Scalable functionalization of azaindole derivatives for medicinal chemistry purposes

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Research Article

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Scalable functionalization of azaindole derivatives for medicinal chemistry purposes

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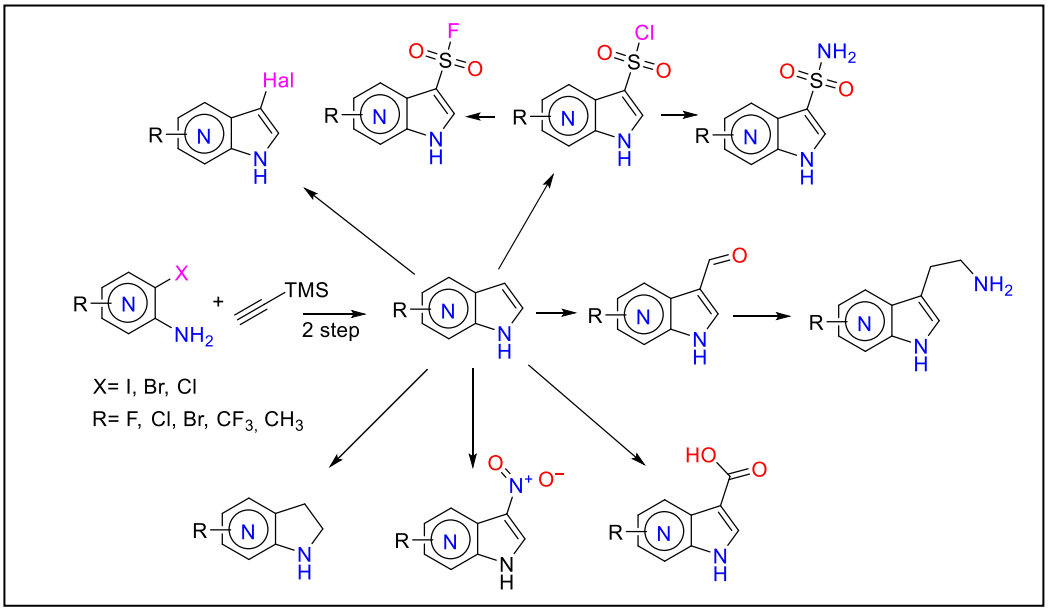


A reliable protocol for the multigram synthesis of a series of functionalized azaindoles was developed. The challenges associated with the synthesis of certain fluorine-substituted azaindole starting materials were investigated. The starting compounds were synthesized via the Sonogashira reaction under optimized conditions. A series of functionalization protocols was subsequently applied, demonstrating access to a wide range of corresponding aldehydes, acids, halogenated derivatives, sulfonyl chlorides, as well as an azatryptamine derivative. The selective hydrogenation developed in this work enabled the synthesis of a series of novel azatryptamine derivatives and 2,3-dihydroazaindoles. The developed azaindoles represents a useful class of building blocks for medicinal chemistry, offering diverse functional groups with significant potential for application in drug design.

Keywords: azaindole, azatryptamine, semi-industrial, Sonogashira reaction, medchem building block

Halogenated fragment of azaindole is a motif of many modern pharmacologically important drug candidates and play an important role as a key precursor for drug design. They are important for wide range of biologically active substances with anticancer activity [1-3] (**Fig. 1**), as well as treatment of multiple sclerosis [4]. Also, in our previous work [5] 6+5 anelated scaffolds showed good biological activity against Mycobacterium tuberculosis. Effective drug design requires application of annelated pyridine fragment bearing functional groups: halogen, carboxyl, sulfochlorides, aldehyde or amino functional group.

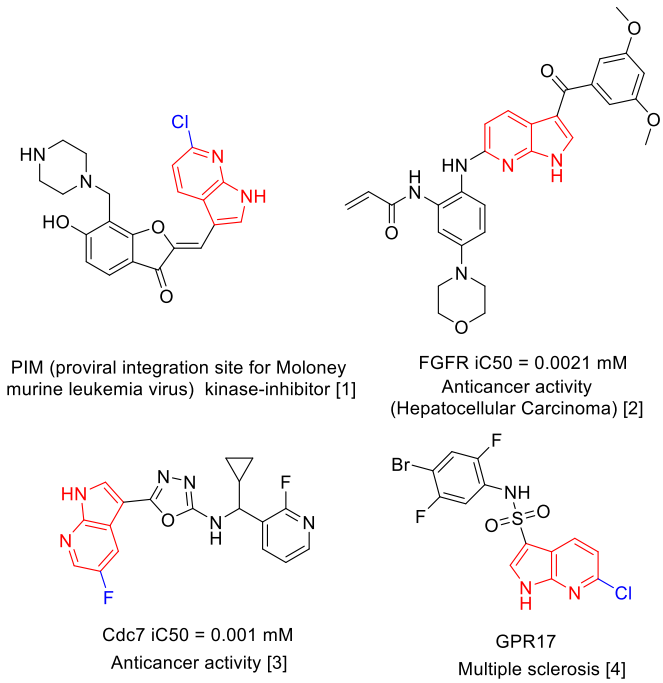


Fig. 1. Biologically active molecules with azaindole motif

Taking into account the Primodivir preparation scheme (**Fig. 2**), orally bioavailable inhibitor of the influenza virus polymerase PB2 subunit, azaindole building block with halogen in 3th position is required [6], which is also demanded for Primodivir analogues development [7, 8].

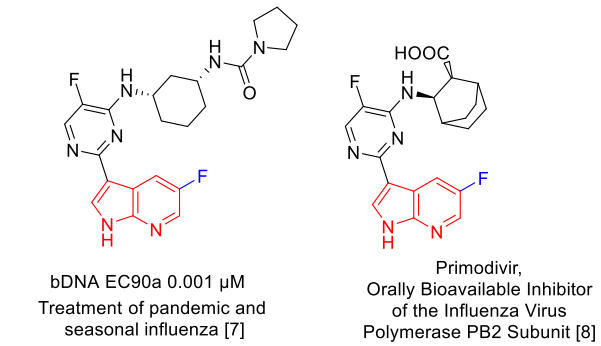


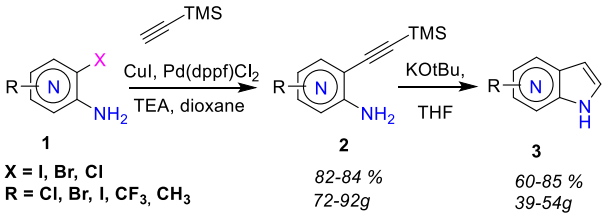
Fig. 2. Primodivir analogues

The analysis of the literature data of synthetic schemes were reliably represented in milligrams or grams scale, which is generally enough to provide the screening of biologically activity. But only few examples of reliable scale-up synthetic procedures were reported for halogenated azaindoles with functional groups suitable for further transformations [9-12]. Therefore, we focused our efforts on the development of scalable and reliable procedure to provide the series of substituted halogenated azaindole building-blocks with a variety of functional groups suitable for drug design.

Results and discussions

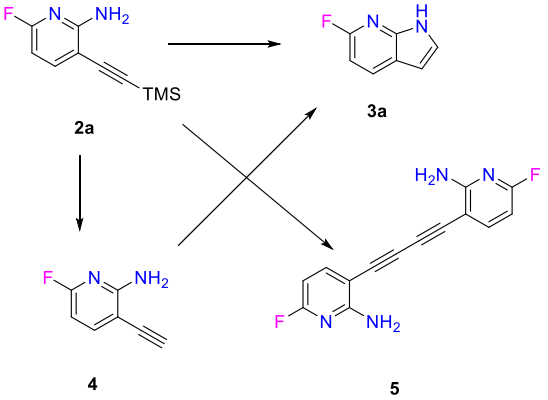
In our recent article [13] we have described Sonogashira/Larock reaction set for some azaindole design. But fluorine substituents provide dramatic challenges for azaindole cyclisation. Despite excellent yields on Sonogashira step (82-84%), starting from commercially accessible halogenated aminopyridines **1a-d**, the previously developed cyclisation Larock-type protocol (**Table 1, entry 1**) [13] didn't work for fluorine substituted derivatives **2a-d**.

In paper [14] for synthesis of **2a** author used N-carbamoyl acetylene without TMS protecting group to mitigate cyclization conditions, but introduction of the last one adds additional stages into the scheme and was difficult to perform. So, we decided to optimize Larock cyclisation step (**Scheme 1**).



Scheme 1. Perspective way for azaindole synthesis

The worst yield was observed on acetylene **2a** – direct cyclisation gives trace of product **3a**, so we searched for better conditions of this cyclisation (**Schema 2, Table 1**):



Scheme 2. Challenges of Larock cyclisation

Table 1: Validation protocols for Larock cyclisation

№	Starting alkyne	Solvent	Reaction conditions	Conversion LCMS, %		
				3a	**4**	**5**
1	**2a**	THF	1.5 eq KOt-Bu, 60°C	0	80	0
2	**2a**	THF	1.5 eq KOt-Bu, crown 18-6, 60°C	0	50	0
3	**2a**	THF	2.0 eq KOt-Bu, 60°C	5	60	0
4	**4**	NMP	2.0 eq KOt-Bu, 120°C	0	100	0
5	**4**	DMF	1.0 eq $AgNO_3$, 80 °C	0	95	0
6	**4**	DMF	0.1eq $[Rh(C_5Me_5)Cl_2]_2$, 85 °C	0	95	0
7	**2a**	DMF	0.1 eq CuI, 120 °C	0	0	50
8	**2a**	DMF	0.2 eq CuI, 120 °C	7	0	60
9	**2a**	DMF	0.5 eq CuI, 120 °C	40	0	40
10	**2a**	DMF	1.0 eq CuI, 120 °C	50	0	40
11	**2a**	DMF	2.0 eq CuI, 100 °C	50	0	30
12	**2a**	DMF	2.0 eq CuI, 120 °C	80	0	15
13	**2a**	DMF	2.0 eq CuI, 130 °C	85	0	10
14	**2a**	DMF	**2.0 eq CuI, 150 °C**	**95**	**0**	**trace**

It was shown that in conditions founded for previous case (entry 1-2) only TMS deprotection was observed, as well harsher conditions or catalyst (entry 3-6) didn't give result**.** In paper [14] was reported that addition of CuI facilitates cyclisation but synthetic procedure was absent for this journal, so we decided to check proper amount. In case of catalytical amount 0.1eq of CuI (entry 7) gives only product of dimerization **5**. Step by step iteration we found that the best conditions 2.0 eq CuI, in DMF at 150

°C (entry 14) gives best results of conversion into **3a**. The analytical sample of the compound **5** was isolated by HPLC purification.

