (**2d**/**4d**), 0.80±0.03 (**2c**/**4c**), 0.76±0.03 (**2b**/**4b**) та 0.56±0.10 (**2a**/**4a**) одиниці Log*P* (середнє значення 0.68±0.12). Цікаво, що літературні дані щодо цього питання є суперечливими [3]; варто, однак, зазначити, що деякі попередні автори використовували різні методики визначення Log*P* для сульфоксімінів і сульфонів, і більшість дослідників погоджуються з даними щодо вищої гідрофільністю сульфоксімінів.

Отже, у цій роботі показано, підхід до синтезу сульфоксімінів, що ґрунтується на окисному імінуванню відповідних сульфідів дією діацетоксийодобензену та карбамату амонію з подальшим кислотним гідролізом, є придатним для одержання флуорованих жирноароматичних сульфоксімінів у багатограмових кількостях. Зокрема, метод є придатним для одержання будівельних блоків з арилбромідним фрагментом, що є перспективними для введення сульфоксімінового фрагменту за реакціями метал-каталізованого крос-сполучення. Виявлено, що введення атомів Флуору підвищує ліпофільність як сульфоксімінів, так і відповідних сульфонів приблизно на 0.6 одиниць LogP; водночас ефект є найнижчим для першого атома Флуору похідних і найвищим – для останнього. Також встановлено, що сульфоксіміни є приблизно на 0.7 одиниць Log*P* більш гідрофільними порівняно з аналогічними сульфонами для всієї досліджуваної серії.

ISSN 1728-2209 (Print)

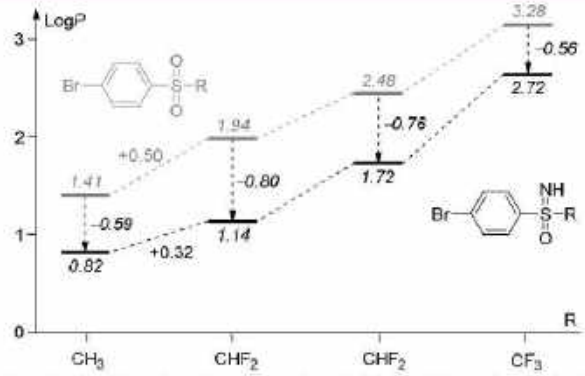


Рис. 3. Ліпофільність (Log*P*) сульфоксімінів 2a–d і сульфонів 4a–d

Внесок авторів: Костянтин Мельников – концептуалізація, методологія, формальний аналіз; Олексій Підвишенний – методологія, формальний аналіз; Олег Смирнов – методологія, валідація даних; Олександр Григоренко – концептуалізація, формальний аналіз, написання – чернетка, написання – перегляд і редагування.

Цю роботу виконано за підтримки ТОВ "НВП "Єнамін", а також Міністерства освіти та науки України (гранти 0121U100387 (21БФ037-01М) і 0122U001962 (22БФ037-02)). Автори висловлюють вдячність А. Скремінському за вимірювання ліпофільності, проф. А. О. Толмачову за підтримку та натхнення, а також усім захисникам України, завдяки яким ця публікація стала можливою.

Список використаних джерел

Bayarmagnai, B., Matheis, C., Jouvin, K., & Goossen, L. J. (2015). Synthesis of difluoromethyl thioethers from difluoromethyl trimethylsilane and organothiocyanates generated in situ. *Angew. Chem. Int. Ed.*, 54, 5753–5756. https://doi.org/10.1002/anie.201500899

Bull, J., Degennaro, L., & Luisi, R. (2017). Straightforward strategies for the preparation of NH-sulfoximines: a serendipitous story. *Synlett*, 28, 2525–2538. https://doi.org/10.1055/s-0036-1590874

Chaabouni, S., Lohier, J., Barthelemy, A., Glachet, T., Anselmi, E., Dagousset, G., Diter, P., Pégot, B., Magnier, E., & Reboul, V. (2018). One-pot synthesis of aryl- and alkyl *S*-perfluoroalkylated *NH*-sulfoximines from sulfides. *Chem. Eur. J.* 24, 17006–17010. https://doi.org/10.1002/chem.201805055

Frings, M., Bolm, C., Blum, A., & Gnamm, C. (2017). Sulfoximines from a medicinal chemist's perspective: physicochemical and in vitro parameters relevant for drug discovery. *Eur. J. Med. Chem.*, 126, 225–245. https://doi.org/10.1016/j.ejmech.2016.09.091

Han, Y., Xing, K., Zhang, J., Tong, T., Shi, Y., Cao, H., Yu, H., Zhang, Y., Liu, D., & Zhao, L. (2021). Application of sulfoximines in medicinal chemistry from 2013 to 2020. *Eur. J. Med. Chem.*, 209, 112885. https://doi.org/10.1016/j.ejmech.2020.112885

Harsányi, A., Dorkó, É., Csapó, Á., Bakó, T., Peltz, C., & Rábai, J. (2011). Convenient synthesis and isolation of trifluoromethylthio-substituted building blocks. *J. Fluorine Chem.*, 132, 1241–1246. https://doi.org/10.1016/j.jfluchem.2011.07.008

Holovach, S., Melnykov, K. P., Skreminskiy, A., Herasymchuk, M., Tavlui, O., Aloshyn, D., Borysko, P., Rozhenko, A. B., Ryabukhin, S. V., Volochnyuk, D. M., & Grygorenko, O. O. (2022). Effect of *gem*-difluorination on the key physicochemical properties relevant to medicinal chemistry: the case of functionalized cycloalkanes. *Chem. Eur. J.*, 28, e202200331. https://doi.org/10.1002/chem.202200331

Mäder, P., & Kattner, L. (2020). Sulfoximines as rising stars in modern drug discovery? Current status and perspective on an emerging functional group in medicinal chemistry. *J. Med. Chem.*, 63, 14243–14275. https://doi.org/10.1021/acs.jmedchem.0c00960

Miao, J., Richards, N. G. J., & Ge, H. (2014). Rhodium-catalyzed direct synthesis of unprotected NH-sulfoximines from sulfoxides. *Chem. Commun.*, 50, 9687–9689. https://doi.org/10.1039/C4CC04349A

Pégot, B., Urban, C., Bourne, A., Le, T. N., Bouvet, S., Marrot, J., Diter, P., & Magnier, E. (2015). Difluoromethyl and chlorofluoromethyl sulfoximines: synthesis and evaluation as electrophilic perfluoroalkylating reagents: difluoromethyl and chlorofluoromethyl sulfoximines. *Eur. J. Org. Chem.*, 3069–3075. https://doi.org/10.1002/ejoc.201500201

Wang, J., Zhang, J., Miao, K., Yun, H., Shen, H. C., Zhao, W., & Liang, C. (2017). Eaton's reagent-mediated metal-free and efficient synthesis of NH-sulfoximines. *Tetrahedron Lett.*, 58, 333–337. https://doi.org/10.1016/j.tetlet.2016.12.031

Webb, E. W., Park, J. B., Cole, E. L., Donnelly, D. J., Bonacorsi, S. J., Ewing, W. R., & Doyle, A. G. (2020). Nucleophilic (radio)fluorination of redox-active esters via radical-polar crossover enabled by photoredox catalysis. *J. Am. Chem. Soc.*, 142, 9493–9500. https://doi.org/10.1021/jacs.0c03125

Yu, H., Li, Z., & Bolm, C. (2018). Iron(II)-catalyzed direct synthesis of NH sulfoximines from sulfoxides. *Angew. Chem. Int. Ed.*, 57, 324–327. https://doi.org/10.1002/anie.201710498

Zenzola, M., Doran, R., Degennaro, L., Luisi, R., & Bull, J. A. (2016). Transfer of electrophilic NH Using convenient sources of ammonia: direct synthesis of nh sulfoximines from sulfoxides. *Angew. Chem. Int. Ed.*, 55, 7203–7207. https://doi.org/10.1002/anie.201602320

References

Bayarmagnai, B., Matheis, C., Jouvin, K., & Goossen, L. J. (2015). Synthesis of difluoromethyl thioethers from difluoromethyl trimethylsilane and organothiocyanates generated in situ. *Angew. Chem. Int. Ed.*, 54, 5753–5756. https://doi.org/10.1002/anie.201500899

Bull, J., Degennaro, L., & Luisi, R. (2017). Straightforward strategies for the preparation of NH-sulfoximines: a serendipitous story. *Synlett*, 28, 2525–2538. https://doi.org/10.1055/s-0036-1590874

Chaabouni, S., Lohier, J., Barthelemy, A., Glachet, T., Anselmi, E., Dagousset, G., Diter, P., Pégot, B., Magnier, E., & Reboul, V. (2018). One-pot synthesis of aryl- and alkyl *S*-perfluoroalkylated *NH*-sulfoximines from sulfides. *Chem. Eur. J.* 24, 17006–17010. https://doi.org/10.1002/chem.201805055

Frings, M., Bolm, C., Blum, A., & Gnamm, C. (2017). Sulfoximines from a medicinal chemist's perspective: physicochemical and in vitro parameters relevant for drug discovery. *Eur. J. Med. Chem.*, 126, 225–245. https://doi.org/10.1016/j.ejmech.2016.09.091

Han, Y., Xing, K., Zhang, J., Tong, T., Shi, Y., Cao, H., Yu, H., Zhang, Y., Liu, D., & Zhao, L. (2021). Application of sulfoximines in medicinal chemistry from 2013 to 2020. *Eur. J. Med. Chem.*, 209, 112885. https://doi.org/10.1016/j.ejmech.2020.112885

Harsányi, A., Dorkó, É., Csapó, Á., Bakó, T., Peltz, C., & Rábai, J. (2011). Convenient synthesis and isolation of trifluoromethylthio-substituted building blocks. *J. Fluorine Chem.*, 132, 1241–1246. https://doi.org/10.1016/j.jfluchem.2011.07.008

Holovach, S., Melnykov, K. P., Skreminskiy, A., Herasymchuk, M., Tavlui, O., Aloshyn, D., Borysko, P., Rozhenko, A. B., Ryabukhin, S. V., Volochnyuk, D. M., & Grygorenko, O. O. (2022). Effect of *gem*-difluorination on the key physicochemical properties relevant to medicinal chemistry: the case of functionalized cycloalkanes. *Chem. Eur. J.*, 28, e202200331. https://doi.org/10.1002/chem.202200331

Mäder, P., & Kattner, L. (2020). Sulfoximines as rising stars in modern drug discovery? Current status and perspective on an emerging functional group in medicinal chemistry. *J. Med. Chem.*, 63, 14243–14275. https://doi.org/10.1021/acs.jmedchem.0c00960

Miao, J., Richards, N. G. J., & Ge, H. (2014). Rhodium-catalyzed direct synthesis of unprotected NH-sulfoximines from sulfoxides. *Chem. Commun.*, 50, 9687–9689. https://doi.org/10.1039/C4CC04349A

Pégot, B., Urban, C., Bourne, A., Le, T. N., Bouvet, S., Marrot, J., Diter, P., & Magnier, E. (2015). Difluoromethyl and chlorofluoromethyl sulfoximines: synthesis and evaluation as electrophilic perfluoroalkylating reagents: difluoromethyl and chlorofluoromethyl sulfoximines. *Eur. J. Org. Chem.*, 3069–3075. https://doi.org/10.1002/ejoc.201500201

Wang, J., Zhang, J., Miao, K., Yun, H., Shen, H. C., Zhao, W., & Liang, C. (2017). Eaton's reagent-mediated metal-free and efficient synthesis of NH-sulfoximines. *Tetrahedron Lett.*, 58, 333–337. https://doi.org/10.1016/j.tetlet.2016.12.031

ISSN 1728-3817

Webb, E. W., Park, J. B., Cole, E. L., Donnelly, D. J., Bonacorsi, S. J., Ewing, W. R., & Doyle, A. G. (2020). Nucleophilic (radio)fluorination of redox-active esters via radical-polar crossover enabled by photoredox catalysis. *J. Am. Chem. Soc.*, 142, 9493–9500. https://doi.org/10.1021/jacs.0c03125

Yu, H., Li, Z., & Bolm, C. (2018). Iron(II)-catalyzed direct synthesis of NH sulfoximines from sulfoxides. *Angew. Chem. Int. Ed.*, 57, 324–327. https://doi.org/10.1002/anie.201710498

Zenzola, M., Doran, R., Degennaro, L., Luisi, R., & Bull, J. A. (2016). Transfer of electrophilic NH Using convenient sources of ammonia: direct synthesis of nh sulfoximines from sulfoxides. *Angew. Chem. Int. Ed.*, 55, 7203–7207. https://doi.org/10.1002/anie.201602320

Отримано редакцією журналу / Received: 04.01.24
Прорецензовано / Revised: 14.01.24
Схвалено до друку / Accepted: 27.01.24

Kostiantyn MELNYKOV[1,2], PhD (Chem.)
ORCID ID: 0009-0003-6522-681X
e-mail: kostiantyn.melnykov@knu.ua

Oleksii PIDVYSHENNYI[1,2], Student
ORCID ID: 0009-0004-0396-1269
e-mail: o.pidvyshennyi@enamine.net

Oleh SMYRNOV[1,2], PhD Student
ORCID ID: 0009-0001-4863-1456
e-mail: ol.smyrnov@enamine.net

Oleksandr GRYGORENKO[1,2], DSc (Chem.), Prof.
ORCID ID: 0000-0002-6036-5859
e-mail: gregor@univ.kiev.ua

[1]Taras Shevchenko National University of Kyiv, Kyiv, Ukraine
[2]Enamine Ltd., Kyiv, Ukraine

AROMATIC SULFOXIMINES WITH FLUORINATED ALKYL SIDE CHAINS: SCALABLE SYNTHESIS AND EFFECTS OF STRUCTURAL ELEMENTS ON LIPOPHILICITY

Background. *Sulfoximines recently gained significant attention of researchers as bioisosteric analogs of sulfone, amide, sulfonamide, and other related structural fragments. On the other hand, incorporation of fluorine atoms is a well-known tool in medicinal chemistry allowing to improve pharmacokinetic and physicochemical parameters of biologically active compounds. Therefore, development of effective approaches towards fluorine-containing sulfoximines, in particular, with additional functional groups, as well as establishing effects of their structure on the main physicochemical properties, is an important task. The goal of this work is to develop scalable protocols for the synthesis of 1-bromo-4-(S-(fluoroalkyl)-sulfonimidoyl)benzenes and to establish effect of the fluorine atoms and the sulfoximine fragment on lipophilicity (as compared to the non-fluorinated analogs and the corresponding sulfones).*

Methods. *Scalable organic synthesis of aromatic sulfoximines with fluorinated alkyl side chains; structure investigation and characterization of the synthesized compounds by ^1H, ^{19}F, ^{13}C NMR spectroscopy and chromatomass-spectrometry; lipophilicity measurement by liquid-liquid extraction in combination with HPLC.*

Results. *Based on the known approach to the sulfoximine synthesis that includes introduction of the imine fragment by oxidation of the corresponding aryl fluoroalkyl sulfide with phenyliodosodiacetate in the presence of ammonium carbamate, scalable protocols for the synthesis of 1-bromo-4-(S-(fluoroalkyl)sulfonimidoyl)benzenes were developed (fluoroalkyl – CH_2F, CHF_2, CF_3). Using liquid-liquid extraction in combination with HPLC ("shake-flask" protocol), lipophilicity of the obtained compounds (i.e., 1-octanol – water distribution coefficient logarithm, LogP) was determined and compared with the values for the non-fluorinated analogs and the corresponding sulfones.*

Conclusions. *It is shown that the approach to the synthesis of sulfoximines that includes oxidation of the corresponding alkyl aryl sulfide with phenyliodosodiacetate in the presence of ammonium carbamate, is efficient to obtain fluorinated derivatives in multigram quantities. It is found that fluorination of 1-bromo-4-(S-methylsulfonimidoyl)benzene at the methyl group leads to the stepwise increase the molecule's lipophilicity (by ca. 0.6 LogP units per each fluorine atom on average), while replacement of the sulfone moiety with sulfoximine in the studied series lowers it by ca. 0.7 LogP units.*

Keywords: *organosulfur compounds, organofluorine compounds, sulfoximines, sulfones, lipophilicity, distribution coefficient.*

Автори заявляють про відсутність конфлікту інтересів. Спонсори не брали участі в розробленні дослідження; у зборі, аналізі чи інтерпретації даних, у написанні рукопису або у прийнятті рішення про публікацію результатів.

The authors declare no conflicts of interest. The funders had no role in the design of the study, in the collection, analysis, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

ISSN 1728-2209 (Print)

C–C Coupling Through Nitrogen Deletion: Application to Library Synthesis

Serhii Holovach,[a] Dr. Kostiantyn P. Melnykov,[a,b] Illia Poroshyn,[a] Dr. Rustam T. Iminov,[a] Dr. Dmytro Dudenko,[a,d] Dr. Ivan Kondratov,[a,c] Prof. Dr. Mark Levin,[e] and Prof. Dr. Oleksandr O. Grygorenko*[a,b]

Dedicated to the memory of Yaroslav Mayboroda, a chemistry student and a volunteer who died in August 2022

[a] Enamine Ltd.
Chervonotkatska Street 78, Kyiv 02094, Ukraine
URL: www.enamine.net
[b] Taras Shevchenko National University of Kyiv
Volodymyrska Street 60, Kyiv 01601, Ukraine
E-mail: gregor@univ.kiev.ua
[c] V. P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine
Akademik Kukhar Street 1, Kyiv 02094, Ukraine
[d] Chemspace
Chervonotkatska Street 85, Kyiv 02094, Ukraine
URL: www.chem-space.com
[e] Department of Chemistry, University of Chicago
5735 S Ellis Ave, Chicago, IL 60637, USA
Supporting information for this article is given via a link at the end of the document

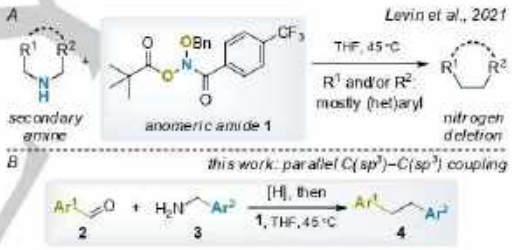
Abstract: A protocol for parallel C(sp^3)–C(sp^3) coupling of (hetero)aromatic aldehydes and (hetero)arylmethyl amines based on a reductive amination – "nitrogen deletion" reaction sequence was developed. After preliminary validation experiments, an illustrative compound library of 25 members was prepared with 76% synthetic efficiency. The estimated chemical space accessible by the proposed approach covers almost 600,000 representatives that are scarcely represented in current compound databases.

Introduction

Drug discovery relies heavily on the availability of suitable starting points, which is, in turn, dependent on the ability of organic chemists to synthesize novel molecules in a timely and efficient manner.[1] Meanwhile, many significant advances in organic synthesis are not immediately implemented in medicinal chemistry; for most, their adaptation into library synthesis tends to be slow.[2] This has previously been suggested to be due to insufficient attention of novel methodology reports to the substrate scope and functional-group tolerance of their methods,[3] often accompanied by over-representation of "positive" results.

Single-atom skeletal editing is a powerful strategy that expands chemists' capabilities for synthetic planning.[4,5] For example, deleting nitrogen atoms in secondary amines provides non-obvious possibilities for late-stage modification.[6] Alternatively, it can be envisaged as a C(sp^3)–C(sp^3) coupling approach, as secondary amines are, in turn, readily accessible from commercially available building blocks by a number of methods.

Recently, several protocols for nitrogen atom deletion were described,[6-8] one of which relies on the use of anomeric amide reagent **1** (Scheme 1, *A*).[6] The method requires unhindered secondary amines bearing an aromatic moiety at the α position in at least one of the substituents, though better yields are observed for doubly benzylic amines. Nevertheless, because the method demonstrated notable functional group tolerance for medicinally relevant substructures, we hypothesized that it would have the potential for library synthesis if combined with any efficient approach capable of providing secondary amines in a parallel fashion (e.g., reductive amination).



Scheme 1. Nitrogen atom deletion in secondary amines

In this work, we have examined the implementation of the above idea into a two-step parallel synthesis protocol, including reductive amination of (hetero)aromatic aldehydes **2** with primary (het)arylmethyl ("benzylic") amines **3**, followed by nitrogen deletion with **1**, without isolation of the intermediate secondary amines in pure form (Scheme 1, *B*). We have also evaluated the applicability of the method for the preparation of drug- and lead-like compound libraries relevant to early drug discovery, as well as the properties of chemical space made accessible by this approach. A few examples of compounds that can be obtained by this method (**4**) were found in the ChemBL database[9] and had biological activity such as P-glycoprotein (P-gp) modulation,[10,11] leukotriene A_4 (LTA_4) hydrolase inhibition,[12] and mineralocorticoid receptor (MR) antagonism[13] (Figure 1).

Throughout this paper, a compound numbering system common for combinatorial chemistry is used. Thus, aldehydes and amines used for the library synthesis are labeled as **2**{*i*} and **3**{*j*}, respectively, where *i* and *j* are positive integer numbers starting

with **1**. The corresponding library members synthesized from reagents **2**{*i*} and **3**{*j*} are designated as **4**{*i,j*}.

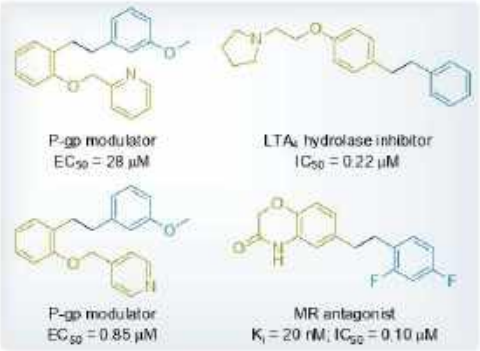


Figure 1. Some biologically active representatives of the compounds of general formula **4** that were found in ChemBL database

Results and Discussion

For the reaction sequence shown in Scheme 1, *B*, we aimed to develop a simple and robust protocol compatible with the available industrial parallel synthesis workflow. To achieve this, the crude product obtained after the reductive amination step should be of acceptable quality to be subjected to the nitrogen deletion step without additional purification. Preliminary experiments showed that among several methods from our collection of parallel reductive amination procedures (AcOH, MeOH or $(CH_2Cl)_2$, rt, 15 min to 12 h, then $NaBH_4$, $NaBH_3CN$ or $NaBH(OAc)_3$, rt, 12–18 h), the approach using $NaBH_3CN$ as the reducing reagent, MeOH as the solvent, and a prolonged imine formation time (12 h) proved the best for the preparation of crude intermediate secondary amines **5** with the highest purity (Table 1). The main side reaction (according to LC/MS) was tertiary amine formation, obviously due to the reaction of amine **5** with an additional molecule of aldehyde **2**. More importantly, crude products **5** obtained according to the above optimized protocol gave reasonable results in the second step, i.e., reaction with compound **1** according to the published procedure.[6] Thus, corresponding products **4**{*1,2*}, **4**{*2,1*}, and **4**{*11,1*} were obtained in 45%, 36%, and 7% yield, respectively.

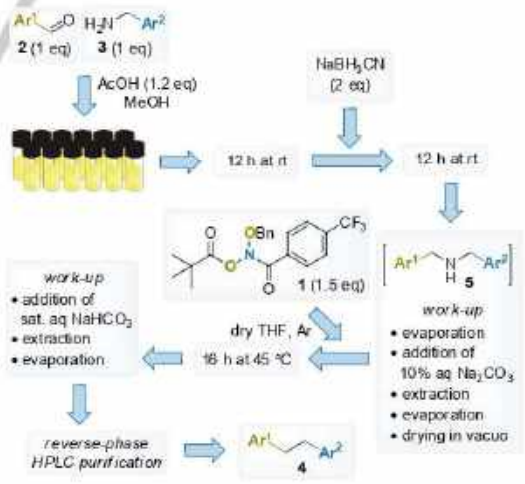
The developed parallel synthesis setup (Scheme 2) was applied to validation experiments involving 17 (hetero)aromatic aldehydes **2**{*2–18*} in reaction with *p*-fluorobenzylamine (**3**{*1*}), as well as *p*-fluorobenzaldehyde (**2**{*1*}) in reaction with ten primary amines **3**{*2–11*} as the starting compounds (Figure 2). It was found that building blocks **2**{*2–9*} and **3**{*2–5*} provided the target products in 10–45% yield; substrates **2**{*10–13*} and **3**{*6–8*} also gave the target compounds, albeit in low yield (4–10%), whereas the corresponding reactions with **2**{*14–18*} and **3**{*9–11*} were not fruitful. In both categories, 2-functionalized azine and many azole (especially 1,3-azole) derivatives were typically problematic substrates, either giving the target product in less than 10% yield or not providing it at all. Building blocks with multiple hydrogen bond donors (e.g., **2**{*17*} or **3**{*8*}) were also of low efficiency, likely due to solubility limitations. Interestingly, in almost all problematic cases, it was the reductive amination step that operated with modest or poor efficiency (according to LCMS data), such that intermediate **5** was introduced into the second step with low purity. The only confirmed exception was compound **2**{*18*}: the corresponding intermediate **5**{*18,1*} was formed (according to LCMS) but gave a complex mixture of products upon reaction with anomeric amide **1**.

Table 1. Optimization of the reductive amination step

#	Aldehyde[a]	Amine[a]	Conditions	Yield, %[b]
1	**2**{*1*}	**3**{*2*}	MeOH, 30 min, then $NaBH_4$ (1 eq), 18 h	21
2	**2**{*1*}	**3**{*2*}	MeOH, 15 min, then $NaBH(OAc)_3$ (2 eq), 18 h	51
3	**2**{*1*}	**3**{*2*}	AcOH (1.2 eq), MeOH, 15 min, then $NaBH(OAc)_3$ (2 eq), 18 h	67
4	**2**{*2*}	**3**{*1*}		34
5	**2**{*11*}	**3**{*1*}		57
6	**2**{*1*}	**3**{*2*}	AcOH (1.2 eq), MeOH, 15 min, then $NaBH_3CN$ (2 eq), 12 h	60
7	**2**{*1*}	**3**{*2*}	AcOH (1.2 eq), MeOH, 12 h, then $NaBH_3CN$ (2 eq), 12 h	85
8	**2**{*2*}	**3**{*1*}		83
9	**2**{*11*}	**3**{*1*}		82

[a] See Figure 2 for the structures of aldehydes **2** and amines **3**

[b] Yield according to LC/MS



Scheme 2. Parallel synthesis setup used in this work

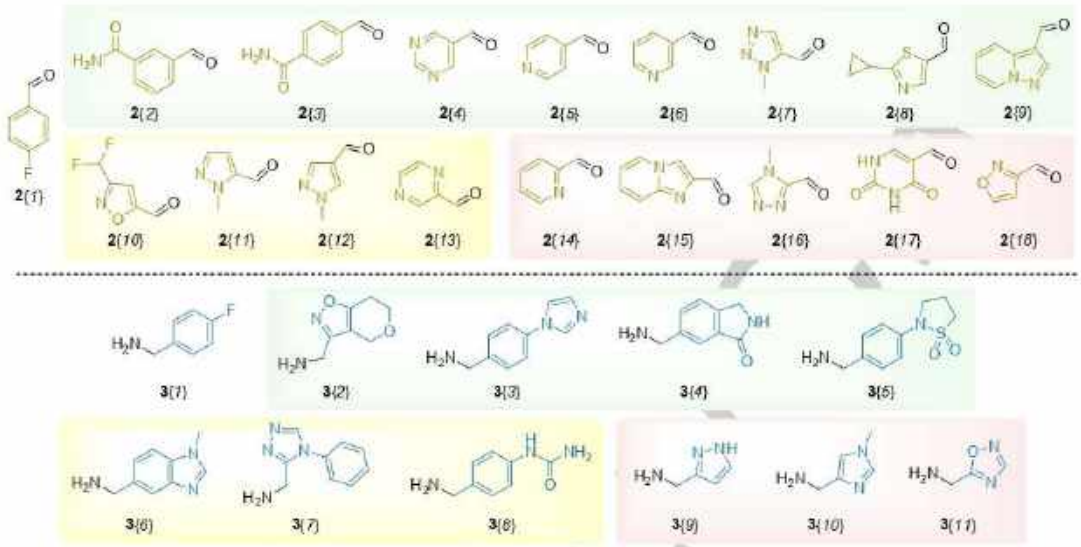


Figure 2. Aldehydes **2**(*1–18*) and amines **3**(*1–11*) used in the validation experiments (green background – the corresponding library member was obtained in at least 10% yield; yellow – in less than 10% yield; red – was not obtained)

Using the obtained results as a guide, we next enriched the reagent sets shown in Figure 2 with additional compounds **2** and **3** having structural features that, in our experience, might be of interest to medicinal chemists (Figure 3). We did not include azine derivatives having the CHO/CH_2NH_2 group at α position of the heterocycle (e.g., **2**(*14*) and **2**(*15*)), compound **2**(*17*) and its analogs, as well as compounds **2**(*1*) and **3**(*1*). Using these extended reagent sets, 33 library members **4** were deliberately selected for further parallel synthesis. Lower priority was given to the derivatives of building blocks bearing the CHO/CH_2NH_2 group at the azole ring, as well as products with calculated Log*P* < 2 (to minimize possible complications at the purification step). Following the workflow shown in Scheme 2, 25 out of 33 library members **4** were prepared successfully (76% synthesis success rate, i.e., a percentage of the planned library members that were obtained and isolated in pure form); 18 of them (54% of the whole library) – in 10–51% yield (see Figure 4 for selected examples and Table S1 in the Supporting Information for the full details, including the product yields). Again, in most of the unsuccessful examples (7 out of 8), it was the first step (i.e., reductive amination) that gave intermediate **5** with moderate or even low purity according to LCMS and/or ^{1}H NMR spectra, which was likely the cause of failure for the overall reaction sequence.