Next part of our research was focused on additional functionalization of azaindole scaffold for of medicinal chemistry relevant building blocks design. Firstly, the core of obtained 4 and 7-azaindoles with unsubstituted 2,3-positions involved to a series of electrophilic substitution reactions. Also, we tested some commercially available compounds **3e** and **3f** (fig. 3), which are prepared by literature data [15, 16] from N-oxides.

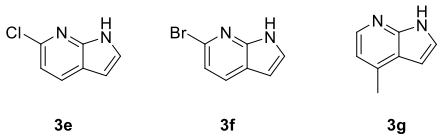
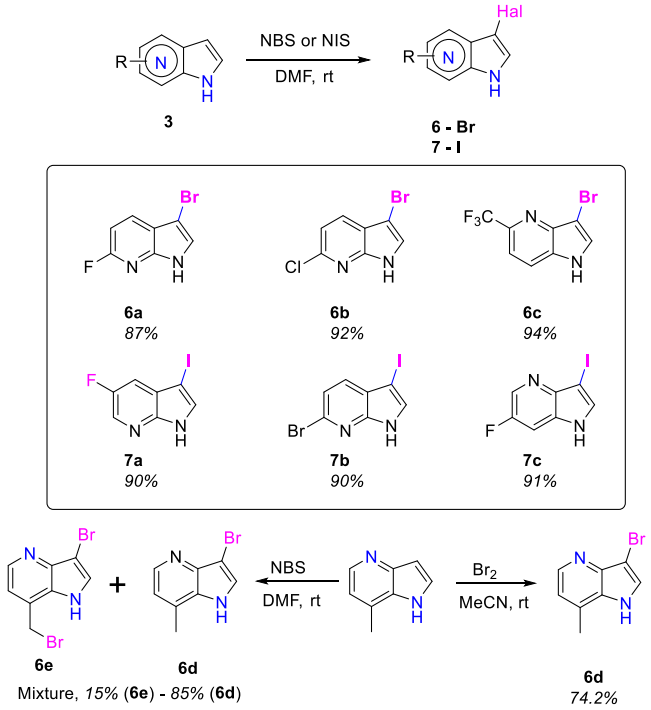


Fig. 3. Commercially available azaindoles **3** used in research

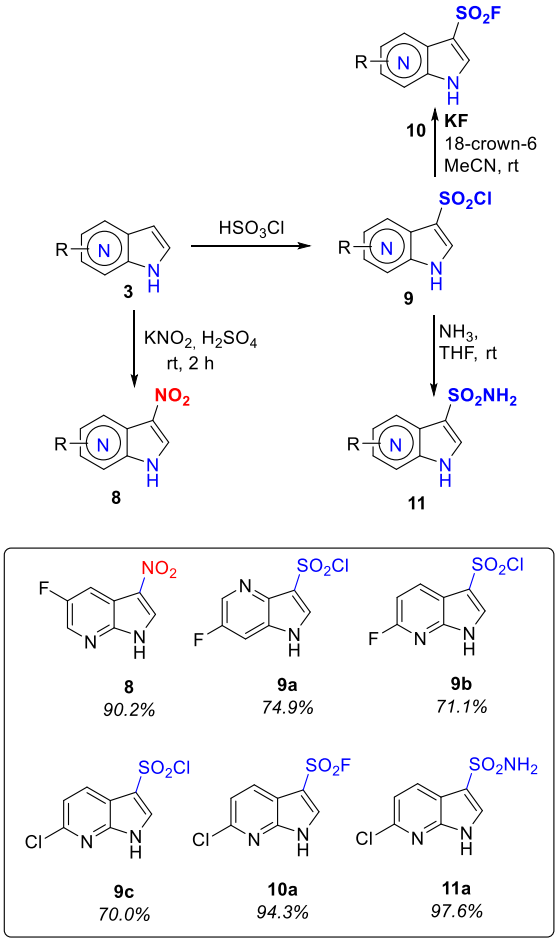
Although the reactions of electrophilic substitution in indoles are well-studied the transfer of the same reaction protocols on azaindoles was not perfectly successful. Probably due to fusion of pyrrole with electron withdrawing pyridine ring S_E reactions don`t occur well. So, development of the reproducible and reliable synthetic procedures for S_E reactions was investigated. Such azaindoles with functional groups will be useful for the drug-like molecules design.

Halogenation with NBS or NIS leads to excellent yields of corresponding halo azaindoles **6** or **7** suitable for further transformations like the coupling reactions, Miyaura reaction, metalorganic transformations etc. Typical conditions were stirring in DMF with NBS or NIS at room temperature provided azaindoles **6a-c,7a-c,** but in case of **3g** bromination in these conditions gave about 15% of by-product **6e**. To avoid bromination of methyl group we found optimized reaction conditions by using Br_2 in acetonitrile that gives pure **6d** obtained without additional purification, due to precipitation from reaction mixture the solid hydrobromide prevented the molecule from its further side bromination (**Scheme 3**).



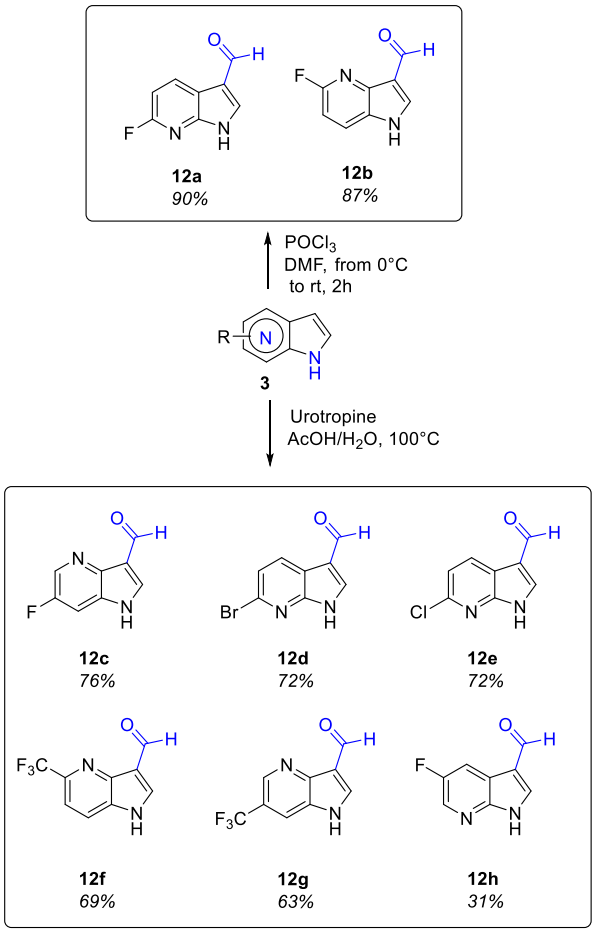
Scheme 3. Halogenation azaindoles

The high yields of sulfonyl chlorides **9a-c** were achieved at 100 °C by reaction with chlorosulfonic acid. In attempt to increase the stability of sulforchloride **9c** towards hydrolysis it was converted to sulfonyl fluoride **10** via reaction with dry potassium fluoride in anhydrous acetonitrile. Also treatment of **9c** with gaseous ammonia in THF produced sulfonyl amide **11**. Reaction of the azaindoles with potassium nitrate in the sulfuric acid produced 3-nitroazaindoles **8** in high yields (**Scheme 4**).



Scheme 4. Synthesis of sulfonyl and nitro derivatives

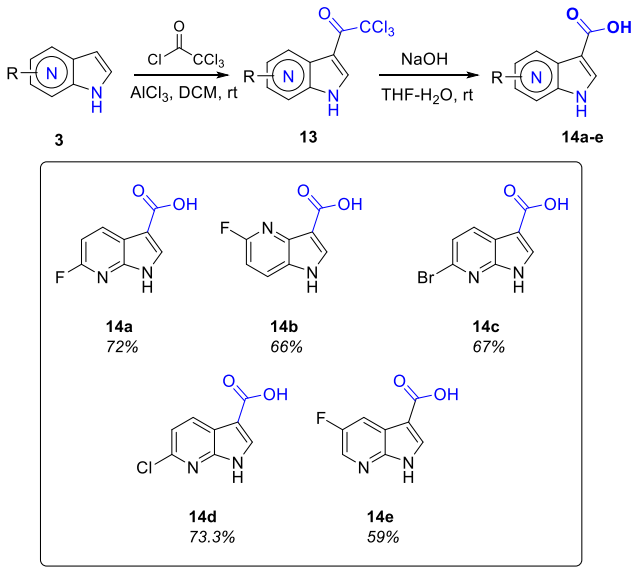
Nitration can be a perfect way to 3-aminoazaindoles precursors [17] and therefore we elaborated this method.



Scheme 5. Installation of aldehyde fragment to azaindoles

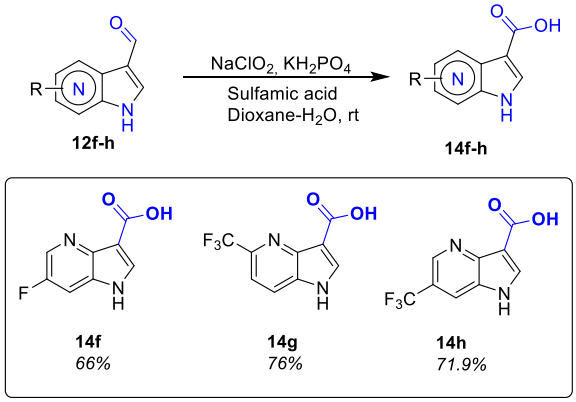
Installation of an aldehyde group to azaindole ring can provide a very promising building blocks, but traditional Vilsmeier-Haack reaction, was suitable only for synthesis of **12a,b** and failed for **3c-e** derivatives. Moreover, attempts of optimization conditions by changing the temperature or ratio of the reagent failed. The suitable results for preparation of **12c-h** were achieved only for Duff procedure (urotropine-acetic acid) reported (**Scheme 5**) [18].