The calculated physicochemical properties (i.e., molecular weight (MW) and octanol–water partition coefficient decimal logarithm (Log*P*))[14] of 61 library members **4** that we have obtained or tried to obtain in all the above experiments are shown in Figure 5. It is apparent that the synthesis success rate was considerably lower for the compounds with MW < 250 and/or Log*P* < 2, although the overall Log*P* drift[15] (i.e., the difference between average Log*P* values for the actually synthesized and planned library members) was only 0.12 units. These results do not comply with the definition of lead-oriented synthesis[15] which covers efficient methods for the preparation of low-molecular-weight hydrophilic ("lead-like") compound libraries. Nevertheless, the proposed approach still can be suitable for the preparation of both lead-like (as defined by Churcher's rules: MW = 200…350, Log*P* = –1…3) and drug-like (as defined by Lipinski's rules: MW < 500, Log*P* < 5, HAcc ≤ 10, HDon ≤ 5) compound libraries, albeit with certain limitations.[1]

To estimate the potential chemical space made accessible by the proposed parallel synthesis approach, we have selected 1100 (hetero)aromatic aldehydes **2** and 651 (het)arylmethyl amines **3** from Enamine's building block collection with proprietary, experimentally validated reactivity in the reductive amination. The following exclusion filters were used upon the selection according to the experimental results obtained in this or previous[6] works:

- azine and 1,3-azole derivatives having the CHO or CH_2NH_2 group at the α position of the heterocycle;
- compounds with free hydroxyl and azole NH moieties;
- α,α'-disubstituted building blocks;
- derivatives of electron-rich heterocycles;
- compounds with strong and/or several electron-donating groups at *o*- and *p*-positions to the CHO or CH_2NH_2 moiety;
- derivatives with the CHO/CH_2NH_2 group at the imidazole or uracil ring;
- hydrochlorides (for compounds **2**) or dihydrochlorides (for compounds **3**).

The selected building blocks were subjected to virtual coupling according to the reaction shown in Scheme 1, *A*. Only the products with MW > 250 having at least one nitrogen atom were generated. These cheminformatic operations led to a chemical space comprising 593 713 members with the following average

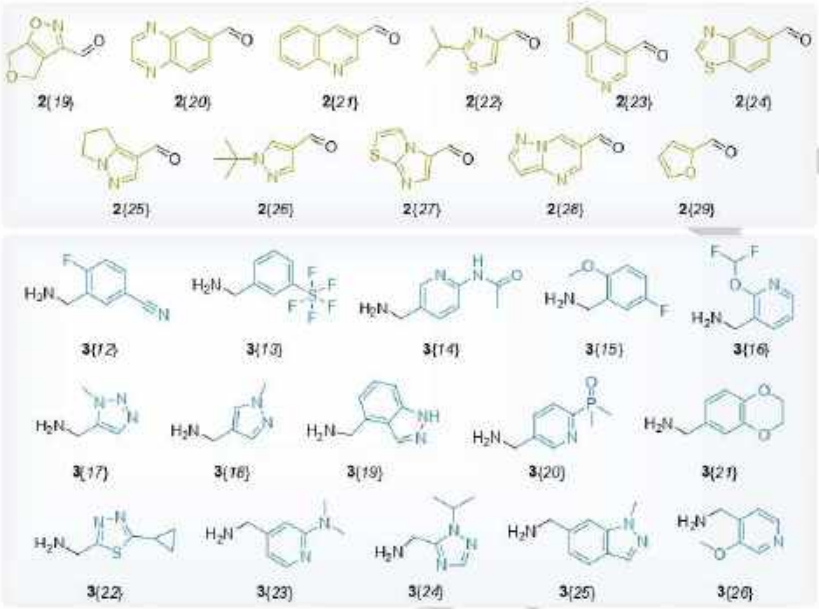


Figure 3. Additional aldehydes **2**(*19–29*) and amines **3**(*12–26*) used in the synthesis of a drug-like compound library

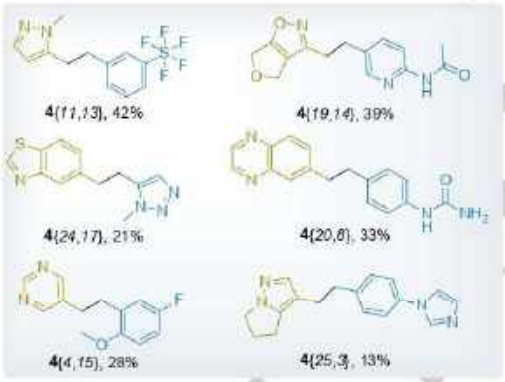


Figure 4. Selected examples of the synthesized library members **4**

physicochemical properties: molecular weight MW = 349, octanol–water partition coefficient decimal logarithm Log*P* = 4.7, hydrogen bond acceptor/donor counts HAcc = 2.6 and HDon = 0.2, respectively, sp^3-hybrid carbon atom fraction Fsp^3 = 0.32, and rotatable bond count RotB = 5.8 (Figure 6). The resulting space contains significant fractions of compounds either compliant with Lipinski drug-likeness rules (MW < 500, Log*P* < 5, HAcc ≤ 10, HDon ≤ 5) (59% members) or beyond the "rule-of-five" (41% members).[16] Furthermore, 178 068 (30%) representatives do not violate the lead-likeness definition according to the "rule-of-four" (MW ≤ 400, Log*P* ≤ 4, HAcc ≤ 8, HDon ≤ 4).[1] Also, there are 55 061 (9.3%) members that comply even with the strictest Churcher's rules for lead-like compounds (MW = 200…350, Log*P* = –1…3).[15]

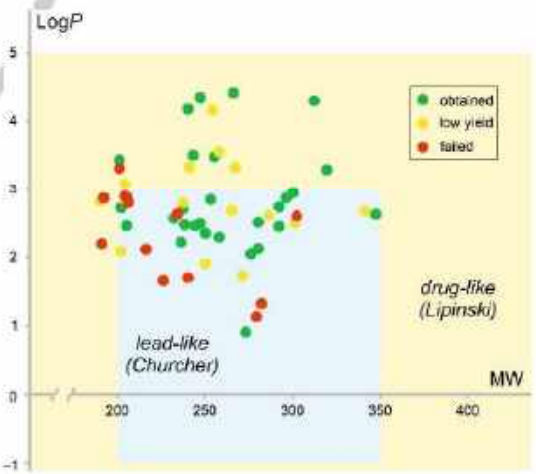


Figure 5. 61 library members **4** evaluated in the synthetic part of this work shown in the MW – Log*P* plot

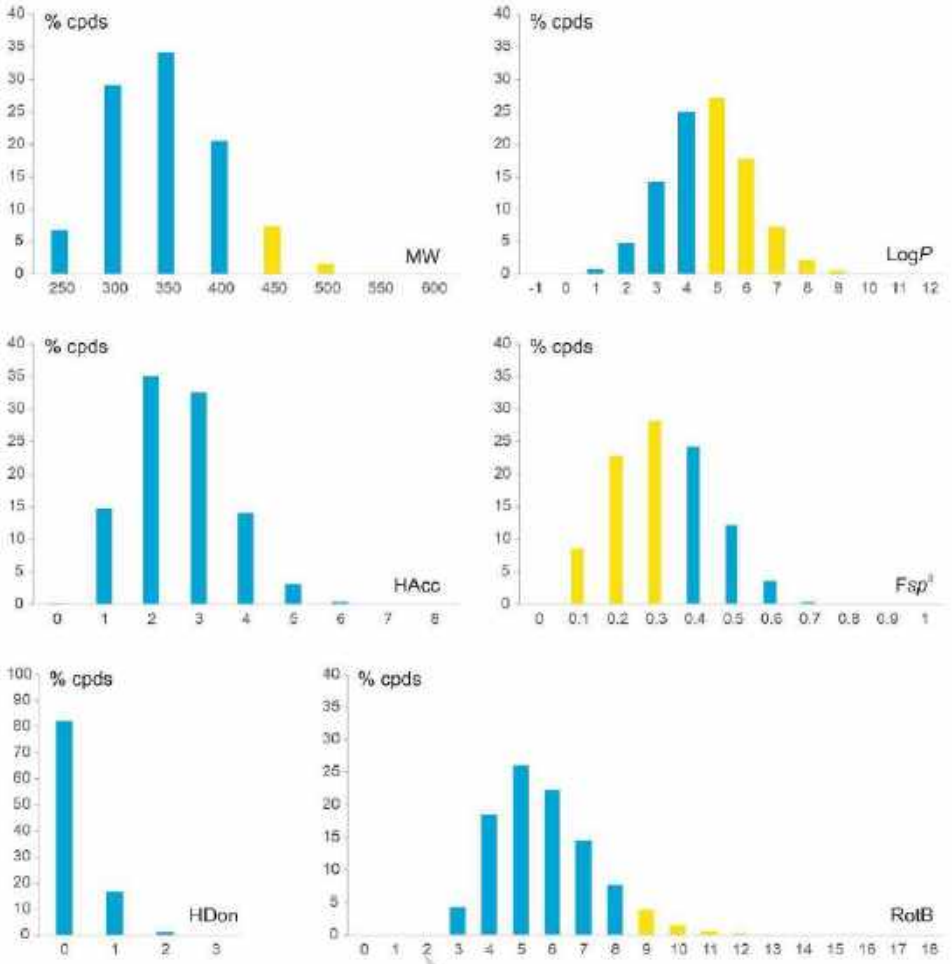


Figure 6. Physicochemical properties of the chemical space of 593 713 members obtained by virtual reductive amination – "nitrogen deletion" sequence (lead-like compounds as defined according to the extended "rule-of-four"[21] (MW ≤ 400, LogP ≤ 4, HAcc ≤ 8, HDon ≤ 4, $Fsp^3 \geq 0.4$, RotB ≤ 8) are highlighted in blue; the rest of the compounds are shown in yellow)

Comparing the generated chemical space with compounds from common chemical databases (ChemBL,[9] PubChem,[17] and ZINC15[18]), as well as Enamine's stock compound collection[19] by pairwise Tanimoto similarity analysis (MFP2 fingerprints[20]) gave average values of the similarity coefficient in the range of 0.51–0.60, which indicates that most generated members are unprecedented in the available collections (Figure 7). This is even better illustrated by applying dimension reduction methods (i.e., principal component analysis (PCA),[21] t-distributed stochastic neighbor embedding (t-SNE),[22] and uniform manifold approximation and projection (UMAP)[23]) (Figure 8, see also Figures S1 and S2 in the Supporting Information). Still, a few representatives of the generated chemical space that were found in the ChemBL database[9] had biological activity, as shown in Figure 1.

Conclusions

The reductive amination – "nitrogen deletion" reaction sequence is an efficient method for compound library synthesis that can be formally considered as a C(sp^3)–C(sp^3) coupling of two "benzylic" synthons (corresponding to (hetero)aromatic aldehydes and (het)arylmethyl amines). The method demonstrated a small positive "Log*P* drift" (+0.18 units) and therefore, cannot be formally considered lead-oriented (according to Churcher and co-workers). Also, lower efficiency was observed for compounds with MW < 250. Nevertheless, it is suitable to produce all types of compound libraries interesting to early drug discovery (i.e., lead-like, drug-like, and "beyond the rule-of-five"). Thus, a library

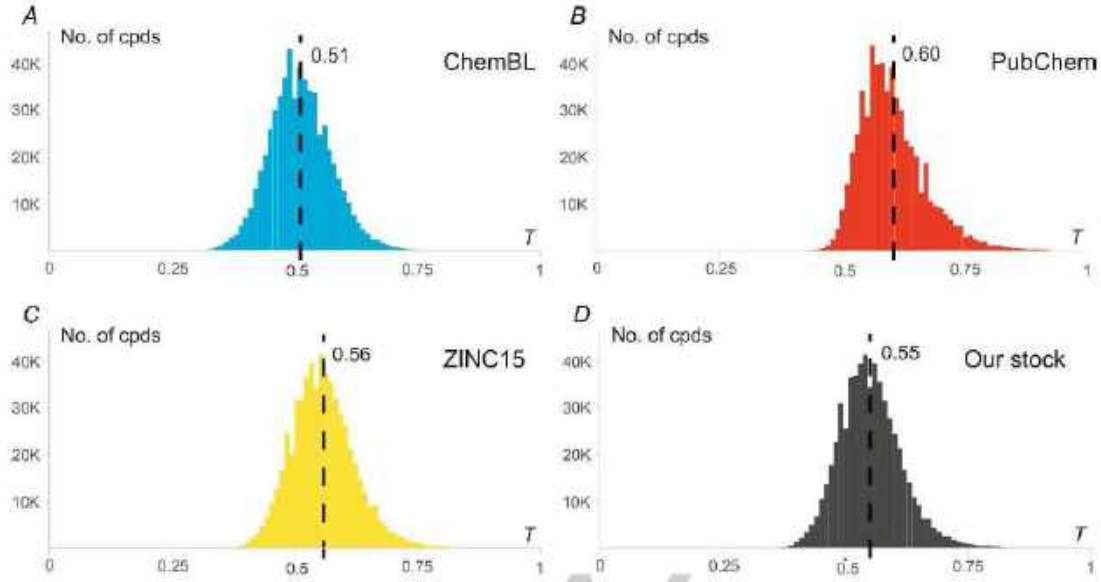


Figure 7. Distribution of maximal values among pairwise-calculated Tanimoto similarities (MFP2 fingerprints[20]) of the generated chemical space members to (*A*) ChEMBL compounds (v. 31); (*B*) PubChem compounds; (*C*) ZINC15 drug-like compounds; (*D*) Enamine's stock collection. Average values are shown by dotted lines

of 25 compounds was obtained, representing an overall 76% synthesis success rate. Moreover, this library synthesis approach allowed us to enumerate substrate features that lead to low efficiency (e.g., azine and 1,3-azole derivatives having the CHO or CH_2NH_2 group at the α position of the heterocycle), which in most cases was due to insufficient purity of the intermediate formed after reductive amination. A constrained library based on these selection criteria nonetheless generates a chemical space of 593 713 members upon virtual coupling of available starting materials. Comparing this space with ChEMBL, PubChem, and ZINC15 databases, as well as Enamine's stock showed that the compounds generated in this work are largely unprecedented in the currently available collections. Accordingly, only 13 representatives of the generated chemical space were found in the ChEMBL database, and of these, some already demonstrated biological activity.

The proposed methodology, as well as the chemical space developed, can serve an example of efforts towards alleviating the problem of over-abundance of amides (and, to a lesser extent – biaryls) in the current medicinal chemistry design and compound collections, which is due to the overwhelming popularity of classical amide and palladium-catalyzed coupling reactions in drug discovery projects.[21]

Experimental Section

All starting materials were available from Enamine Ltd. or purchased from other commercial sources. Melting points were measured on MPA100 OptiMelt automated melting point system. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on an Agilent ProPulse 600 spectrometer (at 600 MHz for ^1H NMR, 151 MHz for $^{13}C\{^1H\}$ NMR), Bruker 170 Avance 500 spectrometer (at 500 MHz for ^1H NMR, 126 MHz for $^{13}C\{^1H\}$ NMR and 470 MHz for ^{19}F NMR) or Varian Unity Plus 400 spectrometer (at 400 MHz for ^1H NMR, 101 MHz for $^{13}C\{^1H\}$ NMR and 376 MHz for ^{19}F NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standardand are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^1H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^1H and ^{13}C in DMSO-d_6. Coupling constants (*J*) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, and coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. LCMS data were recorded on Agilent 1100 HPLC equipped with diode-matrix and mass-selective detector Agilent LC/MSD SL instrument, column: Zorbax SB-C18, 4.6 mm × 15 mm; eluent, A, acetonitrile – water with 0.1% of TFA (95:5), B, water with 0.1% of TFA; flow rate: 1.8 mL/min. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)).

Parallel synthesis was performed in 10-mL or 20-mL vials; loading of the reagents, as well as work-up of the reaction mixtures was performed manually in a parallel fashion. The reactions were performed in ultrasonic baths or laboratory ovens equipped with a shaker. Centrifugal evaporators were used to remove the solvents from the vials in a parallel fashion. Preparative HPLC was performed on Agilent 1260 Infinity systems equipped with DAD and mass-detector using Chromatorex 18 SNB100-5T 100 ×19 mm, 100 A, 5μm column with SunFire C18 Prep Guard Cartridge, 100 A, 10 μm, 19 mm × 10 mm, gradient H_2O – MeCN, or H_2O – MeOH, or H_2O (with 0.2% HCO_2H) – MeOH as eluent, 30 mL/min flow.

General procedure for the preparation of library 4. Amine **3** (1 mmol) was placed into a 10-mL vial, and MeOH (2 mL), aldehyde **2** (1 mmol), and AcOH (1.2 mmol) were added. The reaction mixture was sonicated at rt for 12 h. Then $NaBH_3CN$ (2 mmol) was added, and the reaction mixture was sonicated at rt for additional 12 h. Volatiles were removed in

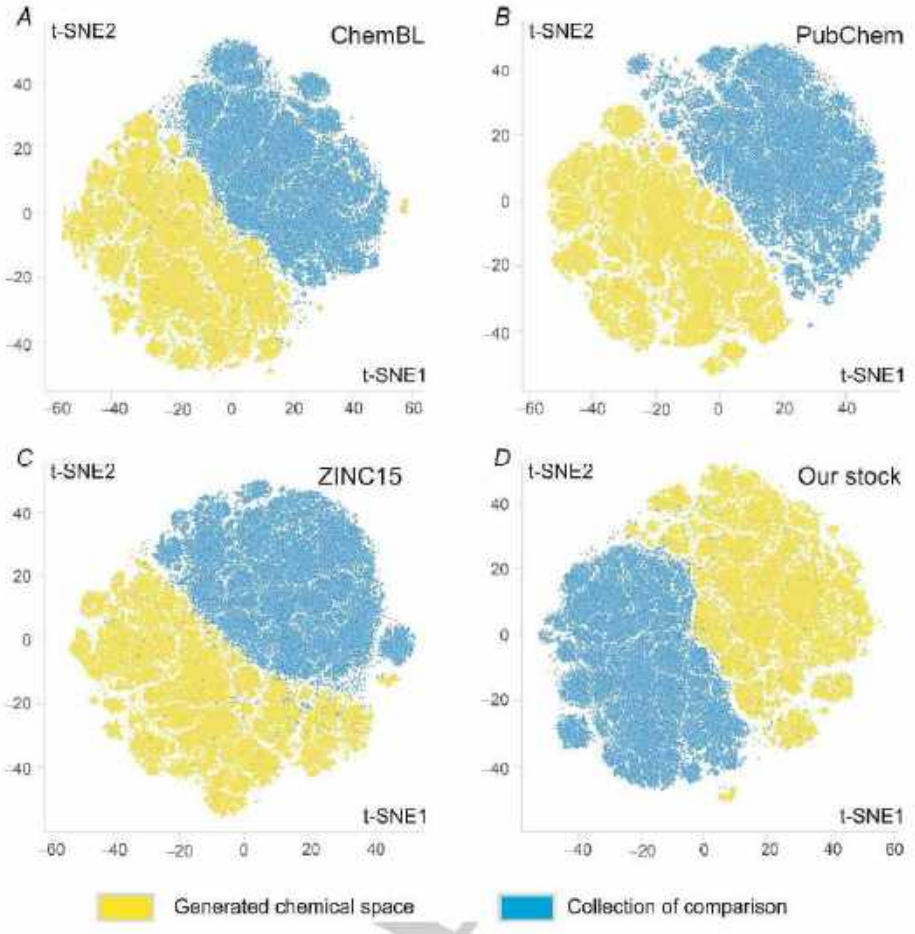


Figure 8. t-Distributed stochastic neighbor embedding (t-SNE) comparative analysis of 50K diverse molecules picked from the generated chemical space and (*A*) ChemBL compounds; (*B*) PubChem compounds; (*C*) ZINC15 compounds; (*D*) Enamine's stock collection

vacuo; the residue was treated with 10% aq Na_2CO_3 (2 mL) and extracted with CH_2Cl_2 (2×2 mL). The combined organic layers were placed into a 20-mL vial and concentrated in vacuo. The residue was dried thoroughly in vacuo and used in the next step without purification.

The vial with crude product **5** was filled with argon, and a degassed solution of anomeric amide **1** (0.3 M in dry THF, 5 mL, 1.5 mmol) was added under an argon flow (CAUTION! Compound **1** can be potentially mutagenic). The mixture was shaken in an oven at 45 °C for 16 h (CAUTION! N_2 evolution is observed), then cooled to rt, saturated aq $NaHCO_3$ (10 mL) was added, and the mixture was extracted with Et_2O (2×5 mL). The combined extracts were evaporated in vacuo, and the residue for subjected to reverse-phase HPLC purification.

For some library members, double loading was used; in this case, the yield value is marked with an asterisk (*).

3-(4-Fluorophenethyl)benzamide (4{2,1}). Yield: 174* mg (36%). Beige solid. Mp 108–111 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.77 (s, 1H), 7.72 – 7.68 (m, 1H), 7.38 – 7.29 (m, 3H), 7.25 (dd, *J* = 8.4, 5.7 Hz, 2H), 7.08 (t, *J* = 8.8 Hz, 2H), 2.97 – 2.81 (m, 4H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 168.0, 160.6 (d, *J* = 241 Hz), 141.3, 137.4 (d, *J* = 3.0 Hz), 134.3, 131.3, 130.1 (d, *J* = 8.0 Hz), 128.0, 127.6, 125.0, 114.9 (d, *J* = 20.9 Hz), 37.0, 35.9. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –117.9. LC/MS (ES-API) *m/z* = 244 [M+H]$^+$. Anal. calcd. for $C_{15}H_{14}FNO$: C 74.06, H 5.80; N 5.76. Found: C 74.30; H 5.89; N 5.70.

4-(4-Fluorophenethyl)benzamide (4{3,1}). Yield: 160* mg (33%). Colorless solid. Mp 184–185 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.90 (s, 1H), 7.78 (d, *J* = 7.8 Hz, 2H), 7.34 – 7.18 (m, 5H), 7.07 (t, *J* = 8.7 Hz, 2H), 2.94 – 2.84 (m, 4H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 167.8, 160.6 (d, *J* = 241 Hz), 144.7, 137.3 (d, *J* = 3.0 Hz), 131.9, 130.1 (d, *J* = 7.9 Hz), 128.2, 127.5, 114.8 (d, *J* = 20.9 Hz), 36.8, 35.7. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –117.9. LC/MS (ES-API) *m/z* = 244 [M+H]$^+$. Anal. calcd. for $C_{15}H_{14}FNO$: C 74.06; H 5.80; N 5.76. Found: C 74.09; H 5.62; N 5.82.

5-(4-Fluorophenethyl)pyrimidine (4{4,1}). Yield: 153* mg (38%). Yellowish solid. Mp 61–63 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.00 (s, 1H), 8.63 (s, 2H), 7.28 – 7.21 (m, 2H), 7.09 (t, *J* = 8.1 Hz, 2H), 2.93 – 2.87 (m, 4H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 160.7 (d, *J* = 242 Hz), 156.8, 156.4, 136.6 (d, *J* = 3.1 Hz), 134.4, 130.2 (d, *J* = 7.9 Hz), 115.0 (d, *J* = 21.0 Hz), 34.9, 31.2. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –117.6. LC/MS (ES-API) *m/z* = 203 [M+H]$^+$. Anal. calcd. for $C_{12}H_{11}FN_2$: C 71.27, H 5.48; N 13.85. Found: C 71.28; H 5.18; N 13.47.

4-(4-Fluorophenethyl)pyridine (4{5,1}). Yield: 78 mg (38%). Yellowish solid. Mp 68–69 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.43 (d, J = 4.9 Hz, 2H), 7.29 – 7.19 (m, 4H), 7.08 (t, J = 8.9 Hz, 2H), 2.96 – 2.79 (m, 4H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 160.7 (d, J = 241 Hz), 150.1, 149.4, 137.0 (d, J = 3.1 Hz), 130.1 (d, J = 7.9 Hz), 124.0, 114.9 (d, J = 21.0 Hz), 36.0, 34.7. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –117.8. LC/MS (ES-API) m/z = 202 [M+H]$^+$. Anal. calcd. for $C_{13}H_{12}FN$: C 77.59; H 6.01; N 6.96. Found: C 77.99; H 5.77; N 6.75.

3-(4-Fluorophenethyl)pyridine (4{6,1}). Yield: 50 mg (25%). Yellowish solid. Mp 41–43 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.43 – 8.34 (m, 2H), 7.61 (d, J = 7.8 Hz, 1H), 7.28 (dd, J = 7.8, 4.9 Hz, 1H), 7.23 (dd, J = 8.3, 5.7 Hz, 2H), 7.08 (t, J = 8.8 Hz, 2H), 2.89 – 2.87 (m, 4H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 160.6 (d, J = 241 Hz), 149.7, 147.2, 137.1 (d, J = 3.0 Hz), 136.6, 135.9, 130.2 (d, J = 7.8 Hz), 123.3, 114.9 (d, J = 21.0 Hz), 35.6, 34.0. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –117.8. LC/MS (ES-API) m/z = 202 [M+H]$^+$. Anal. calcd. for $C_{13}H_{12}FN$: C 77.59; H 6.01; N 6.96. Found: C 77.76; H 6.35; N 7.32.

5-(4-Fluorophenethyl)-1-methyl-1*H*-1,2,3-triazole (4{7,1}). Yield: 143* mg (35%). Beige solid. Mp 103–106 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.47 (s, 1H), 7.28 (dd, J = 8.2, 5.5 Hz, 2H), 7.11 (t, J = 8.8 Hz, 2H), 3.86 (s, 3H), 2.98 – 2.93 (m, 2H), 2.92 – 2.88 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 160.8 (d, J = 242 Hz), 136.7, 136.5 (d, J = 3.0 Hz), 131.7, 130.2 (d, J = 7.9 Hz), 115.0 (d, J = 21.0 Hz), 33.9, 32.4, 24.1. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –117.5. LC/MS (ES-API) m/z = 206 [M+H]$^+$. Anal. calcd. for $C_{11}H_{12}FN_3$: C 64.38; H 5.89; N 20.47. Found: C 64.13; H 5.73; N 20.54.

2-Cyclopropyl-5-(4-fluorophenethyl)thiazole (4{8,1}). Yield: 51 mg (21%). Yellowish amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.29 – 7.20 (m, 3H), 7.09 (t, J = 8.7 Hz, 2H), 3.03 (t, J = 7.7 Hz, 2H), 2.86 (t, J = 7.7 Hz, 2H), 2.31 – 2.24 (m, 1H), 1.06 – 0.95 (m, 2H), 0.88 – 0.78 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 170.7, 160.8 (d, J = 242 Hz), 139.0, 136.6 (d, J = 3.1 Hz), 135.6, 130.2 (d, J = 8.0 Hz), 114.9 (d, J = 20.9 Hz), 35.9, 28.0, 13.9, 10.4. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –117.6. LC/MS (ES-API) m/z = 248 [M+H]$^+$. Anal. calcd. for $C_{14}H_{14}FNS$: C 67.99; H 5.71; N 5.66; S 12.96. Found: C 67.63; H 5.59; N 6.03; S 12.82.

3-(4-Fluorophenethyl)pyrazolo[1,5-*a*]pyridine (4{9,1}). Yield: 30 mg (12%). Brownish amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.61 – 8.47 (m, 1H), 7.80 (s, 1H), 7.60 – 7.49 (m, 1H), 7.30 – 7.20 (m, 2H), 7.11 – 7.02 (m, 3H), 6.83 – 6.72 (m, 1H), 3.02 – 2.94 (m, 2H), 2.93 – 2.86 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 160.6 (d, J = 241 Hz), 140.7, 137.7 (d, J = 3.0 Hz), 137.4, 130.1 (d, J = 7.8 Hz), 128.5, 122.2, 116.8, 114.8 (d, J = 20.9 Hz), 111.5, 109.7, 35.4, 24.9. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –118.0. LC/MS (ES-API) m/z = 241 [M+H]$^+$. Anal. calcd. for $C_{15}H_{13}FN_2$: C 74.98; H 5.45; N 11.66. Found: C 74.66; H 5.65; N 11.99.

3-(Difluoromethyl)-5-(4-fluorophenethyl)isoxazole (4{10,1}). Yield: 37* mg (8%). Yellowish amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.34 – 7.07 (m, 5H), 6.60 (s, 1H), 3.14 (t, J = 7.7 Hz, 2H), 2.99 (t, J = 7.7 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 174.7, 160.9 (d, J = 242 Hz), 158.5 (t, J = 28.5 Hz), 136.1 (d, J = 3.1 Hz), 130.1 (d, J = 8.0 Hz), 115.0 (d, J = 21.0 Hz), 109.5 (t, J = 235 Hz), 98.8, 31.6, 27.6. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –116.4, -117.4. LC/MS (ES-API) m/z = 242 [M+H]$^+$. Anal. calcd. for $C_{12}H_{10}F_3NO$: C 59.75; H 4.18; N 5.81. Found: C 59.73; H 4.23; N 5.93.

5-(4-Fluorophenethyl)-1-methyl-1*H*-pyrazole (4{11,1}). Yield: 30* mg (7%). Brownish amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.32 – 7.22 (m, 3H), 7.10 (t, J = 8.7 Hz, 2H), 6.08 – 5.99 (m, 1H), 3.67 (s, 3H), 2.95 – 2.80 (m, 4H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 160.7 (d, J = 242 Hz), 141.6, 137.1, 137.0 (d, J = 3.0 Hz), 130.1 (d, J = 7.9 Hz), 114.9 (d, J = 21.0 Hz), 103.9, 35.8, 33.1, 26.6. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –117.7. LC/MS (ES-API) m/z = 205 [M+H]$^+$. Anal. calcd. for $C_{12}H_{13}FN_2$: C 70.57; H 6.42; N 13.72. Found: C 70.40; H 6.54; N 13.76.

4-(4-Fluorophenethyl)-1-methyl-1*H*-pyrazole (4{12,1}). Yield: 21* mg (5%). Yellowish amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.41 (s, 1H), 7.23 (dd, J = 8.3, 5.6 Hz, 2H), 7.19 (s, 1H), 7.08 (t, J = 8.7 Hz, 2H), 3.74 (s, 3H), 2.79 (t, J = 7.8 Hz, 2H), 2.67 (t, J = 7.8 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 160.6 (d, J = 241 Hz), 137.8, 137.7 (d, J = 3.1 Hz), 130.0 (d, J = 7.9 Hz), 128.6, 119.9, 114.8 (d, J = 21.0 Hz), 38.3, 35.6, 25.6. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –118.1. LC/MS (ES-API) m/z = 205 [M+H]$^+$. Anal. calcd. for $C_{12}H_{13}FN_2$: C 70.57; H 6.42; N 13.72. Found: C 70.29; H 6.29; N 13.52.

2-(4-Fluorophenethyl)pyrazine (4{13,1}). Yield: 18* mg (4%). Yellowish amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 – 8.54 (m, 1H), 8.50 (s, 1H), 8.48 – 8.43 (m, 1H), 7.25 – 7.20 (m, 2H), 7.10 – 7.05 (m, 2H), 3.07 (t, J = 7.1 Hz, 2H), 3.00 (t, J = 7.1 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 160.7 (d, J = 241 Hz), 156.2, 144.5, 144.0, 142.4, 137.0 (d, J = 3.1 Hz), 130.1 (d, J = 7.9 Hz), 114.9 (d, J = 21.0 Hz), 36.2, 33.5. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –117.8. LC/MS (ES-API) m/z = 203 [M+H]$^+$. Anal. calcd. for $C_{12}H_{11}FN_2$: C 71.27; H 5.48; N 13.85. Found: C 71.34; H 5.16; N 14.21.

3-(4-Fluorophenethyl)-6,7-dihydro-4*H*-pyrano[3,4-*d*]isoxazole (4{1,2}). Yield: 223* mg (45%). Yellowish amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.26 (dd, J = 8.4, 5.6 Hz, 2H), 7.09 (t, J = 8.7 Hz, 2H), 4.40 (s, 2H), 3.82 (t, J = 5.6 Hz, 2H), 2.89 – 2.83 (m, 4H), 2.76 (t, J = 5.6 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 164.9, 160.8 (d, J = 242 Hz), 158.6, 136.7 (d, J = 3.1 Hz), 130.2 (d, J = 7.9 Hz), 114.9 (d, J = 21.0 Hz), 110.8, 63.0, 61.1, 32.0, 26.4, 23.7. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –117.6. LC/MS (ES-API) m/z = 248 [M+H]$^+$. Anal. calcd. for $C_{14}H_{14}FNO_2$: C 68.00; H 5.71; N 5.66. Found: C 67.74; H 5.44; N 5.26.

1-(4-(4-Fluorophenethyl)phenyl)-1*H*-imidazole (4{1,3}). Yield: 104 mg (39%). Beige solid. Mp 66–68 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.75 – 7.65 (m, 1H), 7.54 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 7.28 – 7.21 (m, 2H), 7.14 – 7.00 (m, 3H), 2.98 – 2.81 (m, 4H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 160.6 (d, J = 241 Hz), 140.1, 137.4 (d, J = 3.0 Hz), 135.4, 134.9, 130.1 (d, J = 7.9 Hz, 2C), 129.7 (3C), 120.1 (2C), 117.9, 114.8 (d, J = 20.9 Hz, 2C), 36.3, 35.9. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –117.9. LC/MS (ES-API) m/z = 267 [M+H]$^+$. Anal. calcd. for $C_{17}H_{15}FN_2$: C 76.67; H 5.68; N 10.52. Found: C 77.04; H 5.49; N 10.36.

6-(4-Fluorophenethyl)isoindolin-1-one (4{1,4}). Yield: 84 mg (33%). Beige solid. Mp 196–199 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.49 (s, 1H), 7.51 (s, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.29 – 7.20 (m, 2H), 7.07 (t, J = 8.8 Hz, 2H), 4.31 (s, 2H), 2.96 (t, J = 7.4 Hz, 2H), 2.89 (t, J = 7.4 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 170.0, 160.6 (d, J = 241 Hz), 141.7, 141.0, 137.4 (d, J = 3.1 Hz), 132.7, 131.7, 130.1 (d, J = 7.8 Hz), 123.4, 122.5, 114.8 (d, J = 21.0 Hz), 44.7, 36.8, 36.2. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –117.9. LC/MS (ES-API) m/z = 256 [M+H]$^+$. Anal. calcd. for $C_{16}H_{14}FNO$: C 75.28; H 5.53; N 5.49. Found: C 74.95; H 5.38; N 5.66.

2-(4-(4-Fluorophenethyl)phenyl)isothiazolidine 1,1-dioxide (4{1,5}). Yield: 74 mg (27%). Colorless solid. Mp 134–136 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.24 (dd, J = 8.4, 5.7 Hz, 2H), 7.21 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 7.08 (t, J = 8.8 Hz, 2H), 3.70 (t, J = 6.5 Hz, 2H), 3.48 (t, J = 7.5 Hz, 2H), 2.91 – 2.78 (m, 4H), 2.43 – 2.33 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 160.6 (d, J = 241 Hz), 137.5 (d, J = 3.1 Hz), 136.5, 136.0, 130.1 (d, J = 7.9 Hz), 129.1, 118.5, 114.8 (d, J = 20.9 Hz), 48.1, 46.5, 36.3, 36.1, 18.4. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –118.0. LC/MS (ES-API) m/z = 320 [M+H]$^+$. Anal. calcd. for $C_{17}H_{18}FNO_2S$: C 63.93; H 5.68; N 4.39; S 10.04. Found: C 63.80; H 5.60; N 4.59; S 9.90.

5-(4-Fluorophenethyl)-1-methyl-1*H*-benzo[*d*]imidazole (4{1,6}). Yield: 17 mg (7%). Yellowish solid. Mp 97–100 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.49 – 7.41 (m, 2H), 7.29 – 7.21 (m, 2H), 7.13 (d, J = 8.3 Hz, 1H), 7.06 (t, J = 8.9 Hz, 2H), 3.80 (s, 3H), 2.97 (t, J = 7.4 Hz, 2H), 2.91 (t, J = 7.4 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 160.6 (d, J

= 241 Hz), 144.4, 143.3, 137.7 (d, *J* = 3.2 Hz), 134.6, 133.0, 130.1 (d, *J* = 7.9 Hz), 123.2, 118.5, 114.8 (d, *J* = 20.9 Hz), 109.7, 37.2, 36.8, 30.7. ^{19}F{^{1}H} NMR (376 MHz, DMSO-*d*$_6$) δ –118.1. LC/MS (ES-API) *m/z* = 255 [M+H]$^+$. Anal. calcd. for $C_{15}H_{15}FN_2$: C 75.57; H 5.95; N 11.02. Found: C 75.20; H 6.25; N 11.33.

3-(4-Fluorophenethyl)-4-phenyl-4*H*-1,2,4-triazole (4{*1,7*}). Yield: 17 mg (6%). Yellowish amorphous solid. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.66 (s, 1H), 7.62 – 7.48 (m, 3H), 7.43 (d, *J* = 7.4 Hz, 2H), 7.16 – 7.09 (m, 2H), 7.03 (t, *J* = 8.7 Hz, 2H), 2.99 – 2.94 (m, 2H), 2.83 – 2.88 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ 160.8 (d, *J* = 242 Hz), 152.3, 144.0, 136.6 (d, *J* = 3.2 Hz), 133.9, 130.0 (d, *J* = 8.0 Hz), 129.8, 129.1, 125.6, 114.9 (d, *J* = 21.0 Hz), 31.6, 26.2. ^{19}F{^{1}H} NMR (376 MHz, DMSO-*d*$_6$) δ –117.5. LC/MS (ES-API) *m/z* = 268 [M+H]$^+$. Anal. calcd. for $C_{16}H_{14}FN_3$: C 71.89; H 5.28; N 15.72. Found: C 71.65; H 5.41; N 15.71.

1-(4-(4-Fluorophenethyl)phenyl)urea (4{*1,8*}). Yield: 13 mg (4%). Colorless solid. Mp 174–177 °C. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.39 (s, 1H), 7.27 (d, *J* = 7.3 Hz, 2H), 7.24 – 7.18 (m, 2H), 7.10 – 7.00 (m, 4H), 5.76 (s, 2H), 2.85 – 2.79 (m, 2H), 2.79 – 2.72 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ 160.6 (d, *J* = 241 Hz), 156.0, 138.4, 137.7 (d, *J* = 2.9 Hz), 133.8, 130.1 (d, *J* = 7.9 Hz), 128.4, 117.7, 114.8 (d, *J* = 20.9 Hz), 36.4, 36.3. ^{19}F{^{1}H} NMR (376 MHz, DMSO-*d*$_6$) δ –118.1. LC/MS (ES-API) *m/z* = 259 [M+H]$^+$. Anal. calcd. for $C_{15}H_{15}FN_2O$: C 69.75; H 5.85; N 10.85. Found: C 69.54; H 5.90; N 11.02.

3-(2-(4,6-Dihydrofuro[3,4-*d*]isoxazol-3-yl)ethyl)-4-fluorobenzonitrile (4{*19,12*}). Yield: 263* mg (51%). Yellowish solid. Mp 63–65 °C. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 7.93 (d, *J* = 6.2 Hz, 1H), 7.85 – 7.77 (m, 1H), 7.41 (t, *J* = 9.2 Hz, 1H), 4.81 (t, *J* = 3.2 Hz, 2H), 4.67 (t, *J* = 3.2 Hz, 2H), 2.99 – 2.93 (m, 4H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ 176.2, 163.1 (d, *J* = 253 Hz), 156.9, 135.4 (d, *J* = 6.3 Hz), 133.3 (d, *J* = 9.8 Hz), 129.0 (d, *J* = 17.3 Hz), 121.6, 118.1, 116.9 (d, *J* = 23.9 Hz), 107.7 (d, *J* = 3.5 Hz), 64.7, 64.0, 25.8, 24.4. ^{19}F{^{1}H} NMR (376 MHz, DMSO-*d*$_6$) δ –109.3. LC/MS (ES-API) *m/z* = 259 [M+H]$^+$. Anal. calcd. for $C_{14}H_{11}FN_2O_2$: C 65.11; H 4.29; N 10.85. Found: C 64.77; H 4.37; N 10.94.

***N*-(5-(2-(4,6-Dihydrofuro[3,4-*d*]isoxazol-3-yl)ethyl)pyridin-2-yl)acetamide (4{*19,14*}).** Yield: 214* mg (39%). Yellowish solid. Mp 163–166 °C. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 10.41 (s, 1H), 8.15 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 4.79 (t, *J* = 3.2 Hz, 2H), 4.60 (t, *J* = 3.2 Hz, 2H), 2.93 (t, *J* = 7.5 Hz, 2H), 2.84 (t, *J* = 7.5 Hz, 2H), 2.07 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ 176.0, 169.1, 157.3, 150.6, 147.5, 137.9, 130.8, 121.7, 113.0, 64.7, 64.0, 29.5, 25.8, 23.8. LC/MS (ES-API) *m/z* = 274 [M+H]$^+$. Anal. calcd. for $C_{14}H_{15}N_3O_3$: C 61.53; H 5.53; N 15.38. Found: C 61.75; H 5.80; N 15.77.

1-Methyl-5-(2-[3-(pentafluoro-λ^5-sulfanyl)phenyl]ethyl)-1*H*-pyrazole (4{*11,13*}). Yield: 132 mg (42%). Beige solid. Mp 63–64 °C. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 7.79 (s, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.53 (t, *J* = 7.9 Hz, 1H), 7.32 – 7.19 (m, 1H), 6.11 – 5.97 (m, 1H), 3.68 (s, 3H), 3.01 (t, *J* = 7.7 Hz, 2H), 2.94 (t, *J* = 7.7 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ 153.5 – 152.3 (m), 142.8, 141.3, 137.1, 132.6, 129.3, 125.9 – 124.9 (m), 123.7 – 123.0 (m), 104.1, 35.8, 33.6, 26.2. ^{19}F{^{1}H} NMR (376 MHz, DMSO-*d*$_6$) δ 87.2 (quint, *J* = 151 Hz, 1F), 63.57 (d, *J* = 151 Hz, 4F). LC/MS (ES-API) *m/z* = 313 [M+H]$^+$. Anal. calcd. for $C_{12}H_{13}F_5N_2S$: C 46.15; H 4.20; N 8.97. Found: C 45.79; H 4.42; N 8.57.

2-(Difluoromethoxy)-3-(2-(1-methyl-1*H*-pyrazol-5-yl)ethyl)pyridine (4{*11,16*}). Yield: 62 mg (24%). Yellowish amorphous solid. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.16 – 8.09 (m, 1H), 7.92 – 7.53 (m, 2H), 7.28 – 7.24 (m, 1H), 7.21 (dd, *J* = 7.4, 5.0 Hz, 1H), 6.07 – 5.96 (m, 1H), 3.71 (s, 3H), 2.92 – 2.88 (m, 4H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ 156.5 (t, *J* = 3.3 Hz), 144.9, 141.1, 140.5, 137.2, 123.4, 120.7, 114.9 (t, *J* = 254 Hz), 104.0, 35.7, 27.7, 24.3. ^{19}F{^{1}H} NMR (376 MHz, DMSO-*d*$_6$) δ –87.5. LC/MS (ES-API) *m/z* = 254 [M+H]$^+$. Anal. calcd. for $C_{12}H_{13}F_2N_3O$: C 56.91; H 5.17; N 16.59. Found: C 56.66; H 5.19; N 16.35.

3-(2-(Isoquinolin-4-yl)ethyl)-6,7-dihydro-4*H*-pyrano[3,4-*d*]isoxazole (4{*23,2*}). Yield: 65 mg (23%). Yellowish solid. Mp 108–111 °C. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.81 (d, *J* = 2.2 Hz, 1H), 8.18 (s, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 4.49 (s, 2H), 3.82 (t, *J* = 5.5 Hz, 2H), 3.10 (t, *J* = 7.5 Hz, 2H), 3.03 (t, *J* = 7.5 Hz, 2H), 2.76 (t, *J* = 5.5 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ 165.0, 158.4, 151.8, 146.4, 134.2, 133.5, 128.8, 128.6, 127.61, 127.59, 126.6, 110.8, 63.0, 61.1, 29.9, 25.9, 23.7. LC/MS (ES-API) *m/z* = 281 [M+H]$^+$. Anal. calcd. for $C_{17}H_{16}N_2O_2$: C 72.84; H 5.75; N 9.99. Found: C 73.17; H 5.61; N 9.80.

2-(4-(2-(1-(*tert*-Butyl)-1H-pyrazol-4-yl)ethyl)phenyl)isothiazolidine 1,1-dioxide (4{*23,2*}). Yield: 37 mg (10%). Beige solid. Mp 112–119 °C. ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 7.56 (s, 1H), 7.25 (s, 1H), 7.22 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 3.70 (t, *J* = 6.5 Hz, 2H), 3.47 (t, *J* = 7.5 Hz, 2H), 2.82 – 2.75 (m, 2H), 2.71 – 2.63 (m, 2H), 2.44 – 2.33 (m, 2H), 1.47 (s, 9H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-*d*$_6$) δ 137.2, 137.1, 136.0, 129.0, 124.4, 119.4, 118.6, 57.5, 48.1, 46.6, 35.9, 29.5, 26.0, 18.4. LC/MS (ES-API) *m/z* = 348 [M+H]$^+$. Anal. calcd. for $C_{16}H_{25}N_3O_2S$: C 62.22; H 7.25; N 12.09; S 9.23. Found: C 62.09; H 7.00; N 12.17; S 9.53.

3-(2-(1*H*-Indazol-4-yl)ethyl)benzamide (4{*2,19*}). Yield: 32* mg (6%). Beige solid. Mp 177–179 °C. ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 13.03 (s, 1H), 8.21 (s, 1H), 7.98 (br s, 1H), 7.85 (s, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.38 – 7.30 (m, 3H), 7.24 (dd, *J* = 8.3, 6.9 Hz, 1H), 6.92 (d, *J* = 6.9 Hz, 1H), 3.24 – 3.19 (m, 2H), 3.08 – 3.01 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-*d*$_6$) δ 168.0, 141.6, 139.9, 134.3, 134.2, 132.3, 131.3, 128.1, 127.5, 126.0, 125.2, 122.7, 119.2, 107.9, 36.2, 34.7. LC/MS (ES-API) *m/z* = 266 [M+H]$^+$. Anal. calcd. for $C_{16}H_{15}N_3O$: C 72.43; H 5.70; N 15.84. Found: C 72.83; H 5.64; N 16.01.

(5-(2-(Isoxazol-3-yl)ethyl)pyridin-2-yl)dimethylphosphine oxide (4{*19,20*}). Yield: 37* mg (7%). Beige solid. Mp 122–125 °C. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.82 – 8.78 (m, 1H), 8.65 (s, 1H), 7.89 – 7.78 (m, 2H), 6.56 – 6.51 (m, 1H), 3.10 – 2.97 (m, 4H), 1.63 (d, *J* = 13.5 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ 161.5, 159.6, 155.8 (d, *J* = 125 Hz), 150.2 (d, *J* = 18.5 Hz), 138.2 (d, *J* = 2.8 Hz), 136.2 (d, *J* = 8.9 Hz), 125.5 (d, *J* = 20.3 Hz), 104.4, 30.3, 26.2, 16.3 (d, *J* = 70.9 Hz). LC/MS (ES-API) *m/z* = 251 [M+H]$^+$. Anal. calcd. for $C_{12}H_{15}N_2O_2P$: C 57.60; H 6.04; N 11.19. Found: C 57.87; H 6.42; N 11.29.

5-(2-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)ethyl)imidazo[2,1-*b*]thiazole (4{*27,21*}). Yellowish solid. Mp 91–94 °C. Yield: 32* mg (6%). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 7.84 (d, *J* = 4.5 Hz, 1H), 7.22 (d, *J* = 4.5 Hz, 1H), 6.95 (s, 1H), 6.79 – 6.72 (m, 2H), 6.71 – 6.67 (m, 1H), 4.23 – 4.17 (m, 4H), 3.01 (t, *J* = 7.9 Hz, 2H), 2.80 (t, *J* = 7.9 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ 147.1, 143.1, 141.6, 133.9, 130.9, 126.0, 121.1, 118.4, 116.9, 116.7, 112.5, 64.0, 63.9, 33.0, 26.0. LC/MS (ES-API) *m/z* = 287 [M+H]$^+$. Anal. calcd. for $C_{15}H_{14}N_2O_2S$: C 62.92; H 4.93; N 9.78; S 11.20. Found: C 62.91; H 5.12; N 9.66; S 11.16.

2-Cyclopropyl-5-(2-(pyrazolo[1,5-*a*]pyrimidin-6-yl)ethyl)-1,3,4-thiadiazole (4{*28,22*}). Yield: 18* mg (3%). Brownish solid. Mp 133–135 °C. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 9.07 – 8.99 (m, 1H), 8.53 (d, *J* = 2.1 Hz, 1H), 8.15 (d, *J* = 2.3 Hz, 1H), 6.68 (d, *J* = 2.3 Hz, 1H), 3.44 (t, *J* = 7.6 Hz, 2H), 3.11 (t, *J* = 7.6 Hz, 2H), 2.50 – 2.41 (m, 1H), 1.21 – 1.12 (m, 2H), 1.00 – 0.90 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ 172.9, 166.6, 151.5, 146.9, 144.4, 133.9, 120.4, 95.7, 29.9, 28.4, 11.0, 10.9. LC/MS (ES-API) *m/z* = 272 [M+H]$^+$. Anal. calcd. for $C_{13}H_{13}N_5S$: C 57.55; H 4.83; N 25.81; S 11.82. Found: C 57.40; H 4.69; N 25.86; S 11.70.

***N*-(5-(2-(Quinoxalin-6-yl)ethyl)pyridin-2-yl)acetamide (4{*20,14*}).** Yield: 114 mg (39%). Beige solid. Mp 171–172 °C. ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 10.36 (s, 1H), 8.89 (d, *J* = 1.8 Hz, 1H), 8.87 (d, *J* = 1.8 Hz, 1H), 8.12 (d, *J* = 2.4 Hz, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.97 (d, *J* = 8.6 Hz, 1H), 7.87 (d, *J* = 1.9 Hz, 1H), 7.76 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.65 (dd, *J* = 8.6, 2.4 Hz, 1H), 3.14 (t, *J* = 7.8 Hz, 2H), 2.98 (t, *J* = 7.8 Hz, 2H), 2.06 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-*d*$_6$) δ 169.0, 150.3, 147.5, 145.6,

145.0, 143.7, 142.2, 141.0, 137.9, 131.6, 131.5, 128.8, 127.7, 112.9, 36.5, 32.9, 23.8. LC/MS (ES-API) *m/z* = 293 [M+H]⁺. Anal. calcd. for $C_{17}H_{16}N_4O$: C 69.85; H 5.52; N 19.17. Found: C 70.05; H 5.43; N 19.55.

3-(2-(Quinolin-3-yl)ethyl)-6,7-dihydro-4*H*-pyrano[3,4-*d*]isoxazole (4{*21,2*}). Yield: 97 mg (35%). Colorless solid. Mp 94–97 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.81 (d, *J* = 2.2 Hz, 1H), 8.18 (d, *J* = 2.2 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.72 – 7.66 (m, 1H), 7.61 – 7.54 (m, 1H), 4.49 (s, 2H), 3.82 (t, *J* = 5.5 Hz, 2H), 3.10 (t, *J* = 7.5 Hz, 2H), 3.03 (t, *J* = 7.5 Hz, 2H), 2.76 (t, *J* = 5.5 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 165.0, 158.4, 151.8, 146.4, 134.2, 133.5, 128.8, 128.6, 127.60, 127.59, 126.6, 110.8, 63.0, 61.1, 29.9, 25.9, 23.7. LC/MS (ES-API) *m/z* = 281 [M+H]⁺. Anal. calcd. for $C_{17}H_{16}N_2O_2$: C 72.84; H 5.75; N 9.99. Found: C 72.93; H 5.52; N 10.34.

3-(2-(2-Cyclopropylthiazol-5-yl)ethyl)-6,7-dihydro-4*H*-pyrano[3,4-*d*]isoxazole (4{*8,2*}). Yield: 94 mg (34%). Yellowish solid. Mp 59–61 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.30 (s, 1H), 4.47 (t, *J* = 1.7 Hz, 2H), 3.84 (t, *J* = 5.5 Hz, 2H), 3.05 (t, *J* = 7.5 Hz, 2H), 2.88 (t, *J* = 7.5 Hz, 2H), 2.78 (tt, *J* = 5.5, 1.7 Hz, 2H), 2.33 – 2.25 (m, 1H), 1.08 – 1.02 (m, 2H), 0.89 – 0.85 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 171.1, 165.1, 158.1, 139.3, 134.9, 110.8, 63.0, 61.1, 26.5, 24.0, 23.7, 13.9, 10.4. LC/MS (ES-API) *m/z* = 277 [M+H]⁺. Anal. calcd. for $C_{14}H_{16}N_2O_2S$: C 60.85; H 5.84; N 10.14; S 11.60. Found: C 60.55; H 6.15; N 10.15; S 11.69.

1-(4-(2-(Quinoxalin-6-yl)ethyl)phenyl)urea (4{*20,8*}). Yield: 97 mg (33%). Beige solid. Mp 208–211 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.89 (d, *J* = 1.8 Hz, 1H), 8.87 (d, *J* = 1.8 Hz, 1H), 8.40 (s, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.87 (s, 1H), 7.75 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 5.78 (s, 2H), 3.11 (t, *J* = 7.9 Hz, 2H), 2.93 (t, *J* = 7.9 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 156.0, 145.5, 144.9, 144.2, 142.3, 141.0, 138.5, 133.6, 131.7, 128.7, 128.5, 127.5, 117.7, 37.0, 35.8. LC/MS (ES-API) *m/z* = 293 [M+H]⁺. Anal. calcd. for $C_{17}H_{16}N_4O$: C 69.85; H 5.52; N 19.17. Found: C 69.59; H 5.79; N 18.85.

5-(5-Fluoro-2-methoxyphenethyl)pyrimidine (4{*4,15*}). Yield: 66 mg (28%). Yellowish amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.00 (s, 1H), 8.57 (s, 2H), 7.03 – 6.95 (m, 2H), 6.94 – 6.89 (m, 1H), 3.70 (s, 3H), 2.91 – 2.79 (m, 4H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 156.7, 156.3, 156.0 (d, *J* = 236 Hz), 153.3 (d, *J* = 1.4 Hz), 134.5, 130.2 (d, *J* = 7.3 Hz), 116.4 (d, *J* = 23.0 Hz), 113.2 (d, *J* = 22.5 Hz), 111.8 (d, *J* = 8.5 Hz), 55.8, 30.3, 29.4. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –124.7. LC/MS (ES-API) *m/z* = 233 [M+H]⁺. Anal. calcd. for $C_{13}H_{13}FN_2O$: C 67.23; H 5.64; N 12.06. Found: C 66.83; H 5.28; N 12.01.

4-(2-(1-Methyl-1*H*-pyrazol-4-yl)ethyl)isoquinoline (4{*23,18*}). Yield: 53 mg (22%). Yellowish amorphous solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.17 (s, 1H), 8.34 (s, 1H), 8.18 – 8.08 (m, 2H), 7.82 (t, *J* = 7.6 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.50 (s, 1H), 7.28 (s, 1H), 3.76 (s, 3H), 3.26 – 3.20 (m, 2H), 2.83 – 2.76 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 151.0, 142.5, 137.9, 133.9, 130.52, 130.50, 128.8, 128.2, 128.0, 127.0, 122.9, 119.9, 38.3, 30.8, 24.9. LC/MS (ES-API) *m/z* = 238 [M+H]⁺. Anal. calcd. for $C_{15}H_{15}N_3$: C 75.92; H 6.37; N 17.71. Found: C 76.22; H 6.41; N 17.47.

5-(2-(1-Methyl-1*H*-1,2,3-triazol-5-yl)ethyl)benzo[*d*]thiazole (4{*24,17*}). Yield: 52 mg (21%). Colorless solid. Mp 171–172 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.37 (s, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 8.00 (s, 1H), 7.50 (s, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 3.89 (s, 3H), 3.14 – 2.93 (m, 4H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 156.2, 153.4, 138.9, 136.8, 131.8, 131.3, 126.3, 122.5, 122.2, 33.9, 33.0, 24.2. LC/MS (ES-API) *m/z* = 245 [M+H]⁺. Anal. calcd. for $C_{12}H_{12}N_4S$: C 58.99; H 4.95; N 22.93; S 13.12. Found: C 58.89; H 4.71; N 23.28; S 13.07.

5-(4-(1*H*-Imidazol-1-yl)phenethyl)pyrimidine (4{*4,3*}). Yield: 53 mg (21%). Yellowish solid. Mp 106–108 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.01 (s, 1H), 8.66 (s, 2H), 8.23 (s, 1H), 7.75 – 7.67 (m, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.15 – 7.07 (m, 1H), 3.02 – 2.89 (m, 4H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 156.8, 156.4, 139.3, 135.4, 135.1, 134.4, 129.81, 129.77, 120.2, 118.0, 35.1, 31.0. LC/MS (ES-API) *m/z* = 251 [M+H]⁺. Anal. calcd. for $C_{15}H_{14}N_4$: C 71.98; H 5.64; N 22.38. Found: C 72.03; H 5.76; N 22.53.

3-(2-(1-Methyl-1*H*-1,2,3-triazol-5-yl)ethyl)quinoline (4{*21,17*}). Yield: 45 mg (19%). Colorless solid. Mp 127–130 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.85 (s, 1H), 8.20 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.71 (t, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.52 (s, 1H), 3.93 (s, 3H), 3.18 – 3.05 (m, 4H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 151.8, 146.4, 136.6, 134.2, 133.3, 131.8, 128.8, 128.7, 127.58, 127.56, 126.6, 34.0, 30.4, 23.5. LC/MS (ES-API) *m/z* = 239 [M+H]⁺. Anal. calcd. for $C_{14}H_{14}N_4$: C 70.57; H 5.92; N 23.51. Found: C 70.46; H 6.19; N 23.35.

2-Cyclopropyl-5-(2-(4-phenyl-4*H*-1,2,4-triazol-3-yl)ethyl)thiazole (4{*8,7*}). Yield: 45 mg (15%). Yellowish amorphous solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.68 (s, 1H), 7.60 – 7.51 (m, 3H), 7.46 – 7.41 (m, 2H), 7.19 (s, 1H), 3.11 (t, *J* = 7.3 Hz, 2H), 2.98 (t, *J* = 7.3 Hz, 2H), 2.28 – 2.20 (m, 1H), 1.05 – 0.97 (m, 2H), 0.87 – 0.80 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 171.1, 151.8, 144.1, 139.3, 134.7, 133.8, 129.8, 129.1, 125.5, 26.2, 23.9, 13.8, 10.4. LC/MS (ES-API) *m/z* = 297 [M+H]⁺. Anal. calcd. for $C_{16}H_{16}N_4S$: C 64.84; H 5.44; N 18.90; S 10.82. Found: C 64.61; H 5.20; N 19.09; S 10.55.