Azaindol-3-carboxylic acids are demanded building blocks for drug design. The most effective founded method for preparation of these compounds was acylation of position 3 with trichloroacetic acid anhydride followed by haloform hydrolysis (Scheme 6). This procedure gives best yields for preparation of acids **14a-e**.



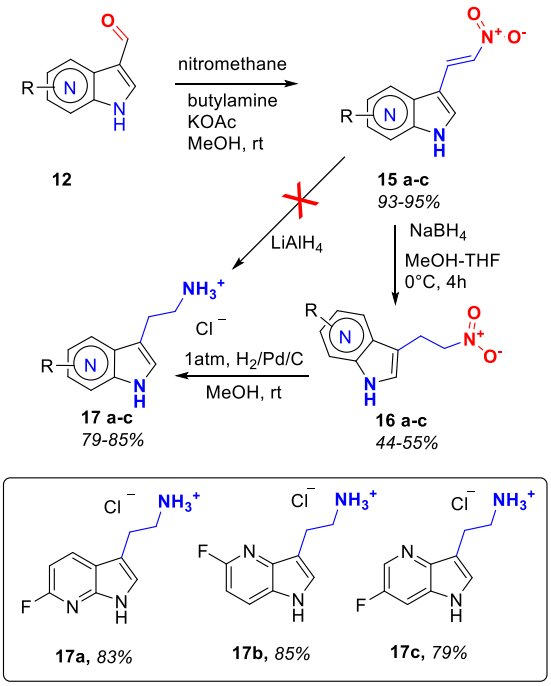
Scheme 6. Haloform reaction for carboxylic acids **14** synthesys

Some of the tested azaindoles, were not suitable for reaction with $AlCl_3$ due to stability issues so we elaborate method *via* oxidation of the aldehydes obtained before. In many synthetic protocols oxidation of pyrrole aldehydes requires protection of pyrrole nitrogen. We tested Pinnick oxidation conditions [19] for preparation of **14f-h** from corresponding aldehydes without their protection. Although some of the azaindole-3-carbaldehydes were scarcely soluble in 1,4-dioxan-water media, their oxidation gave high yield of the target acids even in heterogeneous conditions (**Scheme 7**).



Scheme 7. Pinnick oxidation for preparation of carboxylic acids **14f-14h**

Tryptamines play an important role in the biochemistry of the living organisms as well as in drug discovery [20]. It is well-known that indol-3-carbaldehydes can be versatile starting building-blocks for preparation of tryptamines and therefore we used the set of fluorinated aldehydes **12a-c** for preparation of corresponding tryptamines **17a-c** (**Scheme 8**).



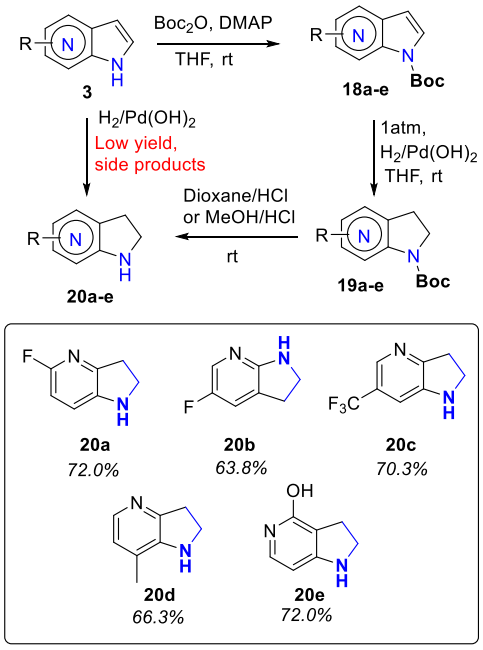
Scheme 8. Synthesis of azatryptamines **17**

At the first step we applied Henry reaction of aldehydes **12** [21] with nitromethane. The optimized protocol of Henry reaction involved butylamine-potassium acetate catalysis at room temperature instead of boiling with ammonium acetate. So, we achieved nitroalkenes **15a-c** with yields close to quantitative. Attempts to carry out direct reduction of **15** in one step using $LiAlH_4$ or Pd/C failed. These reactions were accompanied by the formation of a large number of by-products. To improve the procedure, reduction steps were divided. At first, reduction of the double bond was carried out with sodium borohydride at 0°C in THF-water mixture. The sodium borohydride was added to the clear solutions of **15**, with great dilution (50-60 ml of the solvent mixture per 1 g of the nitroalkene **15)**. Following reduction of nitro-group was carried out as Pd/C catalyzed hydrogenation (1 atm.). Such sequence with separated steps allowed us to obtain azatryptamines **17a-c** in the scale more than 20g with 79-85% overall yields.

Reduction of pyrrole fragment in azaindole is very attractive for drug discovery. It was reported earlier that reduction in the harsh conditions is a good way for preparation of 2,3-dihydroazaindoles, which does not require protection of pyrrole nitrogen [22]. We have modified the protocol applied for derivatives with N-Boc-protected pyrrole fragment. Protection of the nitrogen reduces the Hydrogen pressure which needed for effective reduction to 1-5 atm in contrast with our previous work [23] and also it makes the procedure selective for reduction of pyrrole avoiding the reduction of pyridine cycle, which generally requires higher pressure (80-100 atm.). Test reduction reactions showed that methanol as solvent reacts with Boc-group due to high nucleophilicity of methanol. This problem was solved by changing the solvent on THF.

The **20a-d** was obtained with quantitative yields after Boc-deprotecting **19** with the mixture of acetyl chloride in methanol (**Scheme 9**). In case of **19a** after cleavage of Boc the product **20e** of fluorine hydrolysis was isolated due to high reactivity of fluorine atom.

The reduction procedure was scaled up to 30 g payload in one synthetic run and was performed in one pot procedure: Installation of Boc protection in THF, after that to this reaction mixture Pd(C) 10% was added, and intermediate was further hydrogenated at 1 atm. Deprotection eventually provides target **20a-e** with excellent yields. To avoid methoxylation or hydrolysis on the Boc cleavage stage we used 4M HCl in 1,4-dioxane.



Scheme 9. Reduction pyrrole fragment in azaindoles

Conclusion

Reliable and multi-gram scalable protocols suitable for preparation of 4- and 7-azaindoles with the halogen atoms were developed. The challenges of the synthesis of some starting fluorine substituted azaindole were investigated. Suggested protocols are based on the readily available and commercial cheap starting materials. The highly effective protocols using S_E reactions open access to 4- and 7-azaindoles bearing aldehyde, carboxyl, halogen, sulfonyl chloride and other functional groups at position 3 of the azaindole core. A modification of the Pinnick oxidation of azaindole-3-carbaldehydes proved to be an efficient method for the preparation of azaindole-3-carboxylic acids, which are otherwise difficult to obtain using alternative methods. The scalable and efficient procedures for selective hydrogenation developed in this work enabled the synthesis of a series of novel azatryptamine derivatives and 2,3-dihydroazaindoles.

EXPERIMENTAL

The solvents were purified according to the standard procedures. All starting materials were obtained from Enamine Ltd. All other starting materials were purchased from commercial sources. Melting points were measured on the MPA100 OptiMelt automated melting point system. Flash chromatography was performed on the puriFlash

XS520Plus instrument. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on an Agilent ProPulse 600 spectrometer (at 151 MHz for ^{13}C NMR), a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR and 126 MHz for ^{13}C 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 the NMR chemical shifts are referenced using the solvent signals at 7.26 and 77.1 ppm for ^{1}H and ^{13}C nuclei, respectively, in CDCl3, and 2.48 and 39.5 ppm for ^{1}H and ^{13}C nuclei, respectively, in DMSO-d6. Coupling constants (*J*) are presented in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, coupling constants (Hz), and integration. LCMS and GCMS analyses were performed with the assistance of an Agilent LC/MSD SL 1100 instrument ES-API or an Agilent 5890 Series II 5972 GCMS instrument EI ionization 70 eV respectively. HRMS spectra was obtained on Agilent 6200 Series system TOF and 6500 Series Q-TOF LC/MS. HPLC separations were performed using a hexane/isopropyl alcohol (90:10) mobile phase at a flow rate of 0.6 mL/min, with detection at 215 and 254 nm.

General procedure for Sonogashira reaction (2a-2d)

To solution of commercially available intermediate **1a** 100 g, (0.42 mol), TMS acetylene 72 ml (0.50 mol) and TEA 236 ml (1.68 mol) in 1.0 L Dioxane was stirred for 10 min, then CuI (4.0 g, 0.02 mol) and $PdCl_2(dppf)CH_2Cl_2$ (10.3 g, 0.01 mol) was added in one portion under dry argon atmosphere, the resulting mixture was stirred at 80 °C for 16 h. Upon completion of the reaction, the mixture was concentrated under vacuum, and the crude mixture was purified by flash column chromatography on silica gel in $CHCl_3$)

6-fluoro-3-((trimethylsilyl)ethynyl)pyridin-2-amine (2a)

60 °C for 16 h. Yield 72.8 g (83.2%), Beige solid, M.p. 71 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.21 (9H, s, $Si(CH3)_3$), 6.15 (1H, dd, *J* = 8.8 Hz, *J* = 2.5 Hz, Het-H-4), 6.53 (2H, br s, NH_2), 7.63 (1H, t, *J* = 8.2 Hz, Het-H-5). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): -0.11 ($Si(\underline{C}H_3)_3$), 95.5 (C≡<u>C</u>-TMS), 95.7 (<u>C</u>≡C-TMS), 98.5, 100.3, 145.1 (d, *J* = 9.7 Hz), 159.5 (d, *J* = 19.7 Hz), 162.5 (d, *J* = 235.6 Hz, C-F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 67.04. LCMS, m/z: 209 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_{10}H_{14}FN_2Si$ 209.0905; Found $C_{10}H_{14}FN_2Si$ 209.0907.