4-(2-(4-Phenyl-4*H*-1,2,4-triazol-3-yl)ethyl)isoquinoline (4{*23,7*}). Yield: 43 mg (14%). Yellowish solid. Mp 149–150 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.72 – 8.66 (m, 2H), 8.04 (s, 1H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.68 (t, *J* = 8.1 Hz, 1H), 7.60 – 7.48 (m, 4H), 7.44 (d, *J* = 7.0 Hz, 2H), 3.20 – 3.08 (m, 4H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 152.2, 151.7, 146.4, 144.1, 134.1, 133.8, 133.4, 129.8, 129.1, 128.8, 128.6, 127.6, 127.5, 126.5, 125.5, 29.6, 25.7. LC/MS (ES-API) *m/z* = 301 [M+H]⁺. Anal. calcd. for $C_{19}H_{16}N_4$: C 75.98; H 5.37; N 18.65. Found: C 75.59; H 5.22; N 18.83.

3-(4-(1*H*-Imidazol-1-yl)phenethyl)-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole (4{*25,3*}). Yield: 36 mg (13%). Yellowish amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.73 – 7.67 (m, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.22 (s, 1H), 7.13 – 7.05 (m, 1H), 3.96 (t, *J* = 7.2 Hz, 2H), 2.83 (t, *J* = 7.7 Hz, 2H), 2.67 (t, *J* = 7.6 Hz, 2H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.48 – 2.40 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 143.0, 142.0, 140.5, 135.4, 134.9, 129.72, 129.68, 120.1, 118.0, 112.0, 47.0, 35.5, 26.0, 25.5, 21.6. LC/MS (ES-API) *m/z* = 279 [M+H]⁺. Anal. calcd. for $C_{17}H_{18}N_4$: C 73.35; H 6.52; N 20.13. Found: C 73.46; H 6.87; N 20.11.

2-(4-(2-(Pyrazolo[1,5-*a*]pyridin-3-yl)ethyl)phenyl)isothiazolidine 1,1-dioxide (4{*9,5*}). Yield: 26 mg (8%). Colorless solid. Mp 132–134 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.56 (d, *J* = 7.0 Hz, 1H), 7.81 (s, 1H), 7.59 (d, *J* = 8.9 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.13 – 7.08 (m, 3H), 6.79 (t, *J* = 7.0 Hz, 1H), 3.70 (t, *J* = 6.5 Hz, 2H), 3.48 (t, *J* = 7.4 Hz, 2H), 2.98 (t, *J* = 7.7 Hz, 2H), 2.89 (t, *J* = 7.7 Hz, 2H), 2.41 – 2.35 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 140.7, 137.4, 136.9, 136.0, 129.1, 128.5, 122.2, 118.6, 116.8, 111.5, 109.9, 48.1, 46.5, 35.5, 24.9, 18.4. LC/MS (ES-API) *m/z* = 342 [M+H]⁺. Anal. calcd. for $C_{18}H_{19}N_3O_2S$: C 63.32; H 5.61; N 12.31; S 9.39. Found: C 63.13; H 5.76; N 12.57; S 9.28.

6-(2-(4-Phenyl-4*H*-1,2,4-triazol-3-yl)ethyl)quinoxaline (4{*20,7*}). Yield: 23 mg (8%). Yellowish solid. Mp 128–131 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 (d, *J* = 5.5 Hz, 2H), 8.68 (s, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.79 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.56 – 7.49 (m, 3H), 7.44 (d, *J* = 6.5 Hz, 2H), 3.20 (t, *J* = 7.0 Hz, 2H), 3.15 (t, *J* = 7.0 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 152.2, 145.6, 145.1, 144.0, 143.0, 142.2, 141.0, 133.8, 131.4, 129.7, 129.1, 128.9, 127.6, 125.5, 32.3, 25.7. LC/MS (ES-API) *m/z* = 302 [M+H]⁺. Anal. calcd. for $C_{18}H_{15}N_5$: C 71.74; H 5.02; N 23.24. Found: C 71.71; H 4.74; N 23.42.

1-Methyl-5-(2-(pyridin-3-yl)ethyl)-1*H*-benzo[*d*]imidazole (4(5,6)). Yield: 17 mg (7%). Colorless solid. Mp 121–122 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.39 (d, *J* = 1.9 Hz, 1H), 8.37 (dd, *J* = 4.8, 1.9 Hz, 1H), 8.10 (s, 1H), 7.65 – 7.60 (m, 1H), 7.46 (s, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.27 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 3.80 (s, 3H), 3.04 – 2.98 (m, 2H), 2.97 – 2.90 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 149.7, 147.1, 144.5, 143.6, 136.8, 135.9, 134.2, 133.1, 123.3, 123.1, 118.7, 109.7, 36.7, 34.6, 30.6. LC/MS (ES-API) *m/z* = 238 [M+H]$^+$. Anal. calcd. for $C_{15}H_{15}N_3$: C 75.92; H 6.37; N 17.71. Found: C 75.83; H 6.55; N 17.39.

Chemoinformatic details

Datasets. The ChEMBL "Compounds" dataset (2.3M, version 31) was downloaded from https://chembl.gitbook.io/chembl-interface-documentation/downloads.[9] The PubChem full database (112M)[17] was downloaded from https://pubchem.ncbi.nlm.nih.gov/ and then reduced to 80M using the following filters: MW ≤ 500, sLog*P* ≤ 5, HAcc ≤ 10, HDon ≤ 5, RotB ≤ 10, and TPSA ≤ 140 Å. ZINC15 (drug-like/in-stock) was downloaded from https://zinc15.docking.org.[18] Also, Enamine's in-stock screening collection (3M, October 2022, available upon request at https://enamine.net/compound-collections/screening-collection) was used.[19] The chemical space of 593 713 members obtained by virtual reductive amination – "nitrogen deletion" sequence was generated using a combinatorial mode of the Reactor tool, Instant JChem, version 21.2.0.[14]

Compound descriptors. The retrieved compounds were standardized by removing salts by applying Chem.SaltRemover() function from RDKit package for Python,[24] standardizing charges, deprotonating bases, protonating acids, and generating corresponding Morgan fingerprints with radius 2 (MFP2).[25] For the generated chemical space, as well as ChEMBL, ZINC15, and Enamine stock datasets, the conventional GetMorganFingerprint() RDKit function was applied, while to compare against the PubChem dataset, a simplified 1024-bit version was used, namely, GetMorganFingerprintAsBitVect(). InstantJChem, version 21.2.0, was used to calculate physicochemical descriptors (MW, Log*P*, HAcc, HDon, RotB, and F*sp*^{3}) for the 61-member compound library (Figure 4) and for the generated chemical space (Figure 5 and the accompanying text).[14]

Clustering and dimensionality reduction. As datasets of comparison contain millions of molecules, the scatterplots illustrating their overlap with the generated chemical space would be difficult to prepare and analyze. To simplify the visualization process, we reduced all five datasets to 50K compounds. GetMorganFingerprintAsBitVect() and LazyBitVectorPick() functions from SimDivFilters.MaxMinPicker() (RDKit) were used for that purpose.

Most known methods for dataset visualization[25] still provide large tables of molecular structure diagrams that are inconvenient to inspect.[26] For that reason, the use of dimensionality reduction is inevitable. In this work, principal component analysis (PCA),[21] t-distributed stochastic neighbor embedding (t-SNE),[22] and uniform manifold approximation and projection (UMAP)[23] were used for visualizing the variation and relation of the chemical datasets. PCA and t-SNE models were built with Scikit-learn library for Python[27] with the program's default settings. UMAP models were built using a UMAP package for Anaconda[28] with the program's default settings.

Acknowledgments

The work was supported by Enamine Ltd. and the Ministry of Education and Science of Ukraine (Grants No. 0121U100387 (21BF037-01M) and 0122U001962 (22BF037-02)). The authors thank Mr. Roman Yizhak for HPLC purifications, Dr. Serhii Zhersh for his help with the project management, Prof. Andrey A. Tolmachev for his encouragement and support, and all the people of Ukraine for making finalizing this publication possible.

Conflict of Interest

Ukrainian authors are employees, trainees, or consulting scientists of Enamine Ltd. which offers Levin's nitrogen-deleting reagent and library members synthesized in this paper from the company's catalog.

Keywords: skeletal editing • parallel synthesis • combinatorial chemistry • heterocycles • lead-likeness

[1] O. O. Grygorenko, D. M. Volochnyuk, S. V. Ryabukhin, D. B. Judd, *Chem. Eur. J.* **2020**, *26*, 1196–1237.
[2] D. G. Brown, J. Boström, *J. Med. Chem.* **2016**, *59*, 4443–4458.
[3] D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson, A. Wood, *Nat. Chem.* **2018**, *10*, 383–394.
[4] C. Zippel, J. Seibert, S. Bräse, *Angew. Chem. Int. Ed.* **2021**, *60*, 19522–19524.
[5] J. Jurczyk, J. Woo, S. F. Kim, B. D. Dherange, R. Sarpong, M. D. Levin, *Nat. Synth.* **2022**, *1*, 352–364.
[6] S. H. Kennedy, B. D. Dherange, K. J. Berger, M. D. Levin, *Nature* **2021**, *593*, 223–227.
[7] H. Qin, W. Cai, S. Wang, T. Guo, G. Li, H. Lu, *Angew. Chem. Int. Ed.* **2021**, *60*, 20678–20683.
[8] C. Hui, L. Brieger, C. Strohmann, A. P. Antonchick, *J. Am. Chem. Soc.* **2021**, *143*, 18864–18870.
[9] D. Mendez, A. Gaulton, A. P. Bento, J. Chambers, M. De Veij, E. Félix, M. P. Magariños, J. F. Mosquera, P. Mutowo, M. Nowotka, M. Gordillo-Marañón, F. Hunter, L. Junco, G. Mugumbate, M. Rodriguez-Lopez, F. Atkinson, N. Bosc, C. J. Radoux, A. Segura-Cabrera, A. Hersey, A. R. Leach, *Nucleic Acids Res.* **2019**, *47*, D930–D940.
[10] N. A. Colabufo, F. Berardi, R. Perrone, S. Rapposelli, M. Digiacomo, M. Varni, A. Balsamo, *J. Med. Chem.* **2008**, *51*, 1415–1422.
[11] N. A. Colabufo, F. Berardi, R. Perrone, S. Rapposelli, M. Digiacomo, A. Balsamo, *J. Med. Chem.* **2006**, *49*, 6607–6613.
[12] T. D. Penning, N. S. Chandrakumar, B. B. Chen, H. Y. Chen, B. N. Desai, S. W. Djuric, S. H. Docter, A. F. Gasiecki, R. A. Haack, J. M. Miyashiro, M. A. Russell, S. S. Yu, D. G. Corley, R. C. Durley, B. F. Kilpatrick, B. L. Parnas, L. J. Askonas, J. K. Gierse, E. I. Harding, M. K. Highkin, J. F. Kachur, S. H. Kim, G. G. Krivi, D. Villani-Price, E. Y. Pyla, W. G. Smith, N. S. Ghoreishi-Haack, *J. Med. Chem.* **2000**, *43*, 721–735.
[13] S. D. Lotesta, A. P. Marcus, Y. Zheng, K. Leftheris, P. B. Noto, S. Meng, G. Kandpal, G. Chen, J. Zhou, B. McKeever, Y. Bukhtiyarov, Y. Zhao, D. S. Lala, S. B. Singh, G. M. McGeehan, *Bioorg. Med. Chem.* **2016**, *24*, 1384–1391.
[14] Instant JChem v. 21.2.0, can be found under www.chemaxon.com.
[15] A. Nadin, C. Hattotuwagama, I. Churcher, *Angew. Chem. Int. Ed.* **2012**, *51*, 1114–1122.

[16] C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J. Feeney, *Adv. Drug Deliv. Rev.* **1997**, *23*, 3–25.
[17] S. Kim, J. Chen, T. Cheng, A. Gindulyte, J. He, S. He, Q. Li, B. A. Shoemaker, P. A. Thiessen, B. Yu, L. Zaslavsky, J. Zhang, E. E. Bolton, *Nucleic Acids Res.* **2021**, *49*, D1388–D1395.
[18] T. Sterling, J. J. Irwin, *J. Chem. Inf. Model.* **2015**, *55*, 2324–2337.
[19] O. O. Grygorenko, *Eur. J. Org. Chem.* **2021**, 6474–6477.
[20] D. Rogers, M. Hahn, *J. Chem. Inf. Model.* **2010**, *50*, 742–754.
[21] H. Hotelling, *J. Educ. Psychol.* **1933**, *24*, 417–441.
[22] L. van der Maaten, G. Hinton, *J. Mach. Learn. Res.* **2008**, *9*, 2579–2605.
[23] L. McInnes, J. Healy, N. Saul, L. Großberger, *J. Open Source Softw.* **2018**, *3*, 861.
[24] G. Landrum, RDKit, can be found under https://www.rdkit.org, **2020**.
[25] J. Medina-Franco, K. Martinez-Mayorga, M. Giulianotti, R. Houghten, C. Pinilla, *Curr. Comput. Aided-Drug Des.* **2008**, *4*, 322–333.
[26] P. Ertl, B. Rohde, *J. Cheminform.* **2012**, *4*, 1–8.
[27] F. Pedregosa, V. Michel, O. Grisel, M. Blondel, P. Prettenhofer, R. Weiss, J. Vanderplas, D. Cournapeau, F. Pedregosa, G. Varoquaux, A. Gramfort, B. Thirion, O. Grisel, V. Dubourg, A. Passos, M. Brucher, M. Perrot, É. Duchesnay, *J. Mach. Learn. Res.* **2011**, *12*, 2825–2830.
[28] Anaconda Software Distribution, version 2-2.4.0, can be found under https://anaconda.com, **2016**.

WILEY-VCH

UDC 547.513+546.16

S. M. Holovach,[1,2] K. P. Melnykov,[2,3] M. S. Poluektova,[2,4] O. B. Rozhenko,[1,3] O. O. Grygorenko[2,3]*

[1] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Akademik Kukhar Str. 5, Kyïv, 02660, Ukraine

[2] Enamine Ltd, Chervonotkatska Str. 78, Kyïv, 02094, Ukraine

[3] Taras Shevchenko National University of Kyiv, Volodymyrska Str. 60, Kyïv 01601, Ukraine. E-mail: gregor@univ.kiev.ua

[4] National Technical University of Ukraine «Igor Sikorsky Kyiv Polytechnic Institute», Peremohy Ave. 37, Kyïv 03056, Ukraine

Incorporation of *gem*-difluorocycloalkyl substituents into heterocycles *via* the Levin's "Nitrogen deletion" strategy

Aim. To develop an efficient synthetic approach towards heterocycles decorated with *gem*-difluoroalkyl substituents using the Levin's "Nitrogen deletion" methodology.

Results and discussion. A mini-library of compounds bearing heterocyclic cores and *gem*-difluorocycloalkyl substituents is obtained under the parallel synthesis conditions involving the reductive amination – "Nitrogen deletion" reaction sequence. It is shown that the method is applicable to the preparation compounds with the aforementioned structural fragments separated by either one or two methylene units.

Experimental part. Synthesis of the target compounds commenced from heteroaromatic aldehydes and the corresponding *gem*-difluorocycloalkyl or (gem-difluorocycloalkyl)methyl amines and included $NaBH_3CN$-mediated reductive amination and "Nitrogen deletion" upon the action of Levin's anomeric amide.

Conclusions. The synthetic approach to *gem*-difluorocycloalkane-containing heterocycles based on the reductive amination – Levin's "Nitrogen deletion" reaction sequence allowed for the preparation of a 12-member compound library (67% synthetic

efficiency). Therefore, this novel synthetic methodology is suitable for decorating heterocyclic cores with sp^3-enriched substituents relevant to medicinal chemistry.

Keywords: cycloalkanes; fluorine; Levin's anomeric amide; "Nitrogen deletion"; reductive amination.

С. М. Головач,[1,2] К. П. Мельников,[2,3] М. С. Полуектова,[2,4] О. Б. Роженко,[1,3] О. О. Григоренко[2,3]*

[1] Інститут органічної хімії, Національна Академія Наук України, вул. Академіка Кухаря 5, Київ 02660, Україна

[2] ТОВ НВП «Єнамін», вул. Червоноткацька 78, Київ, 02094, Україна

[3] Київський національний університет імені Тараса Шевченка, вул. Володимирська 60, Київ 01601, Україна. E-mail: gregor@univ.kiev.ua

[4] Національний технічний університет України «Київський політехнічний інститут імені Ігоря Сікорського», пр-т Перемоги 37, Київ 03056, Україна

Введення *гем*-дифлуороциклоалкільних замісників у гетероцикли через стратегію «видалення Нітрогену» Левіна

Мета. Розробка ефективного синтетичного підходу до гетероциклів, декорованих *гем*-дифлуороалкільними замісниками, з використанням методології «видалення Нітрогену» за Левіним.

Результати та їх обговорення. В умовах паралельного синтезу із застосуванням послідовності реакції відновного амінування та «видалення Нітрогену» було одержано міні-бібліотеку сполук, що містять гетероциклічні фрагменти та *гем*-дифлуороциклоалкільні замісники. Було показано, що метод може бути використаним для одержання сполук із вищезгаданими структурними фрагментами, розділеними однією чи двома метиленовими ланками.

Експериментальна частина. Синтез цільових сполук виходив з гетероароматичних альдегідів та відповідних *гем*-дифлуороциклоалкіл- або (*гем*-

дифлуороциклоалкіл)метиламінів та передбачав відновне амінування за участі $NaBH_3CN$ та «видалення Нітрогену» під дією аномерного аміду Левіна.

Висновки. Синтетичний підхід до *гем*-дифлуороциклоалкіл-заміщених гетероциклів, що ґрунтується на послідовності реакцій відновного амінування та «видалення Нітрогену» за Левіним дозволив одержання бібліотеки сполук із 12 представників (синтетична ефективність 67%). Таким чином, ця новітня синтетична методологія є придатною для декорування гетероциклічних систем sp^3-збагаченими замісниками, що є привабливими для медичної хімії.

Ключові слова: циклоалкани; Флуор; аномерний амід Левіна; «видалення Нітрогену»; відновне амінування.

Incorporation of fluorine-containing substituents into organic molecules interest is a well-known approach to drug design, which can be illustrated by numerous success stories [1–5]. In particular, *gem*-difluorocycloalkyl groups have demonstrated their high relevance to modern drug discovery. For example, they have been incorporated into marketed pharmaceuticals Maraviroc, an anti-HIV medication, and Ivosidenib, an anticancer agent, as well as experimental drugs VU6001376, a mGluR4 positive allosteric modulator, IPN60090, a selective glutaminase-1 inhibitor, and RBx 343E48F0, a bronchodilator (Figure 1) [6].

To date, most methods for the incorporation of *gem*-difluorocycloalkyl substituents into the molecules of interest were based on the Carbon – heteroatom bond construction. Building blocks and synthetic methodologies for the C–C bond creation involving these moieties are rare and typically based on the multistep transformations. On the other hand, Levin's "Nitrogen deletion" methodology provides a unique possibility to construct the C–C bond in an unusual manner [7]. Essentially, this approach involves reaction of secondary amines with so-called anomeric amides (e.g., **1**), which results in formal extrusion of the NH moiety and combining alkyl radicals attached to it (Scheme 1, *A*).

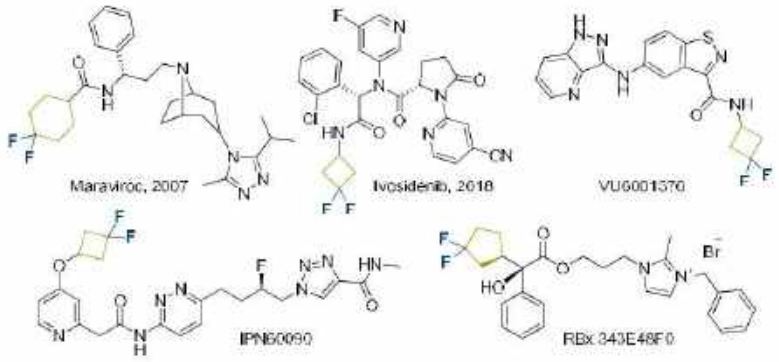
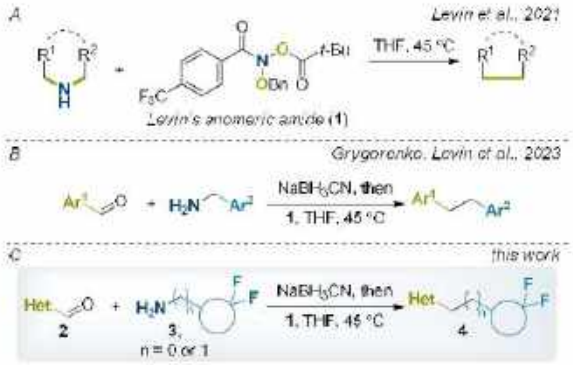


Figure 1



Scheme 1

Recently, we have shown that in combination with reductive amination, this approach can be used for the synthesis of compound libraries by a formal coupling of (hetero)aromatic aldehydes and (het)arylmethylamines (Scheme 1, *B*) [8]. In this work, we have aimed at extending this methodology towards primary amines bearing a *gem*-difluorocycloalkyl moiety (**3**) to enable incorporation of these fluorinated substituents into heterocyclic cores **2** (Scheme 1, *C*).

In this study, a compound numbering system common for combinatorial chemistry was used: the reagents used in the parallel synthesis were denoted as **2**{*i*} and **3**{*j*}, whereas the resulting library members obtained from **2**{*i*} and **3**{*j*} – **4**{*i*,*j*}.

To validate the applicability of the reductive amination – "Nitrogen deletion" sequence for the synthesis of compound library **4**, heteroaromatic aldehydes **2**{*1–6*} and primary amines **3**{*1–8*} were selected (Figure 2). Using the conditions described

in our previous work [8], 18 parallel experiments were performed using different combinations of the starting materials, and in 12 of them, target mini-library members **4**{*1–6,1–8*} were obtained (67% synthesis success rate, Table 1; see Figure 3 for the examples of products obtained).

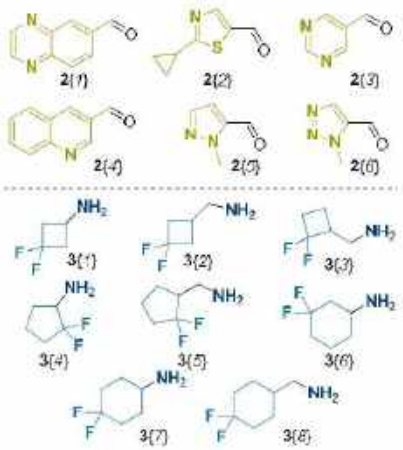


Figure 2

Table 1. Parallel synthesis of mini-library **4**{*1–6,1–8*} according to Scheme 1, *C*

#	Library member	Aldehyde	Amine	Yield of product	
				mg	%
1	**4**{*1,1*}	**2**{*1*}	**3**{*1*}	134	18
2	**4**{*1,2*}	**2**{*1*}	**3**{*2*}	165	19
3	**4**{*1,3*}	**2**{*1*}	**3**{*3*}	137	17
4	**4**{*1,4*}	**2**{*1*}	**3**{*4*}	–	0
5	**4**{*1,5*}	**2**{*1*}	**3**{*5*}	166	33
6	**4**{*1,6*}	**2**{*1*}	**3**{*6*}	179	28
7	**4**{*1,7*}	**2**{*1*}	**3**{*7*}	100	14
8	**4**{*1,8*}	**2**{*1*}	**3**{*8*}	192	32
9	**4**{*2,1*}	**2**{*2*}	**3**{*1*}	–	0
10	**4**{*2,8*}	**2**{*2*}	**3**{*8*}	115	13

11	**4**{*3,1*}	**2**{*3*}	**3**{*1*}	–	0
12	**4**{*3,8*}	**2**{*3*}	**3**{*8*}	–	0
13	**4**{*4,1*}	**2**{*4*}	**3**{*1*}	71	17
14	**4**{*4,8*}	**2**{*4*}	**3**{*8*}	222	27
15	**4**{*5,1*}	**2**{*5*}	**3**{*1*}	–	0
16	**4**{*5,8*}	**2**{*5*}	**3**{*8*}	–	0
17	**4**{*6,1*}	**2**{*6*}	**3**{*1*}	68	10
18	**4**{*6,8*}	**2**{*6*}	**3**{*8*}	105	21



Figure 3

In general, amines with primary alkyl substituents (e.g., **3**{*8*}) gave somewhat higher yields of the products (17–33%) as compared to α-branched ones (e.g., **3**{*1*}) (10–18%), which is in accordance with high sensitivity of the "Nitrogen deletion" step towards steric factors [7]. As for the aldehyde component, compounds that demonstrated somewhat poorer results in our previous study (e.g., pyrimidine **2**{*3*} or pyrazole **2**{*5*}) did not allowed isolating the target products at all. According to LS-MS spectra of the crude reaction mixture, the products were formed, but their purification was not efficient.

Experimental part.

All starting materials were available from Enamine Ltd. and Ukrorgsyntez Ltd. Melting points were measured on MPA100 OptiMelt automated melting point system. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on an Agilent ProPulse 600 spectrometer (at 600 MHz for ^{1}H NMR, 151 MHz for ^{13}C{^{1}H} NMR), Bruker 170 Avance 500

spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for $^{13}C\{^{1}H\}$ NMR and 470 MHz for ^{19}F NMR) or Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for $^{13}C\{^{1}H\}$ NMR and 376 MHz for ^{19}F NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standardand are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6. For $^{19}F\{^{1}H\}$ NMR, $CFCl_3$ in $CHCl_3$ was used as an internal standard. Coupling constants (J) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, and coupling constants (Hz). LCMS data were recorded on Agilent 1100 HPLC equipped with diode-matrix and mass-selective detector Agilent LC/MSD SL instrument, column: Zorbax SB-C18, 4.6 mm +× 15 mm; eluent, A, acetonitrile – water with 0.1% of TFA (95:5), B, water with 0.1% of TFA; flow rate: 1.8 mL/min. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)).

Parallel synthesis was performed in 20-mL vials or 100-mL flasks; loading of the reagents, as well as work-up of the reaction mixtures was performed manually in a parallel fashion. The reactions were performed in ultrasonic baths or laboratory ovens equipped with a shaker. Centrifugal evaporators were used to remove the solvents from the vials in a parallel fashion. Preparative HPLC was performed on Agilent 1260 Infinity systems equipped with DAD and mass-detector using Chromatorex 18 SNB100-5T 100 × 19 mm, 100 A, 5μm column with SunFire C18 Prep Guard Cartridge, 100 A, 10 μm, 19 mm × 10 mm, gradient H_2O – MeCN, or H_2O – MeOH, or H_2O (with 0.2% HCO_2H) – MeOH as eluent, 30 mL/min flow.

For the synthesized library members **4**{*1–6,1–8*}, physical data and mass spectra (Table 2), ^{1}H NMR spectra (Table 3), ^{13}C NMR spectra (Table 4), and ^{19}F NMR spectra (Table 5) are given in a tabular format.

Table 2. Physical data and mass spectra synthesized library members **4**{*1–6,1–8*}.

Compound	Appearance	MS (*m/z*, APCI)
4{*1,1*}	Yellowish oil	235 $[M+H]^+$

4{*1,2*}	Yellowish oil	249 $[M+H]^+$
4{*1,3*}	Yellowish oil	249 $[M+H]^+$
4{*1,5*}	Yellowish oil	263 $[M+H]^+$
4{*1,6*}	Yellowish oil	263 $[M+H]^+$
4{*1,7*}	Brownish oil	263 $[M+H]^+$
4{*1,8*}	Yellowish oil	277 $[M+H]^+$
4{*2,8*}	Yellowish oil	272 $[M+H]^+$
4{*4,1*}	Yellowish oil	234 $[M+H]^+$
4{*4,8*}	Colorless oil	276 $[M+H]^+$
4{*6,1*}	Yellowish oil	188 $[M+H]^+$
4{*6,8*}	Brownish oil	230 $[M+H]^+$

Table 3. ^{1}H NMR spectra data for synthesized library members **4**{*1–6,1–8*}.