5-fluoro-3-((trimethylsilyl)ethynyl)pyridin-2-amine) (2b)

Yield 89.4 g (82.0%), Yellow solid, M.p. 65 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.22 (9H, s, $Si(CH_3)_3$), 6.05 (2H, br s, NH_2), 7.49 (1H, dd, *J* = 8.8 Hz, *J* = 2.7 Hz, Het-H-4), 7.94 (1H, d, *J* = 2.7 Hz, Het -H-6). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): -0.2 ($Si(CH_3)_3$), 99.7 (C≡<u>C</u>-TMS), 101.2 (<u>C</u>≡C-TMS), 101.3, 126.7 (d, *J* = 21.4 Hz), 135.6 (d, *J* = 26.5 Hz), 151.3 (d, *J* = 236.2 Hz, C F), 156.9. ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 67.04. LCMS, m/z: 209 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_{10}H_{14}FN_2Si$ 209.0905; Found $C_{10}H_{14}FN_2Si$ 209.0898.

6-fluoro-2-((trimethylsilyl)ethynyl)pyridin-3-amine (2c)

Yield 91.6 g (84.0%), Yellow solid, M.p. 101 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.23 (9H, s, $Si(CH_3)_3$), 5.43 (2H, br s, NH_2), 6.90 (1H, dd, *J* = 8.8 Hz, *J* = 3.0 Hz, Het-H-4), 7.32-7.22 (1H, m, Het-H-6). ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.3 ($Si(CH3)_3$), 100.8 (C≡<u>C</u>-TMS), 111.4 (<u>C</u>≡C-TMS), 111.7, 120.4, 127.9 (d, *J* = 7.2 Hz), 145.7 (d, *J* = 26.5 Hz), 153.8 (d, *J* = 245.3 Hz, C F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 81.38. LCMS, m/z: 209 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_{10}H_{14}FN_2Si$ 209.0905; Found $C_{10}H_{14}FN_2Si$ 209.0905.

5-fluoro-2-((trimethylsilyl)ethynyl)pyridin-3-amine (2d)

Yield 89.3 g (81.9%), Yellow solid, M.p. 142 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.23 (9H, s, $Si(CH_3)_3$), 5.76 (2H, br s, NH_2), 6.90 (1H, dd, *J* = 11.0 Hz, *J* = 2.5 Hz, Het-H-4), 7.68 (1H, d, *J* = 2.2 Hz, Het -H-6). ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.29 ($Si(CH3)_3$), 99.1, 101.4, 106.8, 123.3, 126.0 (d, *J* = 24.8 Hz), 148.6 (d, *J* = 8.1 Hz), 159.7 (d, *J* = 254.6 Hz, C F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 81.38. LCMS, m/z: 209 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_{10}H_{14}FN_2Si$ 209.0905; Found $C_{10}H_{14}FN_2Si$ 209.0908.

6-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine (3a)

CuI (91.2 g, 0.48 mol) was added in one portion to a stirring solution of product **2a** (50.0 g, 0.24 mol) in 400 ml DMF at rt. The temperature was raised to 150 °C and the resulting mixture was stirred for 15h. After that, the mixture was filtered through Celite, washed with EtOAc (100 ml) and poured into 1 L of water and 100ml ethylenediamine, mixture was stirred for 30 min, filtered and extracted with EtOAc (3x200 ml), combined organic layer was washed with brine (3x200 ml), dried over Na_2SO_4 and concentrated in vacuo.

Yield 21.2 g (65.0%), Brown solid, M.p. 117 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 6.47 (1H, s, Het-H-4), 6.77 (1H, d, *J* = 8.2 Hz, Het-H-3), 7.4 (1H, d, *J* = 2.2 Hz, Het-H-2), 8.07 (1H, t, *J* = 8.2 Hz, Het-H-5), 11.74 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 100.3, 100.7, 117.5, 125.5, 133.1 (d, *J* = 9.5 Hz), 144.7, 158.9 (d, *J* = 232.7 Hz, C F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 76.83. LCMS, m/z: 137 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_7H_6FN_2$ 137.0509; Found $C_7H_6FN_2$ 137.0507.

5-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine (3b)

Synthesis was carried out according to the reported procedure [24]

KOt-Bu (64.6 g, 0.58 mol) was added in one portion to a stirring solution of product **2b** (100.0 g, 0.48 mol) in 500 ml NMP at rt. The temperature was raised to 120 °C and the resulting mixture was stirred for 15h. After that, the mixture was filtered through Celite, into 1L EtOAc the mixture was stirred for 30 min, washed with NH_4Cl water solution (100 g in 300ml) and brine (7x200 ml), organic layer was dried over Na_2SO_4 and concentrated in vacuo.

Yield 39.3 g (60.1%), Yellow solid, M.p. 107 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 6.42 (1H, s, Het-H-4), 7.54 (1H, t, *J* = 3.0 Hz, Het-H-3), 7.80 (1H, dd, *J* = 9.6 Hz, Het-H-6), 8.17 (1H, s, Het-H-2), 11.76 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 99.9, 113.4 (d, *J* = 23.2 Hz), 119.7, 128.5, 130.5 (d, *J* = 30.8 Hz), 145.3, 154.9 (d, *J* = 232.7 Hz, C-F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 140.6. LCMS, m/z: 137 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$

Calcd. for $C_7H_6FN_2$ 137.0509; Found $C_7H_6FN_2$ 137.0509.

5-fluoro-1*H*-pyrrolo[3,2-*b*]pyridine (3c)

KOt-Bu (64.6 g, 0.58 mol) was added in one portion to a stirring solution of product **2c** (100.0 g, 0.48 mol) in 1.4 L THF at 0 °C. The temperature was raised to 60 °C and the resulting mixture was stirred for 15 h. After that, the solvent was evaporated to dryness, the mixture was poured into a solution of 100 ml of concentrated HCl and 300 ml of water, stirred for 30 min, and filtered through Celite. The mother liquid was neutralized with aqueous ammonia to pH 10 (100 ml), stirred for another 30 min, and the precipitate was collected via vacuum filtration. The precipitate was dried, yielding pure compound **3c** without further purification.

Yield 55.3 g (84.6%), Yellow solid, M.p. 137 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 6.43-6.47 (1H, m, Het-H-7), 6.79 (1H, dd, *J* = 8.6 Hz, *J* = 1.7 Hz, Het-H-3), 7.66 (1H, t, *J* = 2.9 Hz, Het-H-2), 7.91 (1H, t, , *J* = 8.0 Hz, Het-H-6), 11.49 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 101.4, 102.2 (d, *J* = 43.5 Hz), 124.3 (d, *J* = 9.9 Hz), 127.1, 130.8 (d, *J* = 30.8 Hz), 142.6 (d, *J* = 19.1 Hz), 158.8 (d, *J* = 226.6 Hz, C F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 76.43. LCMS, m/z: 137 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_7H_6FN_2$ 137.0509; Found $C_7H_6FN_2$ 137.0514.

6-fluoro-1*H*-pyrrolo[3,2-*b*]pyridine (3d)

KOt-Bu (64.6 g, 0.58 mol) was added in one portion to a stirring solution of product **2c** (100.0 g, 0.48 mol) in 1.4 L THF at 0 °C. The temperature was raised to 60 °C and the resulting mixture was stirred for 15h. After that, the solvent was evaporated to dryness, the mixture was poured into a solution of 100 ml concentrated HCl and 300 ml of water, stirred for 30 min, and filtered through Celite. The mother liquid was neutralized with aqueous ammonia to pH 10 (100 ml), stirred for another 30 min, and the precipitate was collected via vacuum filtration. The precipitate was dried, yielding pure compound **3d** without further purification.

Yield 54.4 g (83.2%), Beige solid, M.p. 129 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 6.56 (1H, s, Het-H-7), 7.55-7.70 (2H, m, Het-H-2, Het-H-3), 8.3 (1H, s, Het -H-7), 11.37 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 101.7, 104.8 (d, *J* = 22.2 Hz), 127.7-128.0 (m), 130.1 (d, *J* = 3.0 Hz), 131.0 (d, *J* = 30.8 Hz), 143.4 , 155.5 (d, *J* = 242.3 Hz, C F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 138.27. LCMS, m/z: 137 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_7H_6FN_2$ 137.0509; Found $C_7H_6FN_2$ 137.0511.

3,3'-(buta-1,3-diyne-1,4-diyl)bis(6-fluoropyridin-2-amine) (5)

CuI (0.1 g, 0.5 mmol) was added in one portion to a stirring solution of product **2a** (0.5 g, 2.4 mmol) in 5 ml DMF at rt. The temperature was raised to 120 °C and the resulting mixture was stirred for 15h. After that, the mixture was filtered through Celite, mother liquid was evaporated to dryness, crude product was purified by HPLC (10-10-60% 0-1-5 min H_2O/ACN, flow: 30ml/min (loading pump 4ml/min ACN) target mass 270 column: Chromatorex C18 SMB100-5 100x19mm 5um) to give pure product **5**

Yield 0.12 g (18.8%), Yellow solid, M.p. 183 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 6.23 (2H, d, *J* = 7.8 Hz, Het-H-4), 6.92 (4H, br s, $2NH_2$), 7.76 (1H, t, *J* = 8.2 Hz, Het-H-5). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 78.7 (2(Het-C≡C-)), 79.7 (2(Het-C≡C-)), 96.1 (2C, d, *J* = 38.6 Hz), 96.8 (2C, d, *J* = 4.0 Hz), 146.7 (2C, d, *J* = 10.0 Hz), 161.02 (2C, d, *J* = 19.9 Hz), 162.9 (d, *J* = 238.4 Hz, C-F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 65.28. LCMS, m/z: 271 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_{14}H_8F_2N_4$ 271.2443; Found $C_{14}H_8F_2N_4$ 271.2445.

General procedure for Bromination (6a-c)

NBS (41.2 g, 0.23 mol) was added portion-wise to a stirred solution of **4-** or **7-**azaindole (0.22 mol) in 300 ml DMF at 0 °C over 20 min. The reaction was stirred for 16 h at rt. After that, the mixture was evaporated to dryness and then poured into water (400 ml), stirred for 30 min. The precipitate formed was collected by vacuum filtration. The residue was washed with water (100 ml) and acetonitrile (100 ml) to give compounds **6a-c**.

3-bromo-6-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine (6a)

Yield 41.2 g (86.9%), Brown solid, M.p. 153 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 6.93 (1H, d, *J* = 8.3 Hz, Het-H-4), 7.68 (1H, d, *J* = 2.4 Hz, Het-H-2), 8.00 (1H, t, *J* = 8.1 Hz, Het-H-5), 12.21 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 99.9, 102.4 (d, *J* = 39.3 Hz), 117.3, 125.7, 132.3 (d, *J* = 9.8 Hz), 144.0 (d, *J* = 19.7 Hz), 160.3 (d, *J* = 234.1 Hz, C F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 75.12. LCMS, m/z: 215 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_7H_5BrFN_2$ 214.9616; Found $C_7H_5BrFN_2$ 214.9617.

3-bromo-6-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (6b)

Yield 41.9 g (92.1%), Brown solid, M.p. 229 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.23 (1H, d, *J* = 8.3 Hz, Het-H-4), 7.77 (1H, s, Het-H-2), 7.90 (1H, d, *J* = 8.3 Hz, Het-H-5), 12.31 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 88.0, 116.7, 118.2, 126.8, 130.1, 144.7 , 146.4. LCMS, m/z: 231 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_7H_5BrClN_2$ 230.9319; Found $C_7H_5BrClN_2$ 230.9200.

3-bromo-5-(trifluoromethyl)-1*H*-pyrrolo[3,2-*b*]pyridine (6c)

Yield 44.4 g (93.7%), Brown solid, M.p. 187 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.64 (1H, d, *J* = 8.7 Hz, Het-H-4), 8.06 (1H, d, *J* = 8.3 Hz, Het-H-5), 8.11 (1H, s, Het-H-2), 12.15 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 90.3, 114.3, 121.3, 123.1 (q, *J* = 277.7 Hz, Het-CF3), 130.1, 132.3, 140.7 (q, *J* = 31.2 Hz, C-CF_3), 142.6. ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 64.56. LCMS, m/z: 265 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_8H_5BrF_3N_2$ 264.9582; Found $C_8H_5BrF_3N_2$ 264.9588.

3-bromo-7-methyl-1*H*-pyrrolo[3,2-*b*]pyridine (6d)

Br_2 (7.1 ml, 0.14 mol) was added dropwise to a stirred solution of **4-** or **7-azaindole** (30 g, 0.14 mol) in 300 ml MeCN at 0 °C over 20 min. The reaction was stirred for 16 h at rt. After that, the mixture was filtered through Celite, precipitate was poured into water (400 ml) and basified with K_2CO_3 to pH = 10 (30g K_2CO_3) stirred for 30 min. The precipitate formed was collected by vacuum filtration. The residue was washed with water (100ml) and dried

Yield 35.6 g (74.2%), Yellow solid, M.p. 107 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.49 (3H, s, CH_3), 7.01 (1H, s, Het-H-5), 7.81 (1H, d, *J* = 2.1 Hz, Het-H-6), 8.25 (1H, s, Het-H-2), 11.80 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 16.4, 90.4, 118.8, 128.6, 128.9, 130.8, 142.4 , 143.8. LCMS, m/z:

211 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_8H_8BrN_2$ 210.9865; Found $C_8H_8BrN_2$ 210.9869.

General procedure for Iodination (7a-c)

NIS (34.7 g, 0.15 mol) was added portion-wise to a stirred solution of **4-** or **7-azaindole** (0.15 mol) in 300 ml DMF at 0 °C over 20 min. The reaction was stirred for 16 h at rt. After that, the mixture was evaporated to dryness and then poured into water (400 ml), stirred for 30 min. The precipitate formed was collected by vacuum filtration. The residue was washed with water (100ml) and acetonitrile (100ml) to give compound **7a-c**.

5-fluoro-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine (7a)

Yield 34.5 g (89.6%), Brown solid, M.p. 181 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.53 (1H, d, *J* = 8.8 Hz, Het-H-4), 7.79 (1H, s, Het-H-2), 8.22 (1H, s, Het-H-5), 12.23 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 53.6, 113.6, 122.4, 132.2 (d, *J* = 9.8 Hz), 133.0, 144.8, 155.4 (d, *J* = 241.2 Hz, C F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 138.79. LCMS, m/z: 263 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_7H_5IFN_2$ 262.9469; Found $C_7H_5IFN_2$ 262.9469.

6-bromo-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine (7b)

Yield 29.4 g (89.5%), Brown solid, M.p. 107 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.32 (1H, d, *J* = 8.3 Hz, Het-H-4), 7.65 (1H, d, *J* = 7.8 Hz, Het-H-2), 7.75 (1H, d, *J* = 2.4 Hz, Het-H-5), 12.34 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 55.2, 120.2, 121.8, 131.5, 131.6, 135.2, 147.7. LCMS, m/z: 323 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_7H_5BrIN_2$ 322.8676; Found $C_7H_5BrIN_2$ 322.8674.

6-fluoro-3-iodo-1*H*-pyrrolo[3,2-*b*]pyridine (7c)

Yield 35.2 g (91.3%), Brown solid, M.p. 181 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.71 (1H, d, *J* = 9.3 Hz, Het-H-4), 7.83 (1H, s, Het-H-6), 8.37 (1H, s, Het-H-2), 11.81 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 58.2, 105.6 (d, *J* = 22.7 Hz), 127.7, 132.0 (d, *J* = 26.9 Hz), 132.1, 134.2, 156.2 (d, *J* = 239.5 Hz, C F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 136.89. LCMS, m/z: 263 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_7H_5IFN_2$ 262.9469; Found $C_7H_5IFN_2$ 262.9470.

5-fluoro-3-nitro-1*H*-pyrrolo[2,3-*b*]pyridine (8)

3b (2.0 g, 0.01 mol) was added portion-wise to a stirring solution of concentrated sulfuric acid (10 mL) and potassium nitrate (2.2 g, 0.02 mol) at 0 °C over 10 min. The reaction was stirred for 2 h at 0 °C. The mixture was poured into ice water (50 ml), and the precipitate formed was collected by vacuum filtration. The residue was washed with 2×30 mL of water and MTBE (20ml), yielding the compound **8**.

Yield 2.4 g (90.2%), Yellow solid, M.p. 263 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 8.17 (1H, dd, *J* = 8.9 Hz, *J* = 2.4 Hz, Het-H-4), 8.43 (1H, s, Het-H-2), 8.88 (1H, d, *J* = 2.7 Hz, Het-H-6), 13.42 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 113.5 (d, *J* = 8.5 Hz), 114.3 (d, *J* = 23.2 Hz,), 127.2, 133.0 (d, *J* = 9.8 Hz), 134.8 (d, *J* = 29.4 Hz), 143.8, 157.5 (d, *J* = 245.1 Hz, C F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 134.10. LCMS, m/z: 182 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_7H_5FN_3O$ 182.0361; Found $C_7H_5FN_3O$ 182.0356.

General procedure for Sulfochlorination (9a-c)

4- or **7-**azaindole (10 g) was added portion-wise to 30 mL of chlorosulfuric acid at 0 °C over 10 min. The reaction was heated and stirred at 90 °C for 14h. After that, the mixture was carefully poured into ice (500 ml) with intensive stirring and left for 30 min to form a precipitate. Then the precipitate was collected via vacuum filtration. The residue was washed with water (20 ml) and heptane (50 ml) and dried in a vacuum desiccator, yielding the title compound **9a-c**.

6-fluoro-1*H*-pyrrolo[3,2-*b*]pyridine-3-sulfonyl chloride (9a)

Yield 12.9 g (74.9%), Brown solid, M.p. 115 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 8.25 (1H, d, *J* = 2.5 Hz, Het-H-4), 8.62-8.72 (2H, m, Het-H-2, Het-H-6), 13.00 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 116.9 (d, *J* = 23.2 Hz), 119.5, 125.4 (d, *J* = 37.6 Hz), 130.0, 131.8 (d, *J* = 11.2 Hz), 135.6, 155.3 (d, *J* = 238.7 Hz, C F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 132.70. LCMS, m/z: 235 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_7H_5ClFN_2O_2S$ 234.9734; Found $C_7H_5ClFN_2O_2S$ 234.9734.

6-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine-3-sulfonyl chloride (9b)

Yield 12.3 g (71.1%), Brown solid, M.p. 194 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.66 (1H, d, *J* = 8.6 Hz, Het-H-4), 8.80 (1H, s, Het-H-2), 8.95 (1H, t, *J* = 8.0 Hz, Het-H-5), 11.41 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 101.6 (d, *J* = 39.1 Hz,), 115.5, 122.9 (d, *J* = 37.6 Hz), 124.5 (d, *J* = 4.2 Hz), 133.9 (d, *J* = 9.6 Hz), 144.6, 160.9 (d, *J* = 233.5 Hz, C-F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 73.10. LCMS, m/z: 235 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_7H_5ClFN_2O_2S$ 234.9734; Found $C_7H_5ClFN_2O_2S$ 234.9733.

6-chloro-1*H*-pyrrolo[2,3-*b*]pyridine-3-sulfonyl chloride (9c)

Yield 11.5 g (70.0%), Beige solid, M.p. 229 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.14 (1H, d, *J* = 8.1, Het-H-4), 7.47 (1H, s, Het-H-2), 8.07 (1H, d, *J* = 8.1, Het-H-5), 11.88 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, d-MeCN), δ, ppm (*J*, Hz): 114.1, 118.0, 119.8, 130.4, 133.0 146.5, 147.3. LCMS, m/z: 251 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_7H_5Cl_2N_2O_2S$ 250.9444; Found $C_7H_5Cl_2N_2O_2S$ 250.9451.

6-chloro-1*H*-pyrrolo[2,3-*b*]pyridine-3-sulfonyl fluoride (10a)

9c (10 g, 0.04 mol) was added portion-wise to a mixture of KF (7 g, 0.12 mol) in 100 mL MeCN at 0 °C over 10 min. The reaction was stirred at rt for 14h. After that time, the precipitate was collected *via* vacuum filtration. The residue was washed with water (3x20 ml) and heptane (2x20 ml) and dried in a vacuum desiccator, yielding the title compound **10a**

Yield 8.8 g (94.3%), Beige solid, M.p. 269 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.49 (1H, d, *J* = 8.4, Het-H-4), 8.20 (1H, d, *J* = 8.4 Hz, Het-H-5), 8.85 (1H, s, Het-H-3), 13.70 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 104.0 (d, *J* = 30.1 Hz, C-SO_2F), 115.3, 119.8, 130.7, 136.7, 146.5, 147.5 ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): 70.87. LCMS, m/z: 235 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_7H_5ClFN_2O_2S$ 234.9739; Found $C_7H_5ClFN_2O_2S$ 234.9742.