Compound	**^{1}H NMR** (600 MHz, DMSO-d_6), δ, ppm
4{*1,1*}	8.92 (d, J = 1.8 Hz, 1H), 8.89 (d, J = 1.8 Hz, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.92 (s, 1H), 7.75 (dd, J = 8.6, 1.9 Hz, 1H), 3.05 (d, J = 7.6 Hz, 2H), 2.70 – 2.59 (m, 2H), 2.58 – 2.52 (m, 1H), 2.44 – 2.32 (m, 2H)
4{*1,2*}	8.91 (d, J = 1.8 Hz, 1H), 8.88 (d, J = 1.8 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.90 (s, 1H), 7.75 (dd, J = 8.5, 1.9 Hz, 1H), 2.81 (t, J = 7.8 Hz, 2H), 2.70 – 2.60 (m, 2H), 2.31 – 2.20 (m, 2H), 2.14 – 2.04 (m, 1H), 1.88 (q, J = 7.8 Hz, 2H)
4{*1,3*}	8.89 (d, J = 1.8 Hz, 1H), 8.87 (d, J = 1.8 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.88 (s, 1H), 7.73 (dd, J = 8.6, 1.8 Hz, 1H), 2.83 (t, J = 7.8 Hz, 2H), 2.80 – 2.68 (m, 1H), 2.46 – 2.35 (m, 2H), 2.02 – 1.93 (m, 1H), 1.91 – 1.75 (m, 2H), 1.41 – 1.33 (m, 1H)
4{*1,5*}	8.91 (d, J = 1.8 Hz, 1H), 8.89 (d, J = 1.8 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.90 (s, 1H), 7.76 (dd, J = 8.5, 1.8 Hz, 1H), 2.99 – 2.83 (m, 2H), 2.17 – 1.88 (m, 5H), 1.75 – 1.59 (m, 3H), 1.46 – 1.36 (m, 1H)
4{*1,6*}	8.92 (d, J = 1.8 Hz, 1H), 8.89 (d, J = 1.8 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.88 (s, 1H), 7.73 (dd, J = 8.5, 1.8 Hz, 1H), 2.89 – 2.78 (m, 2H), 1.99 – 1.89 (m, 3H), 1.75 – 1.49 (m, 4H), 1.41 – 1.31 (m, 1H), 1.11 – 1.03 (m, 1H)
4{*1,7*}	8.91 (d, J = 1.8 Hz, 1H), 8.89 (d, J = 1.8 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 1.9 Hz, 1H), 7.72 (dd, J = 8.5, 1.9 Hz, 1H), 2.80 (d, J = 7.2 Hz, 2H), 2.03 – 1.93 (m, 2H), 1.88 – 1.64 (m, 5H), 1.33 – 1.20 (m, 2H)

4{*1,8*}	8.90 (d, *J* = 1.8 Hz, 1H), 8.88 (d, *J* = 1.8 Hz, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.90 (s, 1H), 7.75 (dd, *J* = 8.6, 1.8 Hz, 1H), 2.89 – 2.83 (m, 2H), 2.04 – 1.95 (m, 2H), 1.87 – 1.69 (m, 4H), 1.67 – 1.61 (m, 2H), 1.46 – 1.37 (m, 1H), 1.26 – 1.16 (m, 2H)
4{*2,8*}	7.28 (s, 1H), 2.76 (t, *J* = 7.5 Hz, 2H), 2.32 – 2.26 (m, 1H), 2.02 – 1.92 (m, 2H), 1.83 – 1.67 (m, 4H), 1.51 (q, *J* = 7.5 Hz, 2H), 1.43 – 1.34 (m, 1H), 1.20 – 1.10 (m, 2H), 1.07 – 1.01 (m, 2H), 0.90 – 0.84 (m, 2H)
4{*4,1*}	8.80 (d, *J* = 2.2 Hz, 1H), 8.17 (s, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.92 (d, *J* = 8.3 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 2.99 (d, *J* = 7.7 Hz, 2H), 2.72 – 2.61 (m, 2H), 2.57 – 2.51 (m, 1H), 2.44 – 2.32 (m, 2H)
4{*4,8*}	8.80 (d, *J* = 2.2 Hz, 1H), 8.14 (s, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.71 – 7.66 (m, 1H), 7.57 (t, *J* = 7.2 Hz, 1H), 2.84 – 2.76 (m, 2H), 2.07 – 1.93 (m, 2H), 1.89 – 1.68 (m, 4H), 1.67 – 1.59 (m, 2H), 1.47 – 1.37 (m, 1H), 1.28 – 1.14 (m, 2H)
4{*6,1*}	7.53 (s, 1H), 3.92 (s, 3H), 2.88 (d, *J* = 7.7 Hz, 2H), 2.78 – 2.68 (m, 2H), 2.48 – 2.41 (m, 1H), 2.37 – 2.26 (m, 2H)
4{*6,8*}	7.50 (s, 1H), 3.91 (s, 3H), 2.69 – 2.64 (m, 2H), 2.03 – 1.95 (m, 2H), 1.84 – 1.71 (m, 4H), 1.55 (q, *J* = 7.3 Hz, 2H), 1.45 – 1.38 (m, 1H), 1.23 – 1.15 (m, 2H)

Table 4. ^{13}C NMR spectra data for synthesized library members **4**{*1–6,1–8*}.

Compound	**^{13}C{^{1}H} NMR** (151 MHz, DMSO-d_6), δ, ppm
4{*1,1*}	145.7, 145.1, 142.4, 142.3, 141.1, 131.6, 129.0, 127.7, 120.7 (dd, *J* = 284, 273 Hz), 40.4 (dd, *J* = 3.2, 1.4 Hz), 39.7 (dd, *J* = 22.3, 20.9 Hz), 23.7 (dd, *J* = 13.1, 5.9 Hz)
4{*1,2*}	145.6, 144.9, 144.3, 142.3, 141.0, 131.6, 128.9, 127.4, 120.9 (dd, *J* = 284, 274 Hz), 39.9 (t, *J* = 22.0 Hz), 36.5 (d, *J* = 2.9 Hz), 33.0, 22.3 (dd, *J* = 12.7, 6.0 Hz)
4{*1,3*}	146.1, 145.4, 144.5, 142.8, 141.5, 131.9, 129.4, 127.9, 123.4 (dd, *J* = 288, 277 Hz), 45.8 (t, *J* = 21.0 Hz), 32.9, 32.3 (t, *J* = 22.0 Hz), 29.4 (d, *J* = 4.8 Hz), 16.6 (dd, *J* = 16.5, 3.8 Hz)
4{*1,5*}	145.6, 145.0, 144.4, 142.3, 141.0, 132.8 (t, *J* = 251 Hz), 131.5, 129.0, 127.3, 44.7 (t, *J* = 22.5 Hz), 39.2, 34.5 (t, *J* = 24.6 Hz), 33.0, 28.7 (dd, *J* = 22.3, 6.6 Hz), 19.5 (dd, *J* = 5.7, 3.3 Hz)
4{*1,6*}	145.7, 145.0, 142.4, 142.2, 141.0, 131.9, 128.9, 128.3, 124.4 (dd, *J* = 242, 239 Hz), 41.4, 39.1 (dd, *J* = 24.8, 21.0 Hz), 36.2 (d, *J* = 9.1 Hz), 33.1 (dd, *J* = 24.8, 21.5 Hz), 29.9, 21.5 (d, *J* = 9.8 Hz)
4{*1,7*}	146.1, 145.4, 143.6, 142.7, 141.5, 132.5, 129.2, 128.7, 124.8 (dd, *J* = 241, 239 Hz), 41.5 (d, *J* = 2.5 Hz), 36.9, 33.1 (dd, *J* = 24.8, 22.3 Hz), 28.7 (d, *J* = 9.5 Hz)

4{*1,8*}	145.6, 144.94, 144.85, 142.4, 140.9, 131.6, 128.9, 127.2, 124.4 (dd, *J* = 241, 239 Hz), 36.5 (d, *J* = 2.5 Hz), 34.3 (d, *J* = 1.4 Hz), 32.7 (dd, *J* = 24.8, 22.0 Hz), 32.6, 28.4 (d, *J* = 9.4 Hz)
4{*2,8*}	170.6, 138.6, 136.7, 124.3 (dd, *J* = 241, 239 Hz), 37.0 (d, *J* = 2.4 Hz), 34.0 (d, *J* = 1.4 Hz), 32.7 (dd, *J* = 24.9, 22.1 Hz), 28.3 (d, *J* = 9.5 Hz), 23.8, 13.9, 10.4.
4{*4,1*}	151.9, 146.4, 134.2, 132.8, 128.8, 128.6, 127.7, 127.7, 126.6, 120.7 (dd, *J* = 284, 273 Hz), 39.7, 37.8 (dd, *J* = 3.2, 1.4 Hz), 23.6 (dd, *J* = 13.0, 6.1 Hz)
4{*4,8*}	151.9, 146.2, 135.1, 133.7, 128.6, 128.5, 127.8, 127.5, 126.5, 124.4 (dd, *J* = 241, 239 Hz), 36.5 (d, *J* = 2.4 Hz), 34.3 (d, *J* = 1.4 Hz), 32.7 (dd, *J* = 24.8, 22.1 Hz), 29.8, 28.4 (d, *J* = 9.3 Hz)
4{*6,1*}	135.5, 131.6, 120.5 (dd, *J* = 284, 273 Hz), 39.8 (t, *J* = 20.8 Hz), 34.0, 28.0 (dd, *J* = 3.3, 1.3 Hz), 21.1 (dd, *J* = 13.6, 6.0 Hz)
4{*6,8*}	137.4, 131.4, 124.3 (dd, *J* = 241, 239 Hz), 34.2 (d, *J* = 1.5 Hz), 33.9, 33.0 (d, *J* = 2.5 Hz), 32.7 (dd, *J* = 24.9, 22.1 Hz), 28.3 (d, *J* = 9.4 Hz), 19.9.

Table 5. ^{19}F NMR spectra data for synthesized library members **4**{*1–6,1–8*}.

Compound	**^{19}F{^{1}H} NMR** (376 MHz, DMSO-d_6), δ, ppm
4{*1,1*}	–81.0 (d, *J* = 190 Hz), –94.1 (d, *J* = 190 Hz)
4{*1,2*}	–81.8 (d, *J* = 189 Hz), –110.7 (d, *J* = 189 Hz)
4{*1,3*}	–96.5 (d, *J* = 224 Hz), –104.5 (d, *J* = 225 Hz)
4{*1,5*}	–86.7 (d, *J* = 234 Hz), –98.4 (d, *J* = 234 Hz)
4{*1,6*}	–90.1 (d, *J* = 233 Hz), –99.9 (d, *J* = 232 Hz)
4{*1,7*}	–89.9 (d, *J* = 232 Hz), –100.0 (d, *J* = 232 Hz)
4{*1,8*}	–89.9 (d, *J* = 232 Hz), –100.1 (d, *J* = 232 Hz)
4{*2,8*}	–81.0 (d, *J* = 190 Hz), –94.0 (d, *J* = 190 Hz)
4{*4,1*}	–81.0 (d, *J* = 190 Hz), –94.0 (d, *J* = 190 Hz)
4{*4,8*}	–89.9 (d, *J* = 232 Hz), –100.0 (d, *J* = 232 Hz)
4{*6,1*}	–81.0 (d, *J* = 191 Hz), –94.2 (d, *J* = 191 Hz)
4{*6,8*}	–90.0 (d, *J* = 232 Hz), –100.0 (d, *J* = 232 Hz)

General procedure for the synthesis of compound library 4. The procedure from our previous work [8] was followed. Amine **3** (3 mmol) was placed into a 20-mL

vial, and MeOH (6 mL), aldehyde **2** (3 mmol), and AcOH (3.6 mmol) were added. The reaction mixture was sonicated at rt for 12 h. Then $NaBH_3CN$ (6 mmol) was added, and the reaction mixture was sonicated at rt for additional 12 h. Volatiles were removed in vacuo; the residue was treated with 10% aq Na_2CO_3 (6 mL) and extracted with CH_2Cl_2 (2×6 mL). The combined organic layers were placed into a 100-mL flask and concentrated in vacuo. The residue was dried thoroughly in vacuo and used in the next step without purification. The flask with the crude reductive amination product was filled with argon, and a degassed solution of anomeric amide **1** (0.3 M in dry THF, 15 mL, 4.5 mmol) was added under an argon flow (CAUTION! Compound **1** can be potentially mutagenic). The mixture was shaken in an oven at 45 °C for 16 h (CAUTION! N_2 evolution is observed), then cooled to rt, saturated aq $NaHCO_3$ (30 mL) was added, and the mixture was extracted with Et_2O (2×15 mL). The combined extracts were evaporated in vacuo, and the residue for subjected to reverse-phase HPLC purification.

Conclusions.

Reductive amination – Levin's "Nitrogen deletion" reaction sequence is an efficient approach for introducing *gem*-difluorinated cycloalkyl substituents into heterocyclic systems under the parallel synthesis conditions; the products having these moieties separated by one or two methylene units can be obtained. Using α-branched primary amines as the starting materials results in somewhat lower yields of the corresponding library members. Limitations on the aldehyde component correlate with the results obtained in the previous study on (hetero)aromatic series: thus, pyrimidine and pyrazole derivatives were inefficient due to problems with the product isolation. The resulting lead-like fluorinated compound libraries are of special interest to medicinal chemistry; the method can be potentially also extended to other applications in early drug discovery.

Conflict of interests: the authors are employees or consulting scientists at Enamine Ltd. that offers the title compounds from the company's catalog.

Acknowledgements: The work was supported by Enamine Ltd., Ministry of Education and Science of Ukraine (grants No. 0121U100387 (21BF037-01M) and 0122U001962 (22BF037-02)), and National Academy of Sciences of Ukraine (grant No. 0119U102718). The authors thank Mr. Bohdan Vashchenko and Mr. Bohdan Sosunovych for his help with manuscript preparation, Prof. Dr. A. O. Tolmachev for his encouragement and support, and all the brave defenders of Ukraine for making this publication possible.

References

[1] Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315–8359.

[2] Mei, H.; Remete, A. M.; Zou, Y.; Moriwaki, H.; Fustero, S.; Kiss, L.; Soloshonok, V. A.; Han, J. Fluorine-Containing Drugs Approved by the FDA in 2019. *Chinese Chem. Lett.* **2020**, *31*, 2401–2413.

[3] Yerien, D. E.; Bonesi, S.; Postigo, A. Fluorination Methods in Drug Discovery. *Org. Biomol. Chem.* **2016**, *14*, 8398–8427.

[4] Inoue, M.; Sumii, Y.; Shibata, N. Contribution of Organofluorine Compounds to Pharmaceuticals. *ACS Omega* **2020**, *5*, 10633–10640.

[5] Han, J.; Remete, A. M.; Dobson, L. S.; Kiss, L.; Izawa, K.; Moriwaki, H.; Soloshonok, V. A.; O'Hagan, D. Next Generation Organofluorine Containing Blockbuster Drugs. *J. Fluor. Chem.* **2020**, *239*, 109639.

[6] Grygorenko, O. O.; Melnykov, K. P.; Holovach, S.; Demchuk, O. Fluorinated Cycloalkyl Building Blocks for Drug Discovery. *ChemMedChem* **2022**, *17*, e202200365.

[7] Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. Skeletal Editing through Direct Nitrogen Deletion of Secondary Amines. *Nature* **2021**, *593*, 223–227.

[8] Holovach, S.; Melnykov, K. P.; Poroshyn, I.; Iminov, R. T.; Dudenko, D.;

Kondratov, I.; Levin, M.; Grygorenko, O. O. C–C Coupling through Nitrogen Deletion: Application to Library Synthesis. *Chem. Eur. J.* **2023**, *29*, e202203470.

ACS ORGANIC & INORGANIC Au

pubs.acs.org/orginorgau

This article is licensed under CC-BY-NC-ND 4.0

Article

Parallel Minisci Reaction of *gem*-Difluorocycloalkyl Building Blocks

Serhii Holovach, Illia Poroshyn, Kostiantyn P. Melnykov, Oleksandr S. Liashuk, Olena O. Pariiska, Sergey V. Kolotilov, Alexander B. Rozhenko, Dmytro M. Volochnyuk, and Oleksandr O. Grygorenko*

Cite This: *ACS Org. Inorg. Au* 2024, 4, 424−431

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Parallel Minisci reactions of nonfluorinated and *gem*-difluorinated C_4−C_7 cycloalkyl building blocks (trifluoroborates and carboxylic acids) with a series of electron-deficient heterocycles were studied. A comparison of the reaction's outcome revealed better product yields in the case of carboxylic acids as the radical precursors in most cases, albeit these reagents were used with three-fold excess under optimized conditions. The nature of the heterocyclic core was found to be important for successful incorporation of the cycloalkyl fragment. The impact of the CF_2 moiety on the oxidation potential of fluorinated cycloalkyl trifluoroborates and the reaction outcome, in general, was also evaluated.



KEYWORDS: *radical reactions, trifluoroborates, carboxylic acids, fluorine, cycloalkanes*

Downloaded via 91.218.192.226 on March 7, 2025 at 11:58:38 (UTC).
See https://pubs.acs.org/sharingguidelines for options on how to legitimately share published articles.

INTRODUCTION

Over the last few decades, fluorinated scaffolds have become an integral part of the drug discovery process as a convenient and valuable tool for fine-tuning the compound's physicochemical properties (acidity/basicity, lipophilicity, or solubility).[1−16] Introduction of the fluorine-containing fragment often shows a significant impact on the compound's affinity to the desired biological target and its general metabolic stability.[17−21] On the other hand, an evident trend for an increased use of sp^3-enriched structures in drug discovery gave rise to an intense investigation of fluorinated saturated (hetero)cycles.[22−26] Since aromatic ring systems nevertheless remain essential and most popular structural elements of drug molecules,[27] the synthetic methods allowing their decoration with fluorinated sp^3-enriched fragments are of high demand (Figure 1).[28]

To date, various strategies to introduce the fluorinated cycloalkyl fragment into the aromatic core are known in the literature, including either fluorination of a preformed scaffold[29] or the construction of a complex structure using fluorinated building blocks via common[30−34] or recently (re)introduced[35] chemical transformations. The latter strategy can be especially promising since in many cases $C(sp^2)$−$C(sp^3)$ bond formation is possible. In particular, the radical C−H functionalization of aromatic heterocycles has become recognized as an effective instrument for late-stage modification of electron-deficient heteroaromatic species.[36−38] While the seminal report on such transformations was made by Minisci and co-workers as early as the 1970s (Scheme 1A),[39] only with recent developments by the groups of Baran, Molander, and others, the Minisci reaction and its boron variant received broad attention from the chemical community.

While the classical Minisci reaction involves the use of carboxylic acids as the radical precursors (which was later demonstrated for a wide range of both aromatic[40] and aliphatic[41,42] substrates), boronic acid derivatives (in particular, trifluoroborates)[43−49] have received much attention as a promising alternative (Scheme 1B). Silver species have been widely used as an oxidant (especially in catalytic amounts in the presence of a stoichiometric co-oxidant, e.g. $AgNO_3$/$K_2S_2O_8$[49−52] or $AgNO_3$/Selectfluor[53]) to generate the corresponding radical intermediate; other reagents included molecular oxygen,[43] $CuCl_2$,[54] $Mn(OAc)_3$,[47] etc. Photoredox methods are also worth outlining, both metalo-[55,56] and organocatalytic.[46,50]

While the reactivity and selectivity of various (cyclo)alkyl radical sources and heteroaromatic partners in the Minisci reaction was studied, fluorinated substituents were largely underexplored at these conditions. Thus, several examples of the photocatalytic C−H activation involving 4,4-difluorocyclohexanecarboxylic acid as the radical source were reported.[57−60] In this regard, achievements of Baran and co-workers on the C−H functionalization of heterocyclic rings with fluorinated sulfinates can also be mentioned.[61] In this work, we evaluate the reactivity of *gem*-difluorinated cycloalkane building blocks (carboxylic acids and trifluoroborates, C_4 to C_7) as the radical sources in the Minisci reaction under parallel synthesis conditions (Scheme 1C). In particular, a small compound library following the design principles shown in Figure 1A has been prepared. In addition, an attempted rationalization of the obtained results based on cyclic voltammetry experiments and molecular geometry data is provided.

Received: April 22, 2024
Revised: May 3, 2024
Accepted: May 6, 2024
Published: May 15, 2024



ACS Publications

© 2024 The Authors. Published by American Chemical Society

https://doi.org/10.1021/acsorginorgau.4c00028
ACS Org. Inorg. Au 2024, 4, 424−431

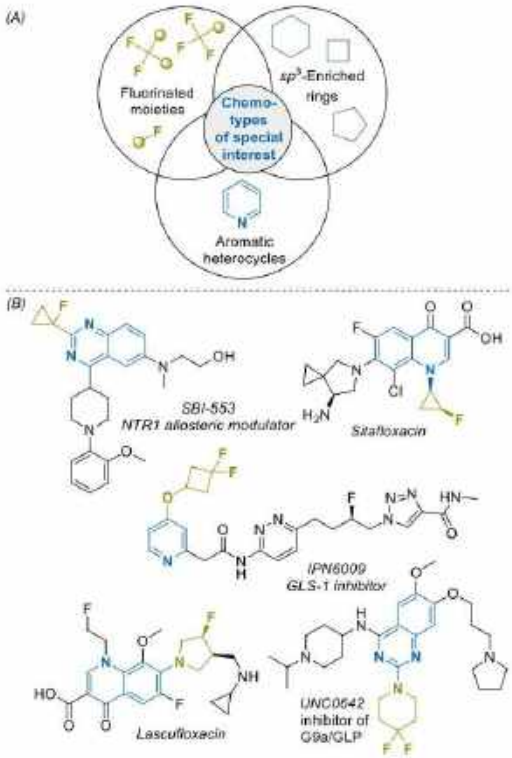
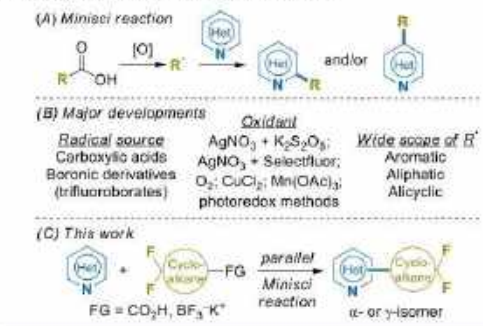


Figure 1. (A) Structural motifs that are increasingly popular in drug discovery. (B) Experimental and marketed drugs designed by a combination of fluorine atoms, saturated rings, and heteroaromatic fragments.

Scheme 1. (A) General Scheme for the Minisci Reaction; (B) Major Developments on the Minisci Reaction; and (C) the Key Transformation of This Work



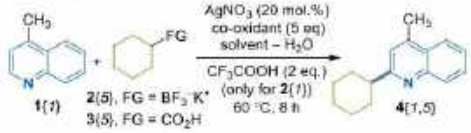
Throughout this paper, a compound numbering system common to combinatorial chemistry has been used. Thus, heterocyclic substrates, carboxylic acids, and trifluoroborates for the library synthesis were labeled as **1**{*i*}, **2**{*j*}, and **3**{*j*}, respectively, where *i* and *j* are positive integer numbers starting with 1. The library members synthesized from reagents **1**{*i*} and **2**{*j*}/**3**{*j*} were designated as **4**{*i*,*j*}.

A preliminary version of this manuscript was published as a preprint.[62]

RESULTS AND DISCUSSION

Keeping in mind the application of the Minisci reaction under parallel synthesis conditions, we have turned our attention to the classical Ag-catalyzed version of the method. We started our experimentation from the model reaction of 4-methylquinoline **1**{1}[43,44,47,63] and cyclohexyl trifluoroborate (**2**{5}) under the conditions proposed by Molander's group ($AgNO_3$ (20 mol %), $K_2S_2O_8$ (5 equiv), TFA (2 equiv), $(CH_2Cl)_2$–H_2O, 60 °C, 8 h).[48] At these conditions, the desired product **4**{1,5} was obtained in 46% isolated yield (Table 1, entry 1).

Table 1. Optimization of the Minisci Reaction Conditions



#	radical source	amount of 2{1}/3{1}, eq	co-oxidant	organic solvent	yield, %[a,b]
1	**2**{5}	1.1	$K_2S_2O_8$	$(CH_2Cl)_2$	85 (46)
2	**2**{5}	3	$K_2S_2O_8$	$(CH_2Cl)_2$	84
3	**2**{5}	1.1	$K_2S_2O_8$	CH_3CN	traces
4	**2**{5}	3	$K_2S_2O_8$	CH_3CN	traces
5	**2**{5}	3	$(NH_4)_2S_2O_8$	CH_3CN	71
6	**3**{5}	1.1	$(NH_4)_2S_2O_8$	$(CH_2Cl)_2$	8
7	**3**{5}	3	$(NH_4)_2S_2O_8$	$(CH_2Cl)_2$	20
8	**3**{5}	1.1	$(NH_4)_2S_2O_8$	CH_3CN	47
9	**3**{5}	3	$(NH_4)_2S_2O_8$	CH_3CN	81 (42)
10	**3**{5}	3	$K_2S_2O_8$	CH_3CN	68

[a]Yield of **4**{1,5} by LC–MS. [b]Isolated yield is given in parentheses.

Meanwhile, carboxylic acid **3**{5} did not work well under the aforementioned conditions: minor amounts of product **4**{1,5} were detected, and starting quinoline **1**{1} was mostly recovered (entry 6).

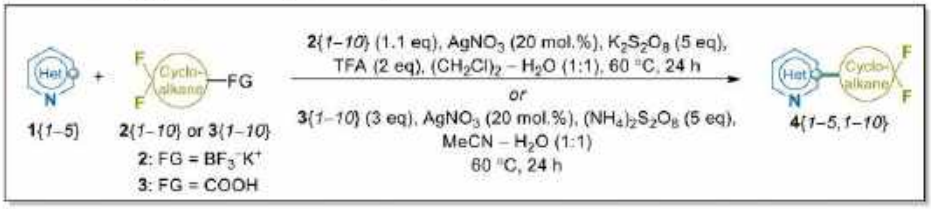
Therefore, an alternative protocol described by Shore and co-authors was considered [$AgNO_3$ (20 mol %), $(NH_4)_2S_2O_8$ (5 equiv), MeCN–H_2O, 60 °C, 8 h].[64] After some additional experiments (entries 6–10), an optimized version of the synthetic protocol with increased quantities of radical precursor **3**{1} (3 equiv), $(NH_4)_2S_2O_8$ as the stoichiometric oxidant, and CH_3CN–H_2O as the solvent was elaborated (42% isolated yield, entry 9) and therefore implemented in further studies with carboxylic acids as the radical sources. Notably, this protocol did not give significant advantages in the case of trifluoroborates.

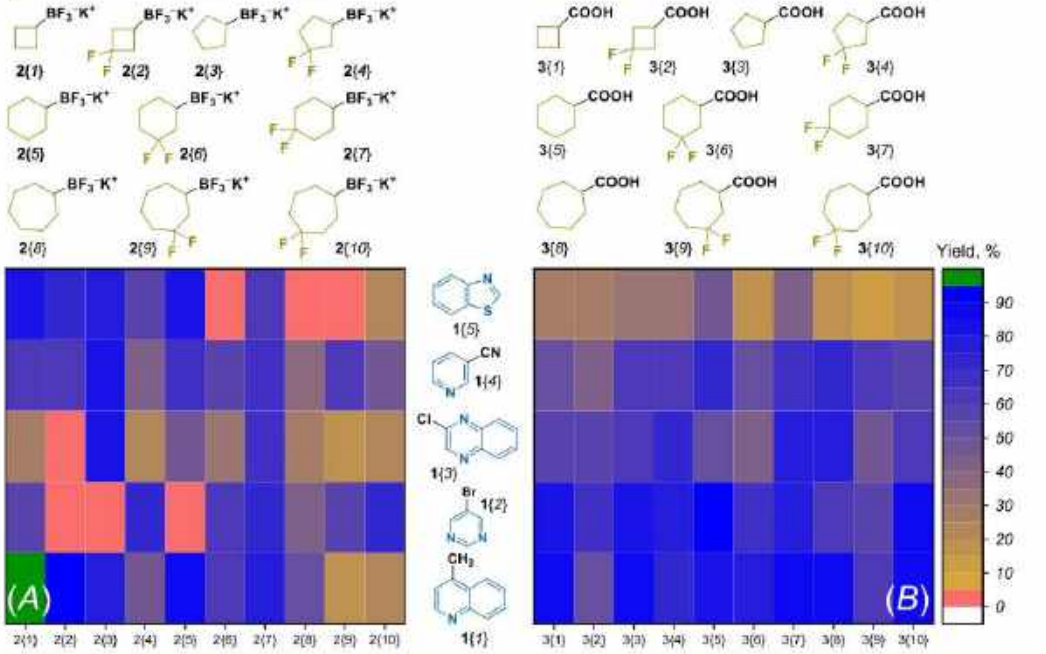
Next, we applied the above-optimized conditions to five model heterocyclic compounds **1**{1–5} covering a variety of chemotypes (quinoline, pyrimidine, quinoxaline, pyridine, and benzothiazole) and functional groups (Cl, Br, and CN), as well as 10 cycloalkane-derived trifluoroborates **2**{1–10}/carboxylic acids **3**{1–10} (C_4 to C_7) for the parallel synthesis of compound library **4**{1–5,1–10} (Scheme 2).