6-chloro-1*H*-pyrrolo[2,3-*b*]pyridine-3-sulfonamide (11a)

To a solution of compound **9c** (10 g, 0.04 mol) in 100 ml THF, cooled to 0 °C, gaseous ammonia was bubbled for 20 min. The reaction mixture was stirred for an additional 30 min at the same temperature. The resulting precipitate was collected by vacuum filtration, the residue was washed with water (3x20 ml) and heptane (2x20 ml) and dried in a vacuum desiccator, yielding the title compound **11a**

Yield 9.0 g (97.6%), Beige solid, M.p. 278 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.30 (2H, br s, NH_2), 7.34 (1H, d, *J* = 8.5 Hz, Het-H-4), 7.97 (1H, s, Het-H-2), 8.25 (1H, d, *J* = 8.5 Hz, Het-H-5), 12.58 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 115.0, 117.6, 119.0, 129.3, 131.6, 145.1, 147.2. LCMS, m/z: 232 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_7H_7ClN_3O_2S$ 231.9942; Found $C_7H_7ClN_3O_2S$ 231.9938.

General procedures for Aldehydes (12a-h)

Method A. To a cooled to 0 °C solution of 250 ml dry DMF, phosphoryl chloride (53 ml, 0.57 mol) was added dropwise over 10 min. The reaction mixture was stirred at 0 °C for 30 min. After that time, **3** (25 g, 0.18 mol) was added portion-wise. The resulting mixture was stirred for 2 h at r.t. After completion of the reaction, the precipitate solid was collected by filtration, the precipitate was dissolved in water (500ml) and the resulting solution was neutralized with potassium carbonate to pH = 10 (30 g). Mixture was stirred for 30 min and precipitate was filtered off, washed with water (200 ml) and dried to afford corresponding aldehydes **12a-b**.

Method B. To a stirred suspension of **3** (0.18 mol) and urotropine (38.6 g, 0.28 mol) in 300 ml water, acetic acid (128 ml, 2.24 mol) was added dropwise. After 30 min, the solution was stirred at reflux for 15h. After that, the mixture was cooled with ice, and another 300 mL of water was added. The mixture was stirred for 30 min, and the precipitate formed was collected by vacuum filtration. The residue was dried and then crystallized from acetonitrile (200 ml). Precipitate was dried to give pure compound **12c-h**.

6-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (12a)

Method A. Yield 27.1 g (90.0%), Yellow solid, M.p. 203 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.01 (1H, d, *J* = 8.0 Hz, Het-H-4), 8.40 (1H, s, Het-H-2), 8.49 (1H, t, *J* = 7.9 Hz, Het-H-5), 9.87 (1H, s, COH), 12.23 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 104.2 (d, *J* = 38.1 Hz), 114.9, 117.3, 134.7 (d, *J* = 9.2 Hz), 138.8, 146.6, 160.4 (d, *J* = 235.2 Hz, C-F), 185.7 (C=O). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 73.57. LCMS, m/z: 165 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_8H_6FN_2O$ 165.0459; Found $C_8H_6FN_2O$ 165.0460.

5-fluoro-1*H*-pyrrolo[3,2-*b*]pyridine-3-carbaldehyde (12b)

Method A. Yield 26.3 g (87.4%), Yellow solid, M.p. 260 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.00 (1H, dd, *J* = 8.8 Hz, *J* = 1.4 Hz, Het-H-7), 8.07 (1H, dd, *J* = 8.5 Hz, *J* = 7.4 Hz, Het-H-6), 8.45 (1H, s, Het-H-2), 10.04 (1H, s, COH), 12.41 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 104.6 (d, *J* = 42.8 Hz), 116.9, 126.1 (d, *J* = 10.5 Hz), 128.3, 138.2, 140.2 (d, *J* = 19.8 Hz), 160.3 (d, *J* = 234.5 Hz, C F), 184.1 (C=O). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 73.57. LCMS, m/z: 165 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_8H_6FN_2O$ 165.0459; Found $C_8H_6FN_2O$ 165.0462.

6-fluoro-1*H*-pyrrolo[3,2-*b*]pyridine-3-carbaldehyde (12c)

Method B. Yield 22.7 g (75.6%), Beige solid, M.p. 225 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.82 (1H, dd, *J* = 9.3 Hz, *J* = 1.4 Hz, Het-H-5), 8.44 (1H, s, Het-H-7), 8.49 (1H, s, Het-H-2), 10.11 (1H, s, COH), 12.39 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 104.2 (d, *J* = 38.1 Hz), 114.9, 117.3, 134.7 (d, *J* = 9.2 Hz), 138.8, 146.6, 160.4 (d, *J* = 235.2 Hz, C-F), 183.9 (C=O). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 134.83. LCMS, m/z: 165 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_8H_6FN_2O$ 165.0459; Found $C_8H_6FN_2O$ 165.0455.

6-bromo-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (12d)

Method B. Yield 21.7 g (71.5%), Yellow solid, M.p. 246 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.47 (1H, d, *J* = 7.9 Hz, Het-H-4), 8.33 (1H, d, *J* = 7.9 Hz, Het-H-5), 8.49 (1H, s, Het-H-2), 9.93 (1H, s, COH), 12.70 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 117.0, 117.1, 122.3, 132.4, 135.9, 139.2, 149.1, 185.9 (C=O). LCMS, m/z: 225 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_8H_6BrN_2O$ 224.9658; Found $C_8H_6BrN_2O$ 224.9657.

6-chloro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (12e)

Method B. Yield 21.9 g (72.3%), Beige solid, M.p. 264 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.32 (1H, d, *J* = 8.0 Hz, Het-H-4), 8.39 (1H, d, *J* = 8.0 Hz, Het-H-5), 8.48 (1H, s, Het-H-2), 9.90 (1H, s, COH), 12.85 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 115.9, 117.1, 118.8, 132.6, 139.3, 145.4, 148.7, 185.9 (C=O). LCMS, m/z: 181 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_8H_6ClN_2O$ 181.0163; Found $C_8H_6ClN_2O$ 181.0162.

5-(trifluoromethyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3-carbaldehyde (12f)

Method B. Yield 19.8 g (68.8%), Light-brown solid, M.p. 221 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.71 (1H, d, *J* = 8.4 Hz, Het-H-7), 8.14 (1H, s, d, *J* = 8.4 Hz, Het-H-6), 8.67 (1H, s, Het-H-2), 10.15 (1H, s, COH), 12.41 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 114.7, 116.8, 121.4, 122.6 (q, *J* = 273.2 Hz, Het-$\underline{C}F_3$), 130.9, 140.1, 141.6 (q, *J* = 33.9 Hz, $\underline{C}$-CF_3), 142.9, 183.7 (C=O). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 64.78. LCMS, m/z: 215 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_9H_6F_3N_2O$ 215.0426; Found $C_9H_6F_3N_2O$ 215.0426.

6-(trifluoromethyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3-carbaldehyde (12g)

Method B. Yield 18.2 g (63.3%), Brown solid, M.p. 260 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 8.27 (1H, s, Het-H-5), 8.66 (1H, s, Het-H-7), 8.83 (1H, s, Het-H-2), 10.20 (1H, s, COH), 12.73 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 116.7, 117.7, 119.4 (q, *J* = 33.6 Hz, Het-CF_3), 124.7 (q, *J* = 272.4 Hz, Het-$\underline{C}F_3$), 127.8, 139.9, 141.1, 146.0, 183.9 (C=O). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*,

Hz): - 59.28. LCMS, m/z: 215 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_9H_6F_3N_2O$ 215.0426; Found $C_9H_6F_3N_2O$ 215.0427.

5-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (12h)

Method B. Yield 9.2 g (30.6%), Brown solid, M.p. 214 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 8.13 (1H, dd, *J* = 8.8 Hz, *J* = 2.7 Hz, Het-H-4), 8.35 (1H, s, Het-H-6), 8.53 (1H, s, Het-H-2), 9.90 (1H, s, COH), 12.84 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 114.6 (d, *J* = 21.4 Hz), 116.5, 116.7, 133.1 (d, *J* = 28.9 Hz), 140.1, 145.9, 155.4 (d, *J* = 242.7 Hz, C-F), 185.2 (C=O). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 136.15. LCMS, m/z: 165 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_8H_6FN_2O$ 165.0459; Found $C_8H_6FN_2O$ 165.0455.

General procedure for the synthesis of carboxylic acids (14)

Method A.

To a solution of the corresponding **azaindole 3** (0.22 mol) in 300 ml DCM, cooled to 0 °C, $AlCl_3$ (58.8 g, 0.44 mol) was added portion-wise The resulting mixture was stirred for 20 min at the same temperature and after this time trichloroacetyl chloride (25 ml, 0.33 mol) in 100 ml DCM was added dropwise. The resulting mixture was stirred at rt. for 10 h. After completion of the reaction, mixture was poured into ice-water mixture (500 g ice and 500 ml water) and stirred for 30 min. The precipitate was collected by vacuum filtration, washed with water (100 ml) and MTBE (100 ml) to afford pure **13a-e**, which were used in the next step without further purification.

Compounds **13a-e** were dissolved in a mixture of 400 ml THF and 100 ml water, sodium hydroxide (26.4 g, 0.66 mol), was carefully added. The reaction mixture was stirred at r.t. for 16 h. After that time, mixture was neutralized with sodium bisulfate (25 g) to pH = 2 and stirred for an additional 30 min. The resulting precipitate was collected by vacuum filtration, washed with water (100 ml) and dried to give pure carboxylic acids **14a-e.**

Method B. To a solution of **12f-h** (0.22 mol) in 300 mL 1,4-dioxane and 600 mL of water, sulfamic acid (106.8 g, 1.10 mol) was added in one portion, the resulting mixture was cooled to 0 °C and mixture of sodium chlorite (29.8 g, 0.33 mol) and monopotassium phosphate (149.7 g, 1.10 mol) in 100 mL water was dropwise during 30 min at 0 °C. The reaction was stirred at rt. for 16 h.