Since analysis of the isolated yields for library **4** can be complicated by product losses after HPLC due to their volatility, we mainly rely on the LC–MS-based yields in the following discussion. It was found that the average yields of the library members (as detected by LC–MS) were somewhat

https://doi.org/10.1021/acsorginorgau.4c00028
ACS Org. Inorg. Au 2024, 4, 424–431

Scheme 2. Synthesis of Compound Library 4{1−5,1−10} and Heatmap of the Reaction Yields According to LC−MS [(A)—for Trifluoroborates 2, (B)—for Carboxylic Acids 3]





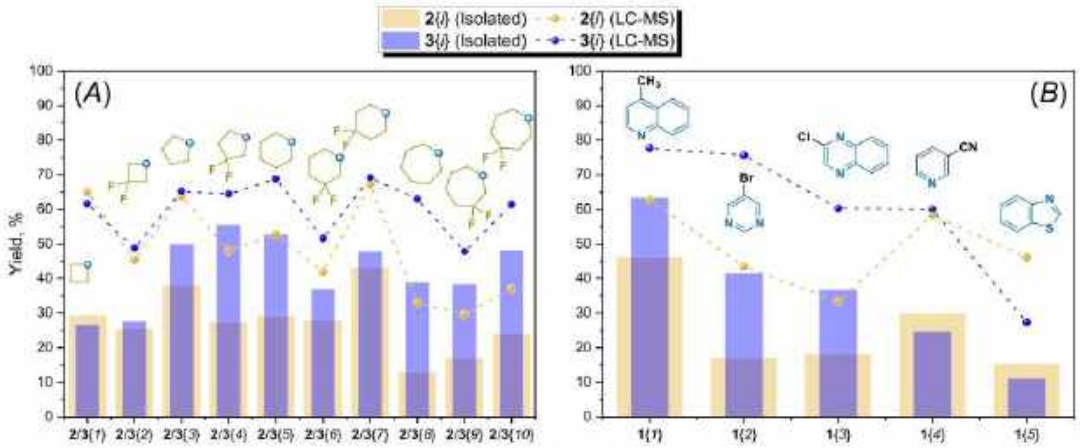


Figure 2. (A) LC−MS-based and isolated yields of products 4 as functions of building blocks 2/3 (A) and heterocycles 1 (B).

https://doi.org/10.1021/acsorginorgau.4c00028
ACS Org. Inorg. Au 2024, 4, 424−431

lower for trifluoroborates **2**{1−10} (48%) than that for carboxylic acids **3**{1−10} (60%). The yield distribution range was narrower for reagents **3**{1−10}, which can be considered as an indicator of better method reproducibility under the parallel synthesis conditions. On the other hand, the optimized protocol involved the use of three-fold excess of carboxylic acids **3**{1−10}, which in some cases resulted in the formation of double alkylation products—up to 36% for **4**{3,9}, as detected by LC−MS.

A more detailed analysis of the studied building block performance revealed several tendencies. In particular, the average product yield was affected by the compound's fluorination pattern in a following manner: nonfluorinated (60%) ≈ 4,4-difluorinated (59%) > 3,3-difluorinated (47%) (Figure 2A). We have also evaluated 2,2-difluorocycloalkanecarboxylic acids (C_4 to C_7) in the reaction with heterocycles under the standard conditions; although minor amounts of the target products were detected by LC−MS, none of them could be isolated in a pure form. Cycloheptane-containing trifluoroborates **2**{7−10} showed relatively poor results compared to other substrates.

On the other hand, the reaction outcome strongly depended on the nature of the heterocyclic partner: the highest average yields were observed for 4-methylquinoline **1**{1} (69%) and the lowest—for benzothiazole **1**{5} (37%) (Figure 2B). The latter fact can be rationalized by limited stability of benzothiazole toward radical oxidants (including $Ag^+/S_2O_8^{2-}$ system).[66] Interestingly, trifluoroborates **2** worked better with this particular heterocycle compared to carboxylic acids **3** (almost 20% higher average product yield).

For aromatic substrates having a singly defined electrophilic center (namely, **1**{1}, **1**{3}, and **1**{5}), only monoalkylation product **4** was formed (Figure 3). For pyrimidine derivatives

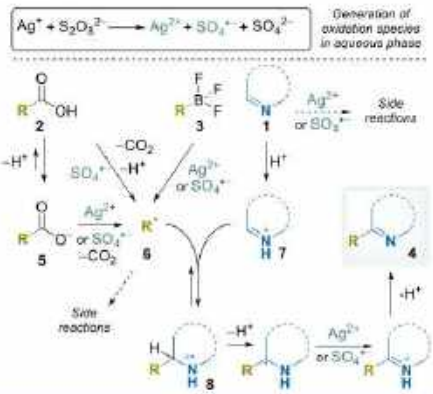


Figure 3. Regioselectivity of the Minisci reaction with heterocycles **1**{1−5}.

4{2,*j*}, regiospecific formation of the C-4 alkylation products was observed, which is in full accordance with the previously reported data.[66] For pyridine-derived compounds **4**{4,*j*}, all possible isomers (i.e., C-2, C-4, and C-6) were formed. In most cases, C-4 substitution occurred predominantly (ca. 50%), and the corresponding products **4a**{4,*j*} were isolated in pure form after reverse phase HPLC. At the same time, separation of C-2 and C-6 isomers appeared to be more challenging, so that their mixtures with varied ratios containing up to 40% of the C-2 isomer (according to ^{1}H NMR spectroscopy) could be obtained.

Somewhat higher efficiency of carboxylic acids **3** as the radical source as compared to trifluoroborates **2** might be rationalized through the radical generation mechanism. According to literature data,[30,67] water-soluble trifluoroborate salts **2** readily undergo direct oxidation to corresponding reactive species **6** (Scheme 3).[68,69] In contrast, the main route

Scheme 3. Plausible Reaction Pathways Based on the Literature Data[36,73]



for carboxylic acids **3** involves in single electron oxidation of corresponding carboxylate anion **5** by reactive species generated in the $Ag^+/S_2O_8^{2-}$ system.[70−72] An alternative pathway, albeit less probable, includes hydrogen atom transfer from carboxylic acid to $SO_4^{\bullet-}$ radical with subsequent decarboxylation generates radical **6**.[68] At the acidic reaction conditions, concentration of carboxylate anions **5** is relatively low, which results in low steady-state concentration of corresponding radicals **6** and their slow release for the reaction with protonated heterocycle **7**. This might lead to suppression of undesired second-order radical side reactions (e.g., dimerization or disproportionation) and therefore to higher product yields. On the other hand, low concentration of the radical species can be disadvantageous in the Minisci reaction with substrates sensitive to oxidation (e.g., benzothiazole **1**{5}). In this case, efficient formation of alkyl radicals **6** from trifluoroborates **2** overcomes slower competitive side reactions of heterocycle **1** and enhances the yield of desired product **4**.

To have a deeper inside in the observed reactivity profiles, we have measured cyclic voltammograms for the trifluoroborates **2**{1−10} (Figure 4).[74] The E_{ap} values for non-

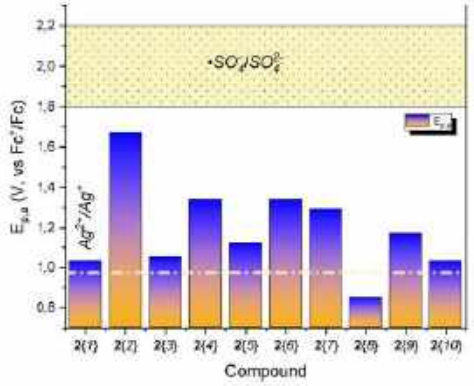


Figure 4. E_{ap} values of trifluoroborates **2**{1−10} obtained from CVA as compared to $E(Ag^{2+}/Ag^+)$ and $E(SO_4^{\bullet-}/SO_4^{2-})$ (recalculated from the literature values[67,68] vs ferrocene).

https://doi.org/10.1021/acsorginorgau.4c00028
ACS Org. Inorg. Au 2024, 4, 424−431

fluorinated trifluoroborates 2{1}, 2{3}, 2{5}, and 2{8} (0.85–1.12 V) are close to those previously reported for analogous cycloalkyl trifluoroborates.[55,68,75−77] At the same time, *gem*-difluorinated compounds 2{2}, 2{4}, 2{6}, 2{7}, 2{9}, and 2{10} demonstrated significantly higher oxidation potentials (1.03–1.67 V) as compared to their nonfluorinated counterparts.[78,79] This effect might be partially responsible for the lower efficiency of some *gem*-difluorinated cycloalkyl building blocks as the radical sources in the Minisci reaction. Nevertheless, other factors (e.g., radical nucleophilicity[80−82]) are likely important since there is no direct correlation between E_{ap} and the reaction outcome. It should also be mentioned that the redox-potentials, measured by CVA, are the potentials of heterogeneous electron transfer involving the solid electrode, while radical generation under Ag-catalyzed oxidation is homogeneous reaction. Thus, 4,4-difluorocyclobutyl derivative 2{2} has the highest oxidation potential (1.67 V), but the corresponding average product yield is not particularly low. Also, 4,4-difluorinated building blocks 2{7} and 2{10} demonstrate even slightly better performance as compared to nonfluorinated counterparts 2{5} and 2{8}, respectively, while the corresponding E_{ap} values are considerably higher.

Comparison of the obtained oxidation potentials with those for the oxidative species [i.e., $E(Ag^{2+}/Ag^{+})$ and $E(SO_4^{\bullet-}/SO_4^{2-})$][70,83,84] shows that in the case of nonfluorinated trifluoroborates 2{1}, 2{3}, 2{5}, and 2{7}, both Ag^{2+} and $SO_4^{\bullet-}$ can participate in the radical generation. On the contrary, for most *gem*-difluorinated trifluoroborates studied, $E(Ag^{2+}/Ag^{+})$ is not sufficient for the reaction, so that $SO_4^{\bullet-}$ is the likely oxidant.

Anomalously low yields for cycloheptane-derived trifluoroborates 2{8–10} might be referred to increased lipophilicity of the corresponding fragments,[85] increasing the role of boundary effects in the biphasic system.[86]

In summary, the Minisci reaction of *gem*-difluorinated cycloalkyl trifluoroborates and carboxylic acids is a very promising approach for the C–H modification of heterocyclic systems with *gem*-diflorocycloalkyl substituents. The corresponding carboxylic acids demonstrate somewhat higher efficiency as the radical sources in the reaction studied under optimized conditions as compared to trifluoroborates. This advantage can be overcome by necessity to use the three-fold excess of the former reagents. Also, trifluoroborates can be advantageous with heterocyclic substrates that are sensitive to oxidation.

The *gem*-difluorination pattern has a significant impact on the reaction outcome. Thus, 4,4-difluorinated cycloalkyl building blocks have nearly the same efficiency as their nonfluorinated counterparts, while 3,3- and especially 2,2-difluorinated analogues demonstrate diminished activity. Oxidation potentials obtained from cyclic voltammograms of the trifluoroborates studied are considerably higher for the fluorinated compounds; therefore, they may only be partially responsible for the observed effects. Other factors like radical nucleophilicity or the cycloalkyl fragment lipophilicity (e.g., for cycloheptane derivatives) should also be taken into account.

The proposed method for the parallel synthesis allows for the preparation of compound libraries comprising structural features attractive from the medicinal chemist's viewpoint: fluorinated substituent, sp^3-rich moiety, and aromatic heterocycle. Therefore, it should be useful for early drug discovery programs as well as for late-stage modification of organic molecules with fluorinated substituents.

EXPERIMENTAL SECTION

The solvents were purified according to the standard procedures.[89] Compounds 1{1–5}, 2{1–10}, and 3{1–10} were obtained from Enamine Ltd.; all other starting materials were available commercially. Melting points were measured on the MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. HPLC purification was performed on a Chromatorex 18 SMB 100-ST 100 × 19 mm 5 μm column, using a H_2O/ACN gradient. ^1H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^1H NMR, 126 MHz for ^{13}C NMR, and 470 MHz for ^{19}F NMR) and a Varian Unity Plus 400 spectrometer (at 400 MHz for ^1H NMR, 101 MHz for ^{13}C NMR, and 376 MHz for ^{19}F NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^1H and ^{13}C in $CDCl_3$ and 2.50 and 39.52 ppm for ^1H and ^{13}C in DMSO-d_6. Coupling constants (J) are given in Hz. Spectra are reported as follows: chemical shift (δ, parts per million), multiplicity, integration, and coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument [chemical ionization (CI)] and Agilent 5890 Series II 5972 MS instrument [electron impact ionization (EI)]. High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer.

General Procedure for the Minisci Reaction with Trifluoroborates 2 (Method A)

Trifluoroborate **2** (0.55 mmol, 1.1 equiv), heteroaromatic compound **1** (0.50 mmol, 1.0 equiv), $AgNO_3$ (17 mg, 0.10 mmol, 0.2 equiv), and $K_2S_2O_8$ (675 mg, 2.50 mmol, 5 equiv) were put into a glass vial equipped with a magnetic stirring bar. To this solid mixture, $ClCH_2CH_2Cl$ (2.5 mL) and H_2O (2.5 mL) were added subsequently (to a total 0.1 M of compound **1**), followed by addition of TFA (76 μL, 1.00 mmol, 2 equiv) with intensive stirring. The reaction mixture was stirred at 60 °C for 24 h, then poured into a mixture of saturated aq $NaHCO_3$ and 10% aq $Na_2S_2O_3$ (1:1 v/v, 25 mL), the organic layer was separated, and the water layer was extracted with CH_2Cl_2 (3× 10 mL). Combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude material was subjected to reverse phase HPLC to give pure product **4** as a thin film.

General Procedure for the Minisci Reaction with Carboxylic Acids 3 (Method B)

Corresponding acid **3** (1.50 mmol, 3 equiv), heteroaromatic compound **1** (0.50 mmol, 1 equiv), $AgNO_3$ (17 mg, 0.10 mmol, 0.2 equiv), and $(NH_4)_2S_2O_8$ (570 mg, 2.50 mmol, 5 equiv) were weighted in a glass vial, equipped with a magnetic stirring bar. To this solid mixture, CH_3CN (2.5 mL) and H_2O (2.5 mL) were subsequently added (to a total 0.1 M of compound **1**), and the obtained slurry was heated to 60 °C with intensive stirring. After 24 h, the reaction mixture was poured into a mixture of saturated aq $NaHCO_3$ and 10% aq $Na_2S_2O_3$ (1:1 v/v, 25 mL), the organic layer was separated, and the water layer was extracted with CH_2Cl_2 (3× 10 mL). Combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude material was subjected to a reverse phase HPLC to give a pure product **4** as a thin film.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

https://doi.org/10.1021/acsorginorgau.4c00028
ACS Org. Inorg. Au 2024, 4, 424–431

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsorginorgau.4c00028.

Synthesized compound characterization data, cyclic voltammograms of the utilized cycloalkyltrifluoroborates, and photographs of the reaction setup (PDF)

AUTHOR INFORMATION

Corresponding Author

Oleksandr O. Grygorenko − *Enamine Ltd., Kyiv 02094, Ukraine; Institute of Organic Chemistry of National Academy of Sciences of Ukraine, Kyiv 02066, Ukraine;* orcid.org/0000-0002-6036-5859; Email: gregor@univ.kiev.ua; www.grygorenko.com

Authors

Serhii Holovach − *Enamine Ltd., Kyiv 02094, Ukraine; Institute of Organic Chemistry of National Academy of Sciences of Ukraine, Kyiv 02066, Ukraine*

Illia Poroshyn − *Enamine Ltd., Kyiv 02094, Ukraine; Taras Shevchenko National University of Kyiv, Kyiv 01601, Ukraine*

Kostiantyn P. Melnykov − *Enamine Ltd., Kyiv 02094, Ukraine; Taras Shevchenko National University of Kyiv, Kyiv 01601, Ukraine*

Oleksandr S. Liashuk − *Enamine Ltd., Kyiv 02094, Ukraine; Taras Shevchenko National University of Kyiv, Kyiv 01601, Ukraine*

Olena O. Pariiska − *L. V. Pisarzhevskii Institute of Physical Chemistry of National Academy of Sciences of Ukraine, Kyiv 03028, Ukraine*

Sergey V. Kolotilov − *Enamine Ltd., Kyiv 02094, Ukraine; L. V. Pisarzhevskii Institute of Physical Chemistry of National Academy of Sciences of Ukraine, Kyiv 03028, Ukraine;* orcid.org/0000-0002-4780-4378

Alexander B. Rozhenko − *Institute of Organic Chemistry of National Academy of Sciences of Ukraine, Kyiv 02066, Ukraine; Taras Shevchenko National University of Kyiv, Kyiv 01601, Ukraine;* orcid.org/0000-0003-4022-7851

Dmytro M. Volochnyuk − *Enamine Ltd., Kyiv 02094, Ukraine; Institute of Organic Chemistry of National Academy of Sciences of Ukraine, Kyiv 02066, Ukraine; Taras Shevchenko National University of Kyiv, Kyiv 01601, Ukraine;* orcid.org/0000-0001-6519-1467

Complete contact information is available at: https://pubs.acs.org/10.1021/acsorginorgau.4c00028

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. CRediT: **Serhii Holovach** investigation, validation; **Illia Poroshyn** investigation, validation; **Kostiantyn P. Melnykov** conceptualization, methodology, project administration; **Oleksandr S. Liashuk** data curation, visualization, writing-original draft; **Olena O. Pariiska** data curation, investigation; **Sergey V. Kolotilov** data curation, resources, supervision; **Alexander B. Rozhenko** project administration, supervision; **Dmytro M. Volochnyuk** conceptualization, funding acquisition, methodology, supervision; **Oleksandr O. Grygorenko** conceptualization, funding acquisition, methodology, project administration, supervision, visualization, writing-review & editing.

Funding

The work was supported by Enamine Ltd. and the Ministry of Education and Science of Ukraine [grant nos. 0121U100387 (21BF037-01M) and 0122U001962 (22BF037-02)].

Notes

The authors declare the following competing financial interest(s): The authors are employees, trainees, or consulting sci-entists of Enamine Ltd. which offers the compounds discussed in this paper in the companys catalog.

ACKNOWLEDGMENTS

The authors thank Prof. Andrey A. Tolmachev for his encouragement and support and all the brave people of Ukraine for making finalizing this publication possible.

ABBREVIATIONS

CVA, cyclic voltammetry; HPLC, high-performance liquid chromatography; LC-MS, liquid chromatography with mass spectral detector; NMR, nuclear magnetic resonance

REFERENCES

(1) Melnykov, K. P.; Nazar, K.; Smyrnov, O.; Skreminskyi, A.; Pavlenko, S.; Klymenko-Ulianov, O.; Shishkina, S.; Volochnyuk, D. M.; Grygorenko, O. O. Mono- and Difluorinated Saturated Heterocyclic Amines for Drug Discovery: Systematic Study of Their Physicochemical Properties. *Chem. Eur. J.* **2023**, *29*, No. e202301383.

(2) Grygorenko, O. O.; Melnykov, K. P.; Holovach, S.; Demchuk, O. Fluorinated Cycloalkyl Building Blocks for Drug Discovery. *ChemMedChem* **2022**, *17*, No. e202200365.

(3) Mei, H.; Han, J.; Fustero, S.; Medio-Simon, M.; Sedgwick, D. M.; Santi, C.; Ruzziconi, R.; Soloshonok, V. A. Fluorine-Containing Drugs Approved by the FDA in 2018. *Chem. Eur. J.* **2019**, *25*, 11797−11819.

(4) Cahard, D.; Ma, J.-A. *Emerging Fluorinated Motifs: Synthesis, Properties and Applications*; Wiley-VCH, 2020.

(5) Li, Y.; Li, P.; Li, Y.; Zhang, R.; Yu, P.; Ma, Z.; Kainov, D. E.; de Man, R. A.; Peppelenbosch, M. P.; Pan, Q. Drug Screening Identified Gemcitabine Inhibiting Hepatitis E Virus by Inducing Interferon-like Response via Activation of STAT1 Phosphorylation. *Antiviral Res.* **2020**, *184*, 104967.

(6) Abdelshaheed, M. M.; Fawzy, I. M.; El-Subbagh, H. I.; Youssef, K. M. Piperidine Nucleus in the Field of Drug Discovery. *Futur. J. Pharm. Sci.* **2021**, *7*, 188.

(7) Vardanyan, R. Classes of Piperidine-Based Drugs. *Heterocyclic Drug Discovery*; Elsevier, 2017; Chapter 10, pp 299−332.

(8) Cao, Y.; Sun, J.; Li, M.; Deng, Y.; Zhang, Y.; Yan, J.; Huang, R.; Yan, X. Inhibition of G9a by a Small Molecule Inhibitor, UNC0642, Induces Apoptosis of Human Bladder Cancer Cells. *Acta Pharmacol. Sin.* **2019**, *40*, 1076−1084.

(9) Melnykov, K. P.; Tavlui, O.; Skreminskiy, A.; Kuchkovska, Y. O.; Grygorenko, O. O. Impact of Fluoroalkyl Substituents on the Physicochemical Properties of Saturated Heterocyclic Amines. *Chem. Eur. J.* **2022**, *28*, No. e202201601.

(10) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II-III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem. Rev.* **2016**, *116*, 422−518.

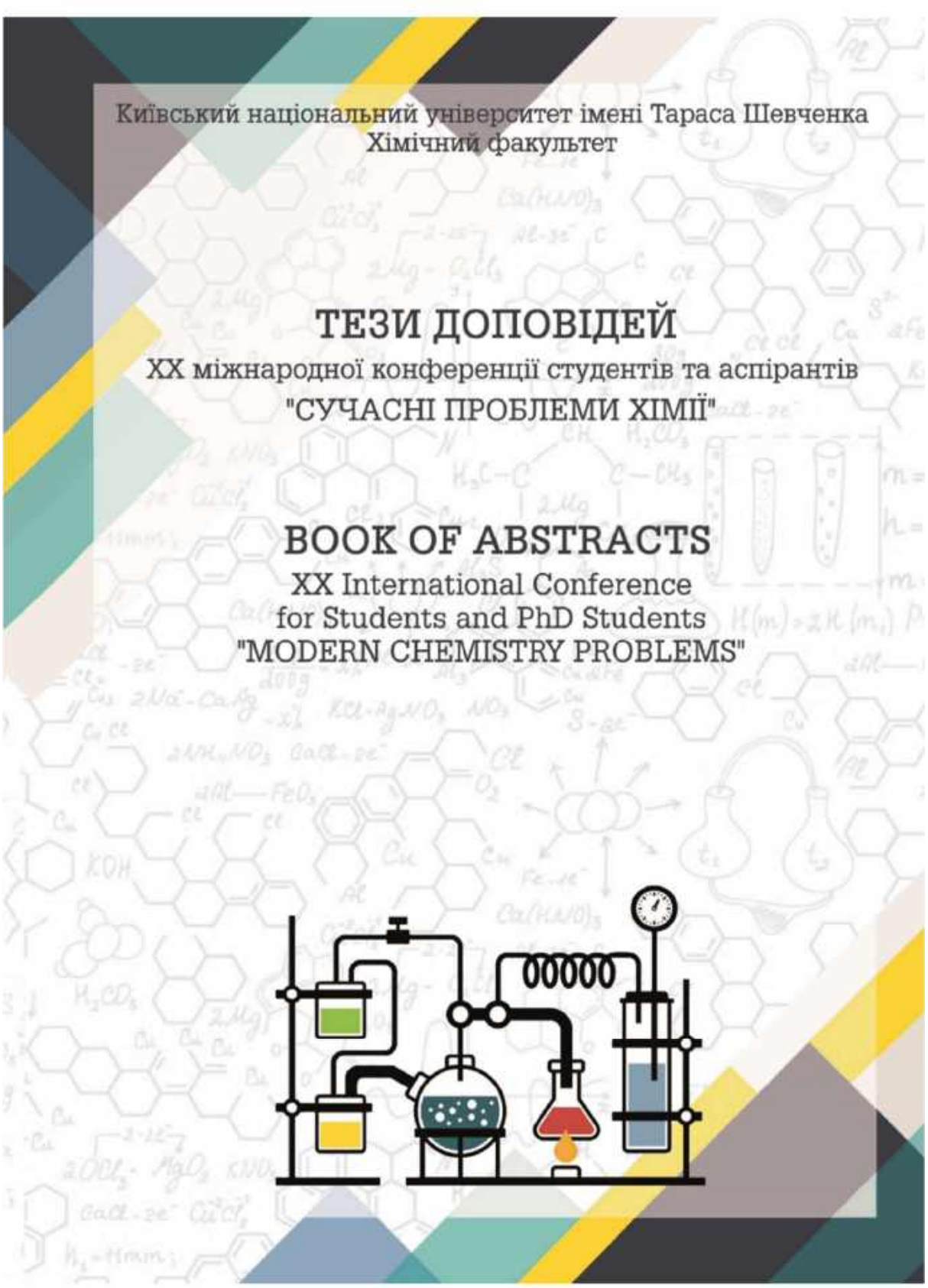
(11) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; Del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001−2011). *Chem. Rev.* **2014**, *114*, 2432−2506.

(12) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in Medicinal Chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320−330.
(13) Isanbor, C.; O'Hagan, D. Fluorine in Medicinal Chemistry: A Review of Anti-Cancer Agents. *J. Fluorine Chem.* **2006**, *127*, 303−319.
(14) Inoue, M.; Sumii, Y.; Shibata, N. Contribution of Organofluorine Compounds to Pharmaceuticals. *ACS Omega* **2020**, *5*, 10633−10640.
(15) Yu, Y.; Liu, A.; Dhawan, G.; Mei, H.; Zhang, W.; Izawa, K.; Soloshonok, V. A.; Han, J. Fluorine-Containing Pharmaceuticals Approved by the FDA in 2020: Synthesis and Biological Activity. *Chin. Chem. Lett.* **2021**, *32*, 3342−3354.
(16) Mei, H.; Remete, A. M.; Zou, Y.; Moriwaki, H.; Fustero, S.; Kiss, L.; Soloshonok, V. A.; Han, J. Fluorine-Containing Drugs Approved by the FDA in 2019. *Chin. Chem. Lett.* **2020**, *31*, 2401−2413.
(17) Xing, L.; Keefer, C.; Brown, M. F. Fluorine Multipolar Interaction: Toward Elucidating Its Energetics in Binding Recognition. *J. Fluorine Chem.* **2017**, *198*, 47−53.
(18) Dalvit, C.; Invernizzi, C.; Vulpetti, A. Fluorine as a Hydrogen-Bond Acceptor: Experimental Evidence and Computational Calculations. *Chem. Eur. J.* **2014**, *20*, 11058−11068.
(19) Zafrani, Y.; Yeffet, D.; Sod-Moriah, G.; Berliner, A.; Amir, D.; Marciano, D.; Gershonov, E.; Saphier, S. Difluoromethyl Bioisostere: Examining the "Lipophilic Hydrogen Bond Donor" Concept. *J. Med. Chem.* **2017**, *60*, 797−804.
(20) Pollock, J.; Borkin, D.; Lund, G.; Purohit, T.; Dyguda-Kazimierowicz, E.; Grembecka, J.; Cierpicki, T. Rational Design of Orthogonal Multipolar Interactions with Fluorine in Protein-Ligand Complexes. *J. Med. Chem.* **2015**, *58*, 7465−7474.
(21) Panini, P.; Chopra, D. Understanding of Noncovalent Interactions Involving Organic Fluorine. *Hydrogen Bonded Supramolecular Structures*; Springer: Berlin Heidelberg, 2015; pp 37−67.
(22) Grygorenko, O. O.; Volochnyuk, D. M.; Ryabukhin, S. V.; Judd, D. B. The Symbiotic Relationship Between Drug Discovery and Organic Chemistry. *Chem. Eur. J.* **2020**, *26*, 1196−1237.
(23) Doveston, R.; Marsden, S.; Nelson, A. Towards the Realisation of Lead-Oriented Synthesis. *Drug Discovery Today* **2014**, *19*, 813−819.
(24) Nadin, A.; Hattotuwagama, C.; Churcher, I. Lead-Oriented Synthesis: A New Opportunity for Synthetic Chemistry. *Angew. Chem., Int. Ed.* **2012**, *51*, 1114−1122.
(25) Lovering, F. Escape from Flatland 2: Complexity and Promiscuity. *Med. Chem. Commun.* **2013**, *4*, 515−519.
(26) Ritchie, T. J.; Macdonald, S. J. F.; Peace, S.; Pickett, S. D.; Luscombe, C. N. The Developability of Heteroaromatic and Heteroaliphatic Rings - Do Some Have a Better Pedigree as Potential Drug Molecules than Others? *MedChemComm* **2012**, *3*, 1062.
(27) Heravi, M. M.; Zadsirjan, V. Prescribed Drugs Containing Nitrogen Heterocycles: An Overview. *RSC Adv.* **2020**, *10*, 44247−44311.
(28) Bemis, G. W.; Murcko, M. A. The Properties of Known Drugs. 1. Molecular Frameworks. *J. Med. Chem.* **1996**, *39*, 2887−2893.
(29) Wang, T.; Phillips, E. M.; Dalby, S. M.; Sirota, E.; Axmanda, S.; Shultz, C. S.; Patel, P.; Waldman, J. H.; Alwedi, E.; Wang, X.; Zawatzky, K.; Chow, M.; Padivitage, N.; Weisel, M.; Whittington, M.; Duan, J.; Lu, T. Manufacturing Process Development for Belzutifan, Part 5: A Streamlined Fluorination-Dynamic Kinetic Resolution Process. *Org. Process Res. Dev.* **2022**, *26*, 543−550.
(30) Rizzo, C.; Amata, S.; Pibiri, I.; Pace, A.; Buscemi, S.; Palumbo Piccionello, A. FDA-Approved Fluorinated Heterocyclic Drugs from 2016 to 2022. *Int. J. Mol. Sci.* **2023**, *24*, 7728.
(31) Haycock-Lewandowski, S. J.; Wilder, A.; Åhman, J. Development of a Bulk Enabling Route to Maraviroc (UK-427,857), a CCR-5 Receptor Antagonist. *Org. Process Res. Dev.* **2008**, *12*, 1094−1103.
(32) Brown, K.; Dixey, M.; Weymouth-Wilson, A.; Linclau, B. The Synthesis of Gemcitabine. *Carbohydr. Res.* **2014**, *387*, 59−73.
(33) Sofia, M. J.; Bao, D.; Chang, W.; Du, J.; Nagarathnam, D.; Rachakonda, S.; Reddy, P. G.; Ross, B. S.; Wang, P.; Zhang, H.-R.; Bansal, S.; Espiritu, C.; Keilman, M.; Lam, A. M.; Steuer, H. M. M.; Niu, C.; Otto, M. J.; Furman, P. A. Discovery of a β-d-2′-Deoxy-2′-α-fluoro-2′-β-C-methyluridine Nucleotide Prodrug (PSI-7977) for the Treatment of Hepatitis C Virus. *J. Med. Chem.* **2010**, *53*, 7202−7218.
(34) Popovici-Muller, J.; Lemieux, R. M.; Artin, E.; Saunders, J. O.; Salituro, F. G.; Travins, J.; Cianchetta, G.; Cai, Z.; Zhou, D.; Cui, D.; Chen, P.; Straley, K.; Tobin, E.; Wang, F.; David, M. D.; Penard-Lacronique, V.; Quivoron, C.; Saada, V.; de Botton, S.; Gross, S.; Dang, L.; Yang, H.; Utley, L.; Chen, Y.; Kim, H.; Jin, S.; Gu, Z.; Yao, G.; Luo, Z.; Lv, X.; Fang, C.; Yan, L.; Olaharski, A.; Silverman, L.; Biller, S.; Su, S.-S. M.; Yen, K. Discovery of AG-120 (Ivosidenib): A First-in-Class Mutant IDH1 Inhibitor for the Treatment of IDH1 Mutant Cancers. *ACS Med. Chem. Lett.* **2018**, *9*, 300−305.
(35) Holovach, S.; Melnykov, K. P.; Poluektova, M. S.; Rozhenko, O. B.; Grygorenko, O. O. Incorporation of *gem*-Difluorocycloalkyl Substituents into Heterocycles *via* the Levin's "Nitrogen Deletion" Strategy. *J. Org. Pharm. Chem.* **2023**, *21*, 11−16.
(36) Proctor, R. S. J.; Phipps, R. J. Recent Advances in Minisci-Type Reactions. *Angew. Chem., Int. Ed.* **2019**, *58*, 13666−13699.
(37) Duncton, M. A. J. Minisci Reactions: Versatile CH-Functionalizations for Medicinal Chemists. *MedChemComm* **2011**, *2*, 1135−1161.
(38) Yan, M.; Lo, J. C.; Edwards, J. T.; Baran, P. S. Radicals: Reactive Intermediates with Translational Potential. *J. Am. Chem. Soc.* **2016**, *138*, 12692−12714.
(39) Minisci, F.; Bernardi, R.; Bertini, F.; Galli, R.; Perchinummo, M. Nucleophilic Character of Alkyl Radicals—VI: A New Convenient Selective Alkylation of Heteroaromatic Bases. *Tetrahedron* **1971**, *27*, 3575−3579.
(40) Seo, S.; Slater, M.; Greaney, M. F. Decarboxylative C−H Arylation of Benzoic Acids under Radical Conditions. *Org. Lett.* **2012**, *14*, 2650−2653.
(41) Liu, X.; Wang, Z.; Cheng, X.; Li, C. Silver-Catalyzed Decarboxylative Alkynylation of Aliphatic Carboxylic Acids in Aqueous Solution. *J. Am. Chem. Soc.* **2012**, *134*, 14330−14333.
(42) Zhao, W.-M.; Chen, X.-L.; Yuan, J.-W.; Qu, L.-B.; Duan, L.-K.; Zhao, Y.-F. Silver Catalyzed Decarboxylative Direct C2-Alkylation of Benzothiazoles with Carboxylic Acids. *Chem. Commun.* **2014**, *50*, 2018−2020.
(43) Zhang, L.; Liu, Z.-Q. Molecular Oxygen-Mediated Minisci-Type Radical Alkylation of Heteroarenes with Boronic Acids. *Org. Lett.* **2017**, *19*, 6594−6597.
(44) Dong, J.; Yue, F.; Song, H.; Liu, Y.; Wang, Q. Visible-Light-Mediated Photoredox Minisci C-H Alkylation with Alkyl Boronic Acids Using Molecular Oxygen as an Oxidant. *Chem. Commun.* **2020**, *56*, 12652−12655.
(45) Lockner, J. W.; Dixon, D. D.; Risgaard, R.; Baran, P. S. Practical Radical Cyclizations with Arylboronic Acids and Trifluoroborates. *Org. Lett.* **2011**, *13*, 5628−5631.
(46) Matsui, J. K.; Molander, G. A. Organocatalyzed, Photoredox Heteroarylation of 2-Trifluoroboratochromanones via C-H Functionalization. *Org. Lett.* **2017**, *19*, 950−953.
(47) Molander, G. A.; Colombel, V.; Braz, V. A. Direct Alkylation of Heteroaryls Using Potassium Alkyl- and Alkoxymethyltrifluoroborates. *Org. Lett.* **2011**, *13*, 1852−1855.
(48) Presset, M.; Fleury-Brégeot, N.; Oehlrich, D.; Rombouts, F.; Molander, G. A. Synthesis and Minisci Reactions of Organotrifluoroborate Building Blocks. *J. Org. Chem.* **2013**, *78*, 4615−4619.
(49) Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. Direct C−H Arylation of Electron-Deficient Heterocycles with Arylboronic Acids. *J. Am. Chem. Soc.* **2010**, *132*, 13194−13196.
(50) Matsui, J. K.; Primer, D. N.; Molander, G. A. Metal-free C−H alkylation of heteroarenes with alkyltrifluoroborates: a general protocol for 1°, 2° and 3° alkylation. *Chem. Sci.* **2017**, *8*, 3512−3522.
(51) Murarka, S.; Studer, A. Zinc Triflate Catalyzed Aerobic Cross-Dehydrogenative Coupling (CDC) of Alkynes with Nitrones: A New Entry to Isoxazoles. *Org. Lett.* **2011**, *13*, 2746−2749.