After completion, the reaction mixture was filtered, and the precipitate was washed with water (200 ml) and dried to give pure carboxylic acids **14f-h.**

6-fluoro-1H-pyrrolo[2,3-b]pyridine-3-carboxylic acid (14a)

Method A. Yield for 2 steps 28.6 g (72.1%), Beige solid, M.p. 312 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 6.98 (1H, d, *J* = 8.8 Hz, Het-H-4), 8.41 (1H, s, Het-H-2), 8.42 (1H, t, *J* = 8.1 Hz, Het-H-5), 12.28 (1H, br s, NH), 12.51 (1H, br s, COOH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 103.3 (d, *J* = 38.1 Hz), 107.5, 116.7, 132.5, 134.5 (d, *J* = 9.2 Hz), 146.5 (d, *J* = 18.5 Hz), 160.0 (d, *J* = 234.7 Hz, C-F), 165.5 (COOH). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 75.25. LCMS, m/z: 181 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_8H_6FN_2O_2$ 181.0408; Found $C_8H_6FN_2O_2$ 181.0408.

5-fluoro-1*H*-pyrrolo[3,2-*b*]pyridine-3-carboxylic acid (14b)

Method A. Yield for 2 steps 26.0 g (65.7%), Beige solid, M.p. 254 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 6.91 (1H, d, *J* = 8.6 Hz, Het-H-7), 8.00 (1H, d, *J* = 8.0 Hz, Het-H-6), 8.24 (1H,s, Het-H-2), 11.95 (1H, br s, NH), 12.16 (1H, br s, COOH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 103.2 (d, *J* = 43.1 Hz), 107.3, 125.2, 127.6, 136.2, 139.7 (d, *J* = 20.6 Hz), 159.2 (d, *J* = 230.2 Hz, C-F), 164.1 (COOH). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 73.83. LCMS, m/z: 181 $[M+H]^+$. HRMS (ESI-TOF) $[M-H]^-$ Calcd. for $C_8H_4FN_2O_2$ 179.0262; Found $C_8H_4FN_2O_2$ 179.0266.

6-bromo-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylic acid (14c)

Method A. Yield for 2 steps 24.6 g (67.0%), Beige solid, M.p. 312 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.41 (1H, d, *J* = 7.9 Hz, Het-H-4), 8.17 (1H, s, Het-H-2), 8.23 (1H, d, *J* = 8.3 Hz, Het-H-5), 12.40 (1H, br s, NH), 12.63 (1H, br s, COOH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 107.3, 117.9, 121.3, 132.2, 133.5, 135.0, 148.4, 165.4 (COOH). LCMS, m/z: 241 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_8H_6BrN_2O_2$ 240.9607; Found $C_8H_6BrN_2O_2$ 240.9605.

6-chloro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylic acid (14d)

Method A. Yield for 2 steps 28.3 g (73.2%), Beige solid, M.p. 292 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.25 (1H, d, *J* = 8.4 Hz, Het-H-4), 8.14 (1H, s, Het-H-2), 8.28 (1H, d, *J* = 8.4 Hz, Het-H-5), 12.35 (1H, br s, NH), 12.57 (1H, br s, COOH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 107.3, 117.7, 117.8, 132.4, 133.5, 144.5, 147.9, 165.5 (COOH). LCMS, m/z: 197 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_8H_6ClN_2O_2$ 197.0118; Found $C_8H_6ClN_2O_2$ 197.0114.

5-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylic acid (14e)

Method A. Yield for 2 steps 23.5 g (59.3%), Beige solid, M.p. 350 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 8.01 (1H, dd, *J* = 9.1 Hz, *J* = 2.5 Hz, Het-H-4), 8.21 (1H, d, *J* = 2.7 Hz, Het-H-6), 8.29 (1H, s, Het-H-2), 12.36 (1H, br s, NH), 12.58 (1H, br s, COOH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 106.5 (d, *J* = 3.7 Hz), 114.2 (d, *J* = 21.4 Hz), 118.7 (d, *J* = 7.7 Hz), 132.1 (d, *J* = 28.9 Hz), 134.7, 145.4, 155.9 (d, *J* = 241.6 Hz, C-F), 165.0 (COOH). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 75.25. LCMS, m/z: 181 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_8H_6FN_2O_2$ 181.0408; Found $C_8H_6FN_2O_2$ 181.0404.

6-fluoro-1*H*-pyrrolo[3,2-*b*]pyridine-3-carboxylic acid (14f)

Method B. Yield 24.5 g (65.7%), Beige solid, M.p. 320 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.76 (1H, d, *J* = 9.1 Hz, Het-H-7), 8.25 (1H, d, *J* = 2.2 Hz, Het-H-5), 8.45 (1H, s, Het-H-2), 11.67 (1H, br s, COOH), 12.08 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 106.3 (d, *J* = 22.1 Hz), 107.5, 128.9, 132.9 (d, *J* = 28.2 Hz), 136.6, 140.4, 157.1 (d, *J* = 241.9 Hz, C-F), 164.1 (COOH). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 136.26. LCMS, m/z: 181 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_8H_6FN_2O_2$ 181.0408; Found $C_8H_6FN_2O_2$ 181.0404.

5-(trifluoromethyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3-carboxylic acid (14g)

Method B. Yield 28.0 g (75.5%), Yellow solid, M.p. 212 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.65 (1H, d, *J* = 8.7 Hz, Het-H-7), 8.08 (1H, d, *J* = 8.4 Hz, Het-H-6), 8.46 (1H, s, Het-H-2), 12.16 (1H, br s, NH), 12.39 (1H, br s, COOH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 108.4, 114.2, 121.4, 123.0 (q, *J* = 275.1 Hz, Het-CF_3), 131.1, 139.1, 141.5 (q, *J* = 32.5 Hz, C-CF_3), 164.4 (COOH). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 64.56. LCMS, m/z: 231 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_9H_6F_3N_2O_2$ 231.0376; Found $C_9H_6F_3N_2O_2$ 230.0380.

6-(trifluoromethyl)-1*H*-pyrrolo[3,2-*b*]pyridine-3-carboxylic acid (14h)

Method B. Yield 26.7 g (71.9%), Yellow solid, M.p. 214 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 8.20 (1H, s, Het-H-7), 8.48 (1H, s, Het-H-5), 8.78 (1H, s, Het-H-2), 11.93 (2H, br s, NH + COOH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 108.4, 117.7, 118.9 (q, *J* = 32.6 Hz, C-CF_3), 125.3 (q, *J* = 272.6 Hz, Het-CF_3), 128.1, 139.5, 140.8, 146.3, 164.4 (COOH). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 59.17. LCMS, m/z: 231 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_9H_6F_3N_2O_2$ 231.0376; Found $C_9H_6F_3N_2O_2$ 230.0385.

General procedure for the synthesis of azatriptamine-analogues (15)

1. Nitromethane (11.8 ml, 0.22 mol) was added one portion to a solution of aldehydes **12** (30 g, 0.18 mol), potassium acetate (7.1 g, 0.07 mol) and butylamine (7.1 ml, 0.07 mol) in 200 ml MeOH. The reaction mixture was stirred at rt. for 16 h. After completion of the reaction, the resulting precipitate was collected by filtration, washed with MeOH (50 ml) and dried to afford the pure products **15a-c.**

6-fluoro-3-(2-nitrovinyl)-1*H*-pyrrolo[2,3-*b*]pyridine (15a)

Yield 35.3 g (93.2%), Yellow solid, M.p. 268 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 6.99 (1H, d, *J* = 8.0 Hz, Het-H-4), 8.09 (1H, d, *J* = 13.2 Hz, CH=C<u>H</u>-NO_2), 8.21-8.40 (2H, m, Het-H-2, C<u>H</u>=CH-NO_2), 8.61 (1H, t, *J* = 7.0 Hz, Het-H-5), 12.83 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 102.9 (d, *J* = 38.1 Hz), 107.2, 115.0, 133.0, 133.5, 134.5 (d, *J* = 10.9 Hz), 132.2, 146.5 (d, *J* = 20.3 Hz), 159.7 (d, *J* = 236.8 Hz, C-F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 74.25. LCMS, m/z: 208 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_9H_7FN_3O_2$ 208.0517; Found $C_9H_7FN_3O_2$ 208.0517.

5-fluoro-3-(2-nitrovinyl)-1*H*-pyrrolo[3,2-*b*]pyridine (15b)

Yield 36.0 g (95.3%), Yellow solid, M.p. 194 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.01 (1H, d, *J* = 8.5 Hz, Het-H-7), 8.09 (1H, t, *J* = 8.3 Hz, Het-H-6), 8.28 (2H, s, C<u>H</u>=CH-NO_2, CH=C<u>H</u>-NO_2), 8.37 (1H, s, Het-H-2), 12.58 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 104.0 (d, *J* = 41.9 Hz), 107.0, 125.6 (d, *J* = 10.0 Hz), 128.7, 132.5, 133.5, 138.0, 139.8 (d, *J* = 18.7 Hz), 159.5 (d, *J* = 232.4 Hz, C-F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 73.79. LCMS, m/z: 208 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_9H_7FN_3O_2$ 208.0517; Found $C_9H_7FN_3O_2$ 208.0514.

6-fluoro-3-(2-nitrovinyl)-1*H*-pyrrolo[3,2-*b*]pyridine (15c)

Yield 35.7 g (94.6%), Yellow solid, M.p. 213 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.86 (1H, d, *J* = 9.3 Hz, Het-H-7), 8.30 (1H, d, *J* = 13.2 Hz, C<u>H</u>=CH-NO_2), 8.36 (1H, s, Het-H-5), 8.47 (1H, d, *J* = 13.2 Hz, CH=C<u>H</u>-NO_2), 8.52 (1H, s, Het-H-2), 12.50 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 107.6 (d, *J* = 22.5 Hz), 108.1, 130.7 (d, *J* = 8.7 Hz), 133.2, 133.7 (d, *J* = 27.2 Hz), 134.0, 139.2, 141.0, 156.6 (d, *J* = 246.2 Hz, C-F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 134.63. LCMS, m/z: 208 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_9H_7FN_3O_2$ 208.0517; Found $C_9H_7FN_3O_2$ 208.0511.

Step 2. To a cooled to 0 °C solution of compounds **15a-c** (20 g, 0.10 mol) in 400ml THF and 200 ml MeOH, sodium borohydride (4.7 g, 0.13 mol) was added portion-wise. The reaction mixture was stirred at 0 °C for 3 h. Upon completion of the reaction (monitored by TLC, eluent: ethyl acetate/hexane 1:1, R*f* = 0.4), the solvents were removed under reduced pressure, resulting residue was treated with 100 ml water and acidified with conc. hydrochloric acid to pH = 2. The mixture was stirred for 30 min and the precipitate was filtered through Celite, washed with cold water (50 ml) and MTBE (30 ml), dried in a desiccator over P_2O_5 to give pure compounds **16a-c**, that used in the next step without further purification.