https://doi.org/10.1021/acsorginorgau.4c00028
ACS Org. Inorg. Au 2024, 4, 424−431

(52) Fujiwara, Y.; Domingo, V.; Seiple, I. B.; Gianatassio, R.; Del Bel, M.; Baran, P. S. Practical C-H Functionalization of Quinones with Boronic Acids. *J. Am. Chem. Soc.* **2011**, *133*, 3292−3295.
(53) Galloway, J. D.; Mai, D. N.; Baxter, R. D. Silver-Catalyzed Minisci Reactions Using Selectfluor as a Mild Oxidant. *Org. Lett.* **2017**, *19*, 5772−5775.
(54) Sorin, G.; Martinez Mallorquin, R.; Contie, Y.; Baralle, A.; Malacria, M.; Goddard, J.-P.; Fensterbank, L. Oxidation of Alkyl Trifluoroborates: An Opportunity for Tin-Free Radical Chemistry. *Angew. Chem., Int. Ed.* **2010**, *49*, 8721−8723.
(55) Yasu, Y.; Koike, T.; Akita, M. Visible Light-Induced Selective Generation of Radicals from Organoborates by Photoredox Catalysis. *Adv. Synth. Catal.* **2012**, *354*, 3414−3420.
(56) Wang, J.; Li, G.-X.; He, G.; Chen, G. Photoredox-Mediated Minisci Alkylation of N-Heteroarenes Using Carboxylic Acids and Hypervalent Iodine. *Asian J. Org. Chem.* **2018**, *7*, 1307−1310.
(57) Lai, X.-L.; Shu, X.-M.; Song, J.; Xu, H.-C. Electrophotocatalytic Decarboxylative C-H Functionalization of Heteroarenes. *Angew. Chem. Int. Ed.* **2020**, *59*, 10626−10632.
(58) Garza-Sanchez, R. A.; Tlahuext-Aca, A.; Tavakoli, G.; Glorius, F. Visible Light-Mediated Direct Decarboxylative C-H Functionalization of Heteroarenes. *ACS Catal.* **2017**, *7*, 4057−4061.
(59) Zhang, X.-Y.; Weng, W.-Z.; Liang, H.; Yang, H.; Zhang, B. Visible-Light-Initiated, Photocatalyst-Free Decarboxylative Coupling of Carboxylic Acids with N-Heterocycles. *Org. Lett.* **2018**, *20*, 4686−4690.
(60) Li, Z.; Wang, X.; Xia, S.; Jin, J. Ligand-Accelerated Iron Photocatalysis Enabling Decarboxylative Alkylation of Heteroarenes. *Org. Lett.* **2019**, *21*, 4259−4265.
(61) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herlé, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. Practical and Innate Carbon-Hydrogen Functionalization of Heterocycles. *Nature* **2012**, *492*, 95−99.
(62) Holovach, S.; Poroshyn, I.; Melnykov, K. P.; Liashuk, O. S.; Pariiska, O.; Kolotilov, S. V.; Rozhenko, O. B.; Volochnyuk, D. M.; Grygorenko, O. O. Parallel Minisci Reaction of *gem*-Difluorocycloalkyl Building Blocks. *ChemRxiv* **2024**. DOI: 10.26434/chemrxiv-2024-3fmn9.
(63) Li, J.; Huang, C.-Y.; Han, J.-T.; Li, C.-J. Development of a Quinolinium/Cobaloxime Dual Photocatalytic System for Oxidative C-C Cross-Couplings via H_2 Release. *ACS Catal.* **2021**, *11*, 14148−14158.
(64) Shore, D. G. M.; Wasik, K. A.; Lyssikatos, J. P.; Estrada, A. A. Minisci Alkylations of Electron-Deficient Pyrimidines with Alkyl Carboxylic Acids. *Tetrahedron Lett.* **2015**, *56*, 4063−4066.
(65) Ma, J.; Ding, Y.; Gu, C.; Zhai, G.; Liu, Y.; Wen, J.; Rong, X.; Luo, C.; Qiu, Y.; Zhang, P. Degradation of Benzothiazole Pollutant by Sulfate Radical-Based Advanced Oxidation Process. *Environ. Technol.* **2022**, *43*, 2834−2843.
(66) O'Hara, F.; Blackmond, D. G.; Baran, P. S. Radical-Based Regioselective C-H Functionalization of Electron-Deficient Heteroarenes: Scope, Tunability, and Predictability. *J. Am. Chem. Soc.* **2013**, *135*, 12122−12134.
(67) Crespi, S.; Fagnoni, M. Generation of Alkyl Radicals: From the Tyranny of Tin to the Photon Democracy. *Chem. Rev.* **2020**, *120*, 9790−9833.
(68) Suzuki, J.; Tanigawa, M.; Inagi, S.; Fuchigami, T. Electrochemical Oxidation of Organotrifluoroborate Compounds. *ChemElectroChem* **2016**, *3*, 2078−2083.
(69) Duan, K.; Yan, X.; Liu, Y.; Li, Z. Recent Progress in the Radical Chemistry of Alkylborates and Alkylboronates. *Adv. Synth. Catal.* **2018**, *360*, 2781−2795.
(70) Lee, J.; von Gunten, U.; Kim, J.-H. Persulfate-Based Advanced Oxidation: Critical Assessment of Opportunities and Roadblocks. *Environ. Sci. Technol.* **2020**, *54*, 3064−3081.
(71) Madhavan, V.; Levanon, H.; Neta, P. Decarboxylation by SO4- Radicals. *Radiat. Res.* **1978**, *76*, 15−22.
(72) van der Klis, F.; van den Hoorn, M. H.; Blaauw, R.; van Haveren, J.; van Es, D. S. Oxidative Decarboxylation of Unsaturated Fatty Acids. *Eur. J. Lipid Sci. Technol.* **2011**, *113*, 562−571.
(73) Tauber, J.; Imbri, D.; Opatz, T. Radical Addition to Iminium Ions and Cationic Heterocycles. *Molecules* **2014**, *19*, 16190−16222.
(74) Bond, A. M.; Oldham, K. B.; Snook, G. A. Use of the Ferrocene Oxidation Process To Provide Both Reference Electrode Potential Calibration and a Simple Measurement (via Semiintegration) of the Uncompensated Resistance in Cyclic Voltammetric Studies in High-Resistance Organic Solvents. *Anal. Chem.* **2000**, *72*, 3492−3496.
(75) Shu, C.; Noble, A.; Aggarwal, V. K. Photoredox-Catalyzed Cyclobutane Synthesis by a Deboronative Radical Addition-Polar Cyclization Cascade. *Angew. Chem., Int. Ed.* **2019**, *58*, 3870−3874.
(76) Liu, S.-P.; He, Y.-H.; Guan, Z. Photoredox-Catalyzed Radical-Radical Cross-Coupling of Sulfonyl Chlorides with Trifluoroborate Salts. *J. Org. Chem.* **2023**, *88*, 11161−11172.
(77) Lima, F.; Sharma, U. K.; Grunenberg, L.; Saha, D.; Johannsen, S.; Sedelmeier, J.; Van der Eycken, E. V.; Ley, S. V. A Lewis Base Catalysis Approach for the Photoredox Activation of Boronic Acids and Esters. *Angew. Chem., Int. Ed.* **2017**, *56*, 15136−15140.
(78) Erb, W.; Richy, N.; Hurvois, J.-P.; Low, P. J.; Mongin, F. From Ferrocene to 1,2,3,4,5-Pentafluoroferrocene: Halogen Effect on the Properties of Metallocene. *Dalton Trans.* **2021**, *50*, 16933−16938.
(79) Pelzer, K. M.; Cheng, L.; Curtiss, L. A. Effects of Functional Groups in Redox-Active Organic Molecules: A High-Throughput Screening Approach. *J. Phys. Chem. C* **2017**, *121*, 237−245.
(80) Minisci, F.; Vismara, E.; Morini, G.; Fontana, F.; Levi, S.; Serravalle, M.; Giordano, C. Polar Effects in Free-Radical Reactions. Selectivity and Reversibility in the Homolytic Benzylation of Protonated Heteroaromatic Bases. *J. Org. Chem.* **1986**, *51*, 476−479.
(81) Minisci, F.; Citterio, A.; Vismara, E.; Giordano, C. Polar Effects in Free-Radical Reactions. New Synthetic Developments in the Functionalization of Heteroaromatic Bases by Nucleophilic Radicals. *Tetrahedron* **1985**, *41*, 4157−4170.
(82) Minisci, F.; Vismara, E.; Fontana, F.; Morini, G.; Serravalle, M.; Giordano, C. Polar Effects in Free-Radical Reactions. Solvent and Isotope Effects and Effects of Base Catalysis on the Regio- and Chemoselectivity of the Substitution of Protonated Heteroaromatic Bases by Nucleophilic Carbon-Centered Radicals. *J. Org. Chem.* **1987**, *52*, 730−736.
(83) Yang, H.; Zhou, W.; Yang, L.; Deng, J.; Hu, Q.; Wei, H.; Au, C.; Yi, B. $Ag^+/S_2O_8^{2-}$ System for the Degradation of Aqueous Flutriafol. *Environ. Prot. Eng.* **2018**, *44*, 57−72.
(84) Oh, W.-D.; Dong, Z.; Lim, T.-T. Generation of Sulfate Radical through Heterogeneous Catalysis for Organic Contaminants Removal: Current Development, Challenges and Prospects. *Appl. Catal., B* **2016**, *194*, 169−201.
(85) Holovach, S.; Melnykov, K. P.; Skreminskiy, A.; Herasymchuk, M.; Tavlui, O.; Aloshyn, D.; Borysko, P.; Rozhenko, A. B.; Ryabukhin, S. V.; Volochnyuk, D. M.; Grygorenko, O. O. Effect of *gem*-Difluorination on the Key Physicochemical Properties Relevant to Medicinal Chemistry: The Case of Functionalized Cycloalkanes. *Chem. Eur. J.* **2022**, *28*, No. e202200331.
(86) Baxter, R. D.; Liang, Y.; Hong, X.; Brown, T. A.; Zare, R. N.; Houk, K. N.; Baran, P. S.; Blackmond, D. G. Mechanistic Insights into Two-Phase Radical C-H Arylations. *ACS Cent. Sci.* **2015**, *1*, 456−462.
(87) Pavlishchuk, V. V.; Addison, A. W. Conversion constants for redox potentials measured versus different reference electrodes in acetonitrile solutions at 25°C. *Inorg. Chim. Acta* **2000**, *298*, 97−102.
(88) Yu, L.; Wang, J.; Guo, D.; You, W.; Liu, M.; Zhang, L.; Li, C. The Kinetics and Mechanism of Photo-Assisted Ag(I)-Catalysed Water Oxidation with $S_2O_8^{2-}$. *Dalton Trans.* **2015**, *44*, 710−717.
(89) Armarego, W. L. F.; Chai, C. *Purification of Laboratory Chemicals*, 5th ed.; Elsevier: Oxford, 2003.

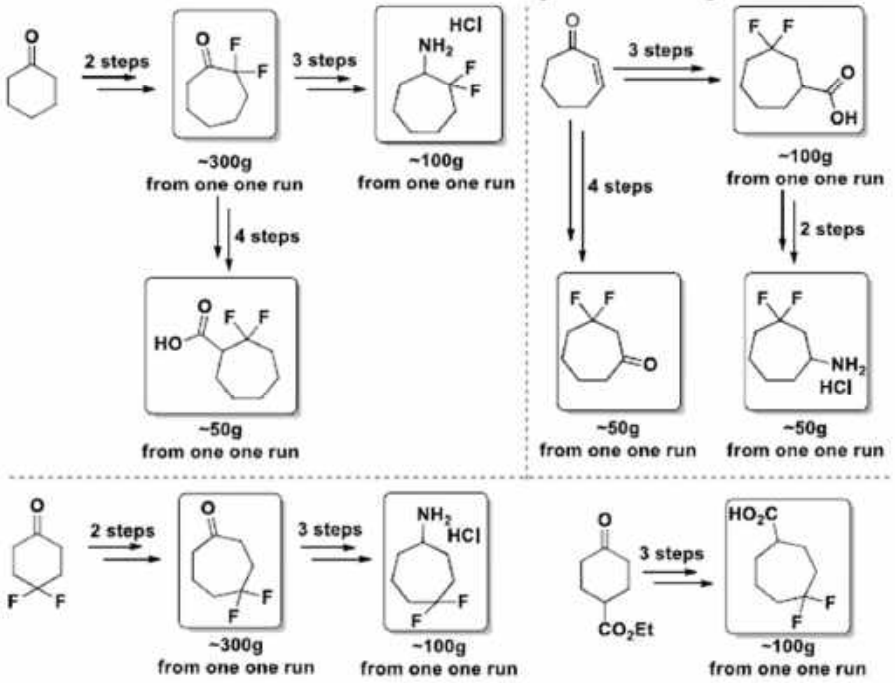
ДОДАТОК 3. ТЕЗИ ДОПОВІДЕЙ НАУКОВИХ КОНФЕРЕНЦІЙ ЗА ТЕМОЮ ДИСЕРТАЦІЇ



СИНТЕЗ БІЛДІНГ-БЛОКІВ НА ОСНОВІ ГЕМ-ДИФТОРЦИКЛОГЕПТАНІВ.

Герасимчук М.В.[1], *Мельников К.П.*[1,2], *Рябухін С.В.*[1,2]
[1] Київський національний університет імені Тараса Шевченка
01601, Київ, вул. Володимирська, 64/13;
[2] ТОВ «НВП «ЄНАМІН»» 02000, Київ, вул. Червоноткацька 78.

Білдінг-блоки на основі фтор заміщених циклоалканів є важливими структурними елементами, значення яких стрімко росте в різних галузях. Основними з них є агрохімія та пошук нових лікарських препаратів. В цій роботі з масштабованого синтезу похідних гем-дифторциклоалканів ми сфокусувались на циклогептанах. Літературний аналіз показав що на данний момент описано синтез лише 3 з 9 можливих речовин в мікрокількостях.

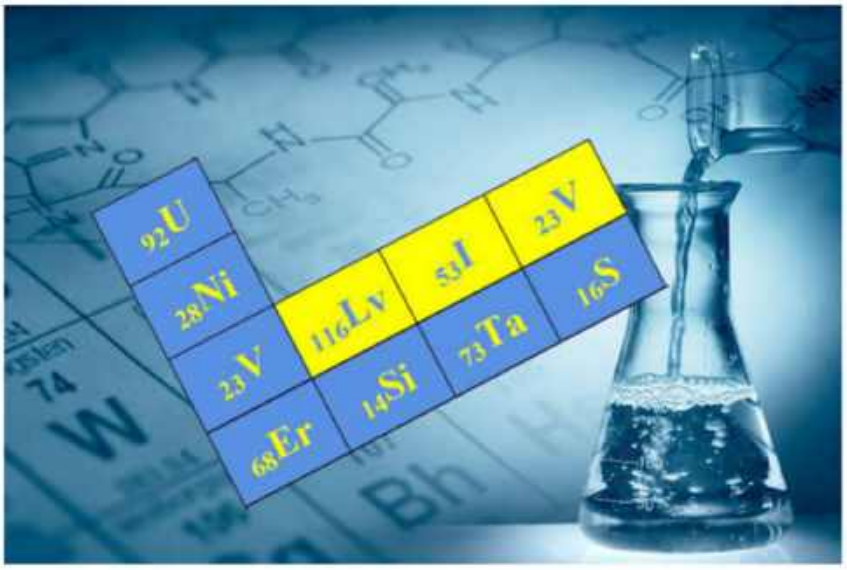


В данній роботі описаний синтез циклогептиламінів, кетонів та карбонових кислот гем-дифтор заміщених по всіх можливих положеннях циклогептанового кільця. Всі процедури є ефективними при масштабуванні синтезів до 50+ грам і можуть бути використані для отримання білдінг-блоків на основі гем-дифторциклогептанів з різним положенням замісників які в свою чергу можуть бути потенційно важливими сруктурними елементами для агрохімії та медичної хімії

XIX НАУКОВА КОНФЕРЕНЦІЯ

“ЛЬВІВСЬКІ ХІМІЧНІ ЧИТАННЯ – 2023”

присвячена 150-річчю
Наукового товариства імені Шевченка



ФІЗИКО-ХІМІЧНІ ВЛАСТИВОСТІ НАСИЧЕНИХ ФЛУОРОВМІСНИХ КАРБО- ТА ГЕТЕРОЦИКЛІВ ДЛЯ ПОТРЕБ МЕДИЧНОЇ ХІМІЇ

Олександр Григоренко,[1,2] Костянтин Мельников,[1,2] Сергій Головач,[1,3] Олександр Демчук,[1,3] Олександр Грищук,[1,2] Антон Черних,[1,2] Богдан Ващенко,[1,2] Дмитро Волочнюк[1,2,3]

[1] ТОВ «НВП «Спамін», вул. Червоноткацька, 78, 02066 Київ, Україна
[2] Київський національний університет імені Тараса Шевченка, вул. Володимирська, 60, 01601 Київ, Україна
[3] Інститут органічної хімії Національної академії наук України, вул. Академіка Кухаря, 5, 02066 Київ, Україна
e-mail: gregor@univ.kiev.ua

Визначна роль флуороорганічних сполук у створенні лікарських засобів є загальновизнаною та широко відомою. Введення атомів флуору в органічні молекули може змінювати їх фізико-хімічні властивості, модулювати зв'язування з біологічною мішенню, а також покращувати метаболічну стабільність. Хоча є багато прикладів, що ілюструють вплив атомів флуору на фізико-хімічні властивості речовин, такі, як ліпофільність (Log*P*) або кислотно-основні властивості (pK_a), систематичні властивості у цій галузі є порівняно нечастими, особливо у випадку насичених (гетеро)циклічних систем.

У даній роботі представлено результати вичерпних досліджень фізико-хімічних властивостей (pK_a, Log*P*, розчинність у воді (S_w)), а також метаболічної стабільності (CL_{int}) наступних класів сполук (Рисунок 1):

- функціоналізовані *гем*-дифлуоровані циклоалкани;
- флуороалкіл-заміщені похідні малих карбоциклів;
- флуороалкіл-замішені похідні насичених гетероциклічних амінів;
- моно- та дифлуоровані насичені гетероциклічні аміни.

На основі діаграм pK_a – Log*P* (типу діаграм Крейга) передбачені можливості для ізостерних замін у ряду флуоровмісних насичених (гетеро)циклічних систем.

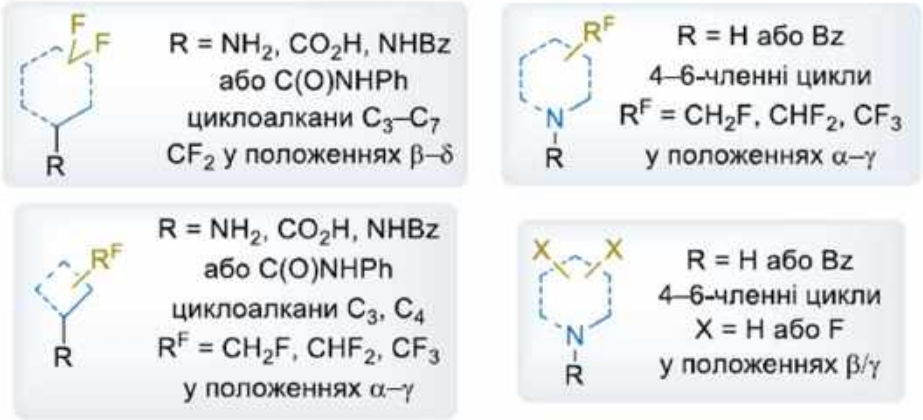


Рисунок 1

П6

12

Київський національний університет імені Тараса Шевченка

Хімічний факультет



Тези доповідей

XXV Міжнародна конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії»

СП ХФ

Київ, 15-17 травня 2024 р.

НОВІ *ПАРА*-НІТРОФЕНОЛЬНІ ЕСТЕРИ *ПАРА*-ЗАМІЩЕНИХ БЕНЗОЙНИХ КИСЛОТ ЯК ПЕРСПЕКТИВНІ СУБСТРАТИ pNP-ТЕСТУ

Бондарук А.А.,[1] *Мельников К.П.*,[1,2] *Ляшук О.С.*,[1,2] *Григоренко О.О.*,[1,2] *Бас Ю.П.*[1], *Кеда Т.Є.*[1]

[1] Київський національний університет імені Тараса Шевченка
01601, Київ, вул. Володимирська, 64/13; nastabondaruk66@gmail.com
[2] ТОВ «НВП «Снамін», вул. Червоноткацька, 78, 02066 Київ, Україна

Біокаталітичні властивості ферментів і препаратів на їхній основі використовують в багатьох галузях, зокрема при виробництві харчових продуктів, лікарських засобів та біодизеля. Одним із найважливіших етапів їхнього ефективного впровадження у промисловість є визначення ферментативної активності, зокрема з використанням спектрофотометричного кінетичного методу з субстратом на основі *пара*-нітрофенольних естерів – pNP-тесту. Вибір субстрату впливає на вибірковість і чутливість реакції гідролізу, що каталізує фермент.

Метою даної роботи було встановити кількісні значення ефекту замісників на перерозподіл електронної густини в пара-заміщених бензойних кислотах та відповідні реакційні властивості нових естерів *пара*-нітрофенолу для їх подальшого використання у pNP-тестах визначення ферментативної активності.

Для досягнення мети було визначено константи дисоціації заміщених похідних бензойної кислоти та константи Гаммета замісників нітрофенілбензоатних естерів на їхній основі.

З використанням методу потенціометрії зі скляним pH-чутливим електродом за температури 25 °C отримано криві титрування розчинів *пара*-заміщених похідних бензойної кислоти, які в подальшому використали для розрахунку констант дисоціації сполук.

Метод молекулярної абсорбційної спектроскопії застосовано для розрахунку констант швидкості гідролізу *пара*-нітрофенілбензоатних естерів за утворенням *пара*-нітрофенолу як основного забарвленого продукту реакції під дією лугу. За рівнянням Гаммета, що пов'язує константи швидкостей реакцій з константою замісника σ, розраховано значення останньої. Отримані значення констант σ дають можливість простежити естерну активність залежно від замісника. Передбачувано, що найвища константа швидкості гідролізу належить естеру на основі *пара*-трифторметил-бензоату. Попередні випробування показали, що рибонуклеаза проявляє ферментативну активність щодо обраної системи. Це вказує на можливість подальшої розробки нового pNP-тесту на цій основі.

Київський національний університет імені Тараса Шевченка

Хімічний факультет



Тези доповідей

XXV Міжнародна конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії»

Київ, 15-17 травня 2024 р.

3,3-ДИФЛУОРООКСЕТАН-2-ІЛ – ПЕРСПЕКТИВНИЙ ФЛУОРОВМІСНИЙ ЗАМІСНИК ДЛЯ ПОТРЕБ МЕДИЧНОЇ ХІМІЇ

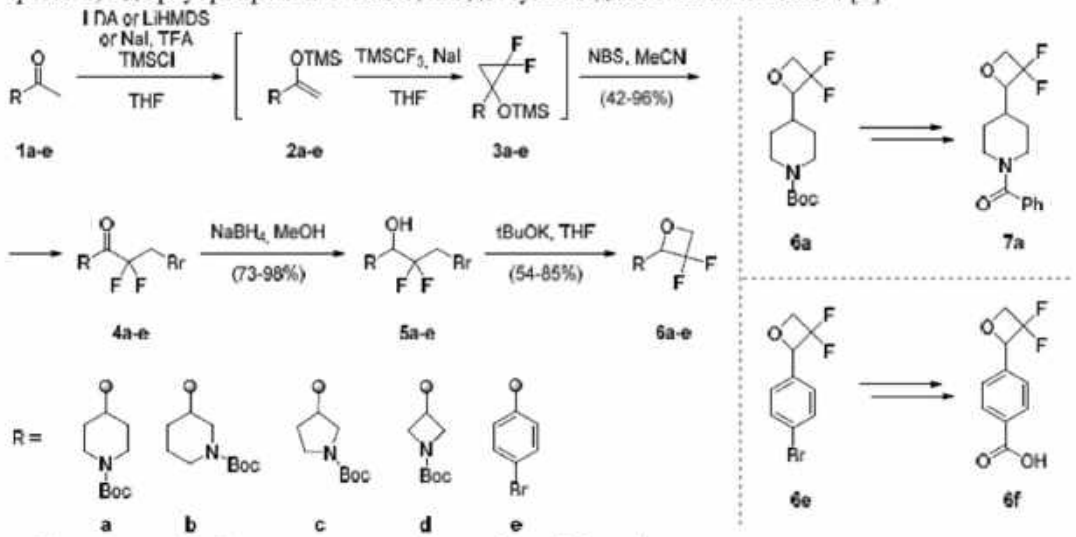
Федінчик А.В.[1,2], *Герасимчук М.В.*[1,2], *Мельников К.П.*[1,2], *Ляшук, О. С.*[1,2], *Григоренко О.О.*[1,2]

[1]Київський національний університет імені Тараса Шевченка
01601, Київ, вул. Володимирська, 64/13. fedinchyk.n@gmail.com
[2]ТОВ НВП "Єнамін", 02094, м. Київ, вул. Вінстона Черчилля, 67

Функціональна група є однією із базових концепції в органічній хімії та суміжних галузях. Розвиток ідей біоізостерії та ізостеричної заміни в медичній хімії призвів до значного зростання попиту на нові функціональні групи з перспективними комбінаціями хімічних та фізико-хімічних властивостей.

Кільце оксетану у створенні лікарських засобів є порівняно маловивченим структурним мотивом, який при цьому виявляє привабливі властивості, як-от низька молекулярна маса, висока полярність та виражена тривимірність [1]. Поєднання оксетанового циклу та фторованих замісників може привести до створення більш ефективних та безпечних біологічно активних сполук з мінімальними побічними ефектами.

У роботі розроблено ефективний підхід до масштабованого синтезу будівельних блоків з 3,3-дифлуороксетан-2-ільним замісником. Метод ґрунтується на гетероциклізації 3-бромо-2,2-дифлуоропропан-1-олів **5**, які доступні відновленням кетонів **4** [2]:



У рамках роботи вивчено потенціал 3,3-дифлуороксетанового угрупування як перспективної функціональної групи для потреб медичної хімії. Так, досліджено ідко фазном бензаміду **7a** та порівняно із властивостями низки структурних аналогів. Похідну карбонової кислоти **6f** використано у дослідженнях швидкості гідролізу естерного зв'язку. Також сполуку **6f** використано як структурний елемент аналогу протиракового препарату теновіну.

References

[1]. Rojas J. J., Bull J. A. *J. Med. Chem.* **2023**, *66*(18), 12697–12709.

[2]. Fedinchyk A., Herasymchuk M., Smirnov V. O., Melnykov K. P., Yarmoliuk D. V., Kyrylchuk A. A., Grygorenko O. O., *Eur. J. Org. Chem.* **2022**, *e202200274*

Київський національний університет імені Тараса Шевченка

Хімічний факультет



Тези доповідей

XXV Міжнародна конференція студентів, аспірантів та молодих вчених «Сучасні проблеми хімії»

Київ, 15-17 травня 2024 р.

ДОСЛІДЖЕННЯ ФІЗИКО-ХІМІЧНИХ ВЛАСТИВОСТЕЙ *ГЕМ*-ДИФТОРОВАНИХ *О*-ГЕТЕРОЦИКЛІВ

Шатня В.Ю.[1,3], *Горбенко А.Е.*[1], *Головач С.М*[1,2], *Мельников К.П.*[1,4], *Ляшук О.С.*[1,4] *Григоренко О.О.*[1, 4]
[1]ТОВ «НВП «Єнамін», вул. Червоноткацька, 78, 02066 Київ, Україна [2]Інститут органічної хімії НАН України, вул. Академіка Кухаря, 5, 02066 Київ, Україна
[3]НТУУ «КПІ ім. Ігоря Сікорського», проспект Перемоги, 37, Київ, 03056
[4]Київський національний університет імені Тараса Шевченка
01601, Київ, вул. Володимирська, 64/13
v.schatniaya@gmail.com

Введення флуоровмісних замісників в органічні молекули є добре відомим інструментом, що використовується у процесі розробки лікарських засобів, ефективність якого можна проілюструвати численними комерційно успішними флуоровмісними лікарськими засобами.

Циклічні системи є основними структурними мотивами, що поширені в широкому спектрі біологічно активних сполук. Розуміння впливу конфігурації даних систем на властивості ліків є невід'ємним для раціонального дизайну сполук – потенційних лікарських засобів у фармацевтичних дослідженнях та розробках.

Відомо, що введення *гем*-дифлуорциклоалкільної групи (однієї із основних представників флуоровмісних груп) суттєво впливає на фізико-хімічні та фармакологічні властивості лікарських засобів, шляхом змін заселеностей конформерів, модуляції кислотно-основних властивостей та ліпофільності досліджуваної молекули.

Ми синтезували бібліотеку сполук, що містить *О*-вмісні насичені гетероцикли задля порівняння фізико-хімічних властивостей молекул до та після введення *гем*-дифторованих фрагментів. Після ряду вимірювань отримано графік залежності зміни pK_a (Рис.), з якого можна зробити висновок що введення *гем*-дифторованих фрагментів підвищує здатність дисоціювати у водному розчині. Поруч із цим, спостережене підвищення ліпофільності сприяє пасивному проникненню через біологічні мембрани, підвищуючи оральну біодоступність та розподіл препаратів у тканинах.

Фторування відкриває унікальні можливості для модуляції фізико-хімічних характеристик циклічних структур, тим самим впливаючи на їх взаємодію з біологічними мішенями та на фармакологічну поведінку. Використовуючи унікальні властивості атомів Флуору, медичні хіміки можуть адаптувати циклічні структури відповідно до потреб розробки сучасних ліків, покращуючи терапевтичні властивості і таким чином – розширюючи можливості лікування.

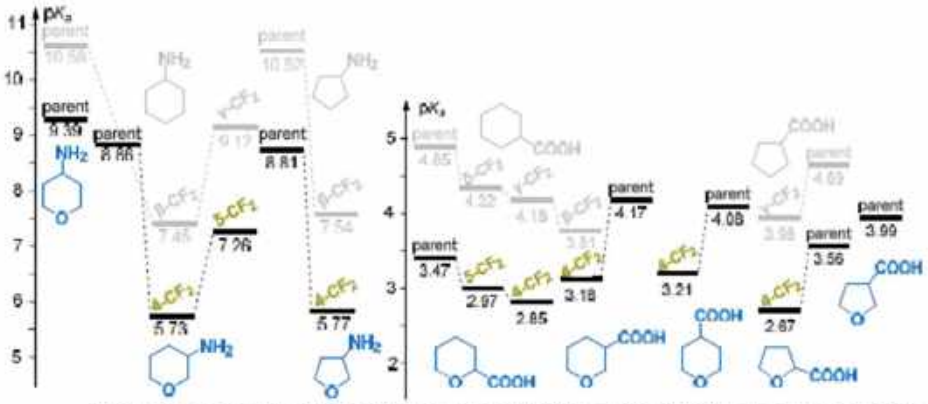


Рис. Вплив *гем*-дифторування на здатність дисоціювати у водному розчині

Київський національний університет імені Тараса Шевченка
Хімічний факультет

Тези доповідей

XXIII Міжнародна конференція
студентів, аспірантів та молодих вчених
"Сучасні проблеми хімії"

Book of abstracts

23rd International Conference for Students,
PhD students and young scientists
"Modern Chemistry Problems"





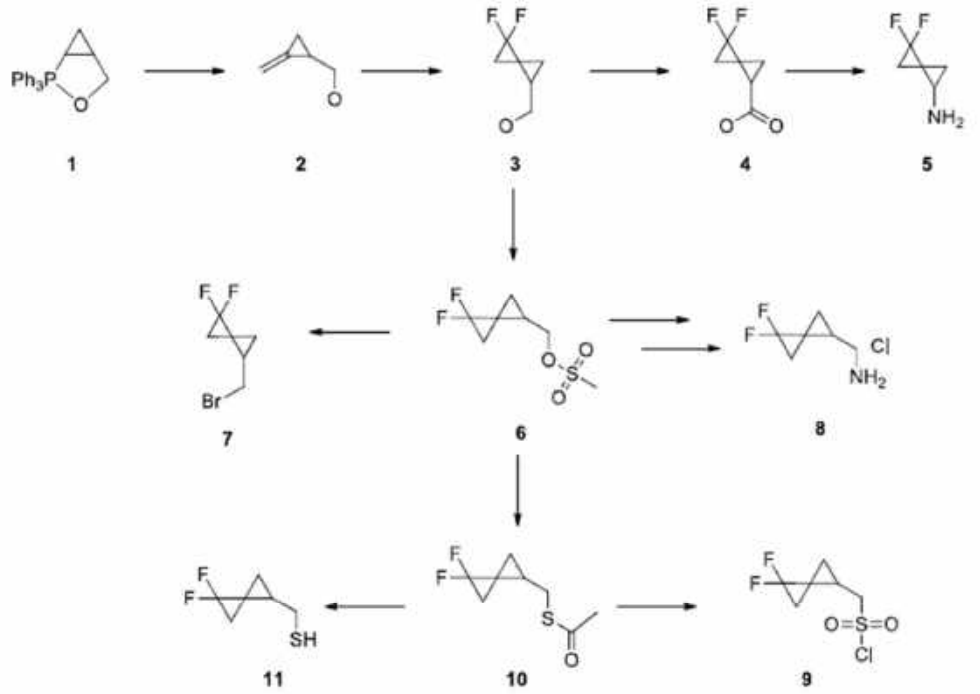
18 - 20 травня 2022 рік

ФУНКЦІОНАЛІЗОВАНІ ПОХІДНІ 4,4-ДИФЛУОРОСПІРО[2.2]ПЕНТАНУ

Волошина О.В.[1,2], *Мельников К.П.*,[1,2] *Шабликіна О.В.*,[1] *Григоренко О.О.*[1,2]
[1] Київський національний університет імені Тараса Шевченка
01601, Київ, вул. Володимирська, 64/13
[2]Enamine Ltd, 02094, Київ, вул. Червоноткацька, 78

Спіроциклічні сполуки становлять все більший інтерес в сучасній медичній хімії. Конформаційна обмеженість і велика кількість sp^3-гібридних атомів Карбону зумовлюють широке використання даного хемотипу в оптимізації сполук-лідерів. Введення спіроциклічного фрагменту дозволяє створити сполуки визначеної просторової будови, завдяки чому покращується ефективність зв`язування з мішенню. В той же час введення Флуору впливає на фізико-хімічні властивості органічних молекул, що дозволяє регулювати ADME параметри майбутніх лікарських засобів.

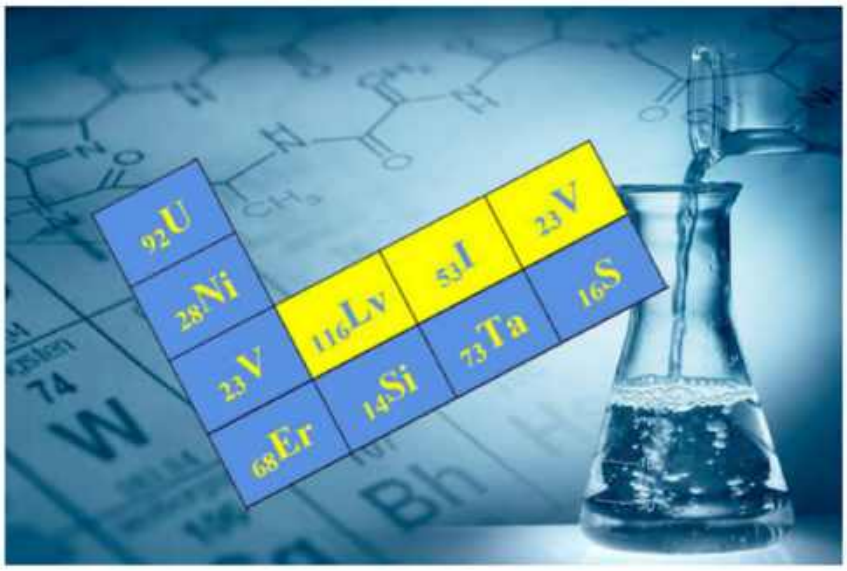
В даній роботі описано синтетичний підхід до фунукціоналізованих похідних 4,4-дифлуороспіро[2.2]пентану з комерційно доступних реагентів. Ключовими стадіями є розкриття оксафосфолану **1** з подальшим дифлуороциклопропануванням інтермедіату **3**. В якості джерела дифлуороркарбену був використаний $TMSCF_3$. Отримано ряд будівельних блоків даного типу. Оптимізовані методи синтезу дозволили отримати похідні 4,4-дифлуороспіро[2.2]пентану у мультиграмових кількостях з високими виходами. Встановлено вплив атомів Флуору на фізико-хімічні характеристики (pK_a та $\log P$) одержаних похідних.



ХІХ НАУКОВА КОНФЕРЕНЦІЯ

“ЛЬВІВСЬКІ ХІМІЧНІ ЧИТАННЯ – 2023”

присвячена 150-річчю
Наукового товариства імені Шевченка



ВПРОВАДЖЕННЯ МЕТОДУ УТВОРЕННЯ С–С ЗВ'ЯЗКУ ШЛЯХОМ «ВИДАЛЕННЯ АЗОТУ» У КОМБІНАТОРНУ ХІМІЮ

Сергій Головач,[1,2] Костянтин Мельников,[1,3] Ілля Порошин,[1,3] Олександр Григоренко,[1,3] Дмитро Волочнюк,[1,2] Олександр Роженко[2]

[1] ТОВ «НВП «Єнамін», вул. Червоноткацька, 78, 02066 Київ, Україна

[2] Інститут органічної хімії НАН України, вул. Академіка Кухаря, 5, 02066 Київ, Україна

[3] Київський національний університет імені Тараса Шевченка, вул. Володимирська, 60, 01601 Київ, Україна

e-mail: s.holovach@enamine.net

Створення нових лікарських засобів залежить від доступності відповідних початкових речовин, що, в свою чергу, залежить від здатності хіміків синтезувати нові молекули вчасно та ефективно. Тим часом, багато значних досягнень у синтезі органічних сполук не відразу впроваджуються в медичну та комбінаторну хімію; для більшості з них адаптація до синтезу бібліотек сполук зазвичай відбувається повільно. З іншого боку, модифікація карбонового ланцюга за допомогою «видалення азоту», розроблена науковою групою Левіна, є потужною стратегією, яка значно розширює можливості планування синтезу нових сполук. Використання цього підходу надає неочевидні можливості для модифікації сполук на пізній стадії синтезу. З іншого боку, цей метод можна розглядати як підхід до утворення зв'язків $C(sp^3) - C(sp^3)$. Оскільки вторинні аміни можна легко синтезувати з комерційно доступних вихідних речовин за допомогою низки добре відомих методів, це дозволяє суттєво урізноманітнити доступні бібліотеки синтезованих сполук.

Нами було розроблено метод паралельного $C(sp^3) - C(sp^3)$ сполучення ароматичних та гетероароматичних альдегідів та (гет)арилметиламінів на основі послідовності реакцій відновного амінування – «видалення азоту». Після попередніх експериментів було успішно синтезовано модельну бібліотеку сполук із 25 представників зі синтетичною ефективністю 76%. Оцінений хімічний простір, що став досяжним завдяки розробленому методу, охоплює майже 600 000 представників, які майже не представлені у наявних колекціях сполук.

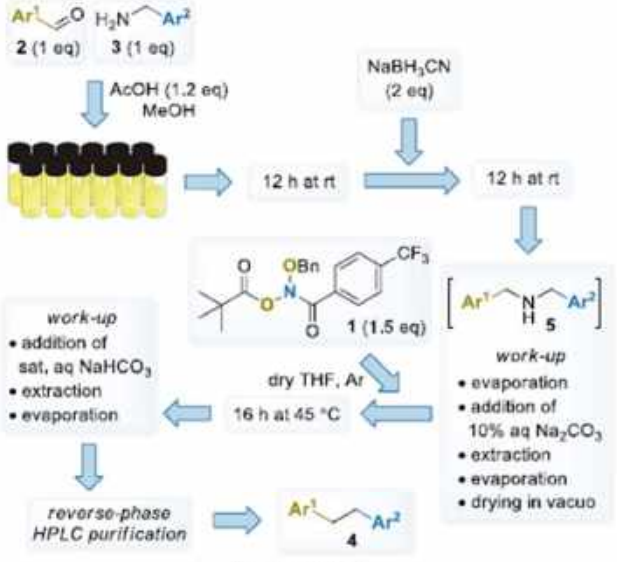


Рисунок 1.

У28


Київський національний університет імені Тараса Шевченка
Хімічний факультет
Тези доповідей
XXIV Міжнародна конференція
студентів, аспірантів та молодих вчених
"Сучасні проблеми хімії"
17-19 травня 2023 рік
СП
ХФ

ВВЕДЕННЯ ГЕМ-ДИФЛУОРОЦИКЛОАЛКІЛЬНИХ ЗАМІСНИКІВ У ГЕТЕРОЦИКЛИ ЧЕРЕЗ СТРАТЕГІЮ «ВИДАЛЕННЯ НІТРОГЕНУ» ЛЕВІНА

Полуектова М.[1,4], *Головач С.*[1,2], *Мельников К.П.*[1,3], *Григоренко О.О.*[1,3]

[1] ТОВ «НВП «Єнамін», вул. Червоноткацька, 78, 02066 Київ, Україна
mpoluektova356@gmail.com
[2] Інститут органічної хімії НАН України,
вул. Академіка Кухаря, 5, 02066 Київ, Україна
[3] Київський національний університет імені Тараса Шевченка,
вул. Володимирська, 60, 01601 Київ, Україна
[4] НТУУ «КПІ ім. Ігоря Сікорського», проспект Перемоги, 37, Київ, 03056

Введення флуоровмісних замісників в органічні молекули, що представляють інтерес для медичної хімії, є добре відомим підходом до розробки ліків, який можна проілюструвати численними флуоровмісними лікарськими засобами. Зокрема, *гем*-дифлуороциклоалкільні групи продемонстрували свою високу актуальність для відкриття сучасних ліків. Наприклад, вони були включені до фармацевтичних препаратів Маравірок і Івосиденіб.

На сьогоднішній день більшість методів включення *гем*-дифлуороциклоалкільних замісників у молекули базувалися на утворенні зв'язку Карбон – гетероатом. Будівельні блоки та синтетичні методології для створення зв'язку С–С за участю цих фрагментів є рідкісними та зазвичай базуються на багатостадійних перетвореннях. З іншого боку, методологія «виделення азоту» Левіна надає унікальну можливість побудувати зв'язок С–С незвичайним способом. По суті, цей підхід передбачає реакцію вторинних амінів з так званими аномерними амідами, що призводить до формальної екструзії фрагмента NH та об'єднання приєднаних до нього алкільних радикалів (рис.1). Нами було розроблено ефективний синтетичний підхід до синтезу гетероциклів, декорованих *гем*-дифлуороалкільними замісниками, з використанням методології «видалення Нітрогену» за Левіним. В умовах паралельного синтезу із застосуванням послідовності реакції відновного амінування та «видалення Нітрогену» було одержано міні-бібліотеку сполук, що містять гетероциклічні фрагменти та *гем*-дифлуороциклоалкільні замісники (рис.1). Було показано, що метод може бути використаним для одержання сполук із вищезгаданими структурними фрагментами, розділеними однією чи двома метиленовими ланками. Таким чином, ця новітня синтетична методологія є придатною для декорування гетероциклічних систем sp^3-збагаченими замісниками, що є привабливими для медичної хімії.

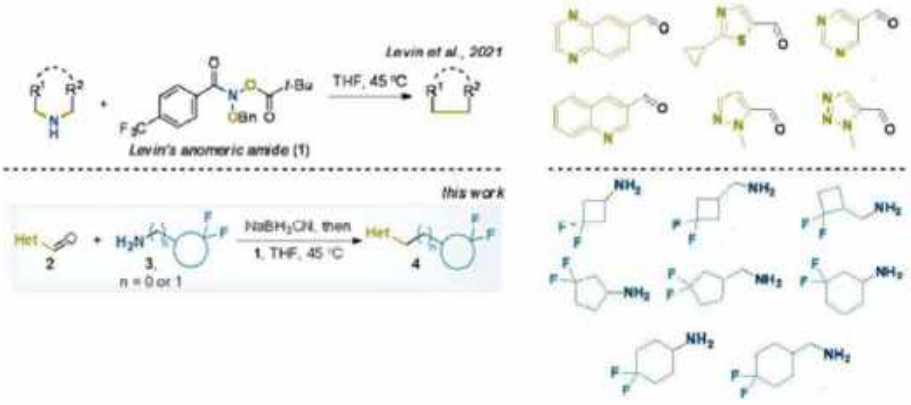


Рис.1. Загальна схема перетворення та вихідні речовини для побудови нових гетероциклічних сполук

Київський національний університет імені Тараса Шевченка
Хімічний факультет

Тези доповідей

XXIII Міжнародна конференція
студентів, аспірантів та молодих вчених
"Сучасні проблеми хімії"

Book of abstracts

23rd International Conference for Students,
PhD students and young scientists
"Modern Chemistry Problems"





18 - 20 травня 2022 рік

СИНТЕЗ ФЛУОРОВАНИХ ПІРАЗОЛІВ ТА ПІРИМІДИНІВ З ФРАГМЕНТАМИ НАСИЧЕНИХ ГЕТЕРОЦИКЛІЧНИХ АМІНІВ

Федінчик А.В.[1,2], *Герасимчук М.В.*[1,2], *Мельников К.П.*[1,2], *Григоренко О.О.*[1,2]
[1] Київський національний університет імені Тараса Шевченка
01601, Київ, вул. Володимирська, 64/13; e-mail: fedinchyk.n@gmail.com
[2] ТОВ НВП "Єнамін", 02094, м.Київ, вул. Червоноткацька, 67

Фторовані гетероциклічні ядра є одними з найпривабливіших структурних фрагментів у відкритті лікарських засобів [1]. Вони є ключовими елементами різних препаратів, розроблених на сьогоднішній день. Постійний пошук нових лікарських засобів робить розробку надійних і універсальних шляхів синтезу фторованих гетероциклів важливою проблемою, з якою стикається органічна та медична хімія.

Важливою тенденцією, що спостерігається на ранніх стадіях відкриття ліків протягом останніх двох десятиліть, є особлива увага до sp^3-збагачених молекул [2, 3]. У зв'язку з цим розробка нових підходів до біологічно значущих гетероциклів, що містять циклічні (гетеро)аліфатичні замісники, здається важливим завданням. Таким чином, доповнення фторованого піразолу або піперидину такими фрагментами, як піперидин, піролідин або азетидин дає дуже перспективні хемотипи для відкриття лікарських засобів.

У даній роботі було досліджено ефективні підходи до масштабованого синтезу флуорованих піразолів та піримідинів з фрагментами насичених гетероциклічних амінів. Дані методи ґрунтуються на гетероциклізації sp^3-збагачених β-бромо-α,α-дифторкетонів та фторованих енаміонів; ці сполуки самі по собі є корисними синтетичними проміжними продуктами.

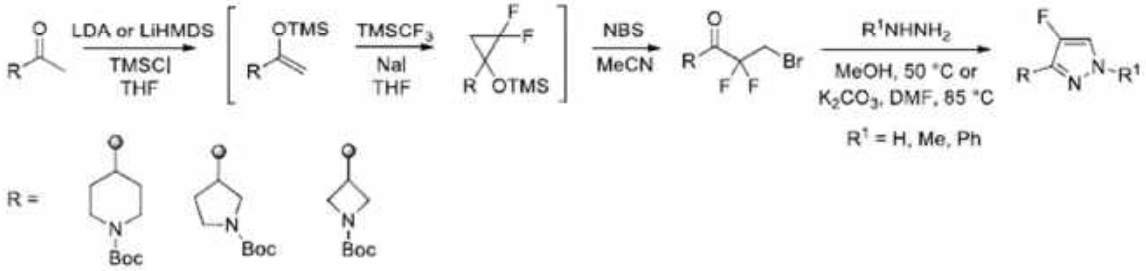


Схема 1. Синтез фторованих піразолів

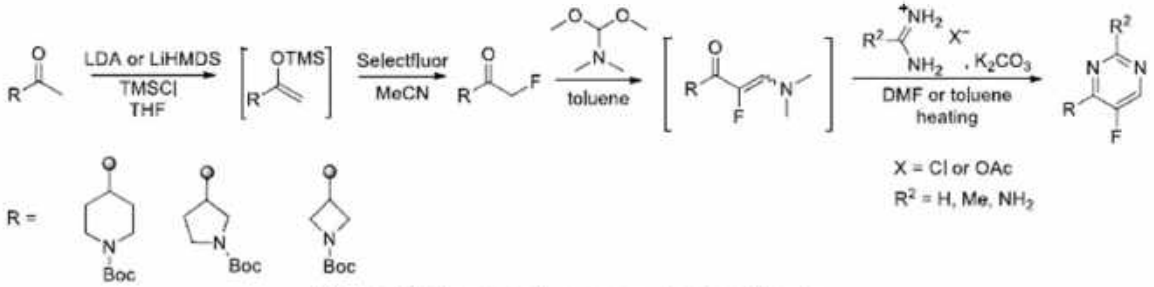


Схема 2. Синтез фторованих піримідинів

1. N. A. Meanwell, K. J. Eastman, E. P. Gillis, in *Fluorine in Heterocyclic Chemistry Volume 1*, Springer International Publishing, Cham, **2014**, pp. 1–54.
2. O. O. Grygorenko, D. M. Volochnyuk, S. V. Ryabukhin, D. B. Judd, *Chem. Eur. J.* **2020**, *26*, 1196–1237.
3. R. Doveston, S. Marsden, A. Nelson, *Drug Discov. Today* **2014**, *19*, 813–819.

Київський національний університет імені Тараса Шевченка
Хімічний факультет

Тези доповідей

XXIII Міжнародна конференція
студентів, аспірантів та молодих вчених
"Сучасні проблеми хімії"

Book of abstracts

23rd International Conference for Students,
PhD students and young scientists
"Modern Chemistry Problems"





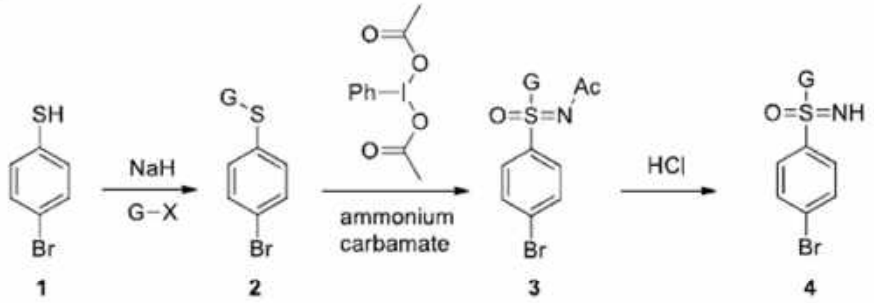
18 - 20 травня 2022 рік

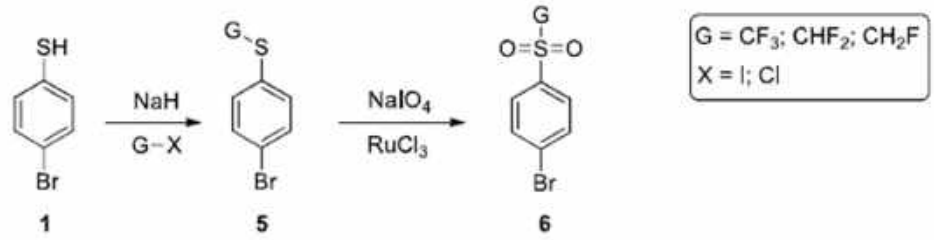
СУЛЬФОКСІМІНИ АРОМАТИЧНОГО РЯДУ З ФЛУОРОВМІСНИМИ ЗАМІСНИКАМИ

Підвишенний О.Р.[1,2], *Смирнов О.К.*[2], *Мельников К.П.*[2], *Григоренко О.О.*[1,2]
[1]Київський національний університет імені Тараса Шевченка
01601, Київ, вул. Володимирська, 64/13;
[2]Enamine Ltd., 02094, м. Київ, вул. Червоноткацька, 78

Аналіз літератури показує, що сульфоксіміни ароматичного ряду та їх фторовані похідні є перспективними сполуками в сучасній органічній та медичній хімії [1]. Відомо, що ароматичні фрагменти, і в першу чергу бензенове кільце, є одними з найпоширеніших структурних елементів у складі біологічно активних сполук. Тому важливим завданням органічного синтезу є дослідження нових функціоналізованих похідних бензенового кільця, а особливо тих, що в меншому об'ємі вивчалися в 20 ст. До таких сполук належать сульфоксіміни ароматичного ряду.

Більшість публікацій стосуються майже виключно синтезу даних сполук, а також поодиночних прикладів модифікації з утворенням похідних з додатковим функціональними групами.





Представлена робота грунтується на дослідженні впливу фторованих замісників на фізичні властивості сульфоксімінів у порівнянні з відповідними сульфонами. [2] Синтезовані сульфоксіміни з фторованими замісниками у більшості випадків демонструють безпосередній вплив атомів фтору на ліпофільність молекули. Також робота висвітлює функціоналізацію вже синтезованих раніше будівельних блоків з різними замісниками як в бензеновому ядрі, так і фторованими аліфатичними замісниками біля атому сірки.

[1] Zenzola, M., Doran, R., Degennaro, L., Luisi, R., & Bull, J. A., *Angewandte Chemie International Edition*. **2016**, 7203–7207.
[2] Das, P., Shibata, N. *The Journal of Organic Chemistry*, **2017**, *11915–11924*.