6-fluoro-3-(2-nitroethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (16a)

Yield 11.2 g (55.5%), Beige solid, M.p. 157 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 3.32-3.30 (2H, m, overlap with water, C<u>H$_2$</u>-CH_2-NO_2), 4.83 (2H, t, *J* = 6.9 Hz, CH_2-C<u>H$_2$</u>-NO_2), 6.79 (1H, d, *J* = 8.5 Hz, Het-H-4), 7.27 (1H, s, Het-H-2), 8.61 (1H, t, *J* = 8.2 Hz, Het-H-5), 11.62 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 22.9 (<u>CH_2</u>-CH_2-NO_2), 75.7 (CH_2-<u>CH_2</u>-NO_2), 100.2 (d, *J* = 39.1 Hz), 108.8, 116.9, 123.5, 131.8, 146.5 (d, *J* = 19.3 Hz), 159.3 (d, *J* = 233.5 Hz, C-F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 76.50. LCMS, m/z: 210 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_9H_9FN_3O_2$ 210.0673; Found $C_9H_9FN_3O_2$ 210.0676.

5-fluoro-3-(2-nitroethyl)-1*H*-pyrrolo[3,2-*b*]pyridine (16b)

Yield 9.9 g (48.9%), Brown solid, M.p. 122 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 3.31 (2H, t, *J* = 7.0 Hz, <u>CH_2</u>-CH_2-NO_2), 4.87 (2H, t, *J* = 7.0 Hz, CH_2-<u>CH_2</u>-NO_2), 6.81 (1H, dd, *J* = 8.5 Hz, *J* = 1.1 Hz, Het-H-7), 7.54 (1H, s, Het-H-2), 7.86-7.91 (1H, m, Het-H-6), 11.36 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 22.5 (<u>CH_2</u>-CH_2-NO_2), 75.6 (CH_2-<u>CH_2</u>-NO_2), 100.4 (d, *J* = 42.9 Hz), 109.2, 124.7 (d, *J* = 1=9.5 Hz), 127.4, 129.1, 141.0 (d, *J* = 18.3 Hz), 158.7 (d, *J* = 228.1 Hz, C-F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 76.50. LCMS, m/z: 210 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_9H_9FN_3O_2$ 210.0673; Found $C_9H_9FN_3O_2$ 210.0673.

6-fluoro-3-(2-nitroethyl)-1*H*-pyrrolo[3,2-*b*]pyridine (16c)

Yield 9.0 g (44.4%), Brown solid, M.p. 166 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 3.32-3.30 (2H, m, overlap with water, <u>CH_2</u>-CH_2-NO_2), 4.91 (2H, t, *J* =

7.5 Hz, CH_2-$\underline{CH_2}$-NO_2),

7.51 (1H, s, Het-H-5), 7.63 (1H, d, *J* = 8.5 Hz , Het-H-7), 8.31 (1H, s, Het-H-2), 11.24 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 22.7 ($\underline{CH_2}$-CH_2-NO_2), 75.6 (CH_2-$\underline{CH_2}$-NO_2), 105.6 (d, *J* = 22.5 Hz), 109.8, 128.6 ,128.7, 131.2 (d, *J* = 26.6 Hz), 142.7, 156.3 (d, *J* = 242.7 Hz, C-F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 137.18. LCMS, m/z: 210 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_9H_9FN_3O_2$ 210.0673; Found $C_9H_9FN_3O_2$ 210.0669.

Step 3. To a solution compounds **16a-c** (20 g, 0.10 mol) in 200 ml MeOH, 5 % $Pd(OH)_2$ on activated charcoal (2 g) was added. The reaction mixture was vacuumed, flushed three times with hydrogen, and stirred under a hydrogen atmosphere (1 atm) for 16 h. Upon completion of the reaction, the catalyst was removed by filtration, and the solvent was evaporated in vacuo. The residue was dissolved in 50 ml DCM and 4M HCl in dioxane was added to pH = 1 (30ml), stirred for 30 min, precipitate was filtered off, washed with MTBE (20 ml) and isopropyl alcohol(20 ml) and dried to give pure hydrochloric salts **17a-c**.

2-{6-fluoro-1H-pyrrolo[2,3-b]pyridin-3-yl}ethan-1-amine hydrochloride (17a)

Yield 17.0 g (82.6%), Brown solid, M.p. 243 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.96-3.09 (4H, m, CH_2-$\underline{CH_2}$-NO_2 , $\underline{CH_2}$-CH_2-NH_2), 6.80 (1H, d, *J* = 8.5 Hz, Het-H-4), 7.31 (1H, s, Het-H-2), 8.01 (3H, br s, NH_3^+), 8.15 (1H, t, *J* = 8.3 Hz, Het-H-5), 11.63 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 23.5 ($\underline{CH_2}$-CH_2-NO_2), 39.6 (CH_2-$\underline{CH_2}$-NO_2), 100.5 (d, *J* = 39.2 Hz), 109.8, 117.7, 124.0, 132.2 (d, *J* = 9.8 Hz), 145.3 (d, *J* = 19.1 Hz), 159.8 (d, *J* = 232.3 Hz, C-F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 76.61. LCMS, m/z: 180 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_9H_{11}FN_3$ 180.0932; Found $C_9H_{11}FN_3$ 180.0940.

2-{5-fluoro-1H-pyrrolo[3,2-b]pyridin-3-yl}ethan-1-amine hydrochloride (17b)

Yield 17.5 g (85.0%), Brown solid, M.p. 199 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.95-3.02 (2H, m, $\underline{CH_2}$-CH_2-NO_2), 3.05-3.14 (2H, m, CH_2-$\underline{CH_2}$-NO_2), 6.81 (1H, d, *J* = 8.2 Hz, Het-H-7), 7.59 (1H, s, Het-H-2), 7.90 (1H, t, *J* = 8.0 Hz, Het-H-6), 8.01 (3H, br s, NH_3^+), 11.64 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 22.3 ($\underline{CH_2}$-CH_2-NO_2), 39.1 (CH_2-$\underline{CH_2}$-NO_2), 102.2 (d, *J* =43.75 Hz),, 110.0, 124.5 (d, *J* = 1=9.8 Hz), 127.5, 129.1, 141.1 (d, *J* = 17.9 Hz), 158.6 (d, *J* = 228.3 Hz, C-F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 76.77. LCMS, m/z: 180 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_9H_{11}FN_3$ 180.0932; Found $C_9H_{11}FN_3$ 180.0935.

2-(6-fluoro-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl)ethan-1-amine (17c)

Yield 16.3 g (79.3%), Beige solid, M.p. 254 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 3.12-3.25 (4H, m, $\underline{CH_2}$-CH_2-NO_2, CH_2-$\underline{CH_2}$-NO_2), 8.01 (1H, s, Het-H-5), 8.39 (1H, d, *J* =8.0 Hz Het-H-7), 8.75 (1H, s,, Het-H-2), 12.64 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 22.3 ($\underline{CH_2}$-CH_2-NO_2), 39.1 (CH_2-$\underline{CH_2}$-NO_2), 107.5, 113.6, 125.5, 132.1, 135.3, 135.9, 155.1 (d, *J* = 239.3 Hz, C-F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 135.41. LCMS, m/z: 180 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_9H_{11}FN_3$ 180.0932; Found $C_9H_{11}FN_3$ 180.0928.

General procedure for the Boc-protection of Azaindoles (18)

Boc_2O (83.0 ml, 0.36 mol) was added dropwise to a stirring solution of **3** (0.30 mol) and DMAP (1.70 g, 0.01 mol) in THF (400 ml) at r.t over 30 min. The reaction was stirred at rt. for 16 h. Afterward, the mixture was poured into water (200 ml), stirred for 30 min, and extracted with $CHCl_3$ 3 times (100 ml each). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*, yielding the compound **18a-e**, which used in the next step without further purification.

Example of pure ***tert*-butyl 5-fluoro-1*H*-pyrrolo[3,2-*b*]pyridine-1-carboxylate (18a)**

Yield 55.0 g (79.2%), Beige solid, M.p. 89 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.62 (9H, s, O-C$(CH_3)_3$), 6.74 (1H, d, *J* = 3.8 Hz, Het-H-3), 7.07 (1H, dd, *J* = 8.8 Hz, Het-H-7), 8.01 (1H, d, *J* = 3.8 Hz, Het-H-2), 8.41 (1H, d, , *J* = 8.0 Hz, Het-H-6). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 27.5 (O-C($\underline{C}H_3)_3$), 84.9 (O-$\underline{C}(CH_3)_3$), 104.5 (d, *J* = 41.4 Hz), 107.0, 126.1, 127.3 (d, *J* = 9.5 Hz), 127.1, 130.8, 145.1 (d, *J* = 21.9 Hz, C-F), 148.2 (N-$\underline{C}$(O)-C), 159.7 (d, *J* = 235.3 Hz, C F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 76.43. LCMS, m/z: 237 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_{12}H_{14}FN_2O_2$ 237.1034; Found $C_{12}H_{14}FN_2O_2$ 237.1027.

General procedure for the Reduction pyrrole fragment (19)

In a 1 L autoclave equipped with a stirrer, a solution of Boc-protected azaindole **18a-e** (50.0 g) in 500 ml THF and 5 g $Pd(OH)_2$ on on activated charcoal (5%) was added. The reaction mixture was vacuumed, flushed three times with hydrogen, and stirred under a hydrogen atmosphere (20 atm) for 16 h. Upon completion of the reaction, the catalyst was removed by filtration, and the solvent was evaporated in vacuo to give pure products **19a-e**, which was used in the next step without further purification.

Example of pure ***tert-butyl* 5-fluoro-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-1-carboxylate (19a)**

Product was purified by flash column chromatography on silica gel in using $CHCl_3$ – MeCN (1:1) system as eluent.

Yield 44.2 g (87.7%), Beige solid, M.p. 81 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.48 (9H, s, O-C$(CH_3)_3$), 3.10 (2H, t, *J* = 8.8 Hz, $\underline{C}H_2$-CH_2-N-Boc), 3.94 (1H, t, *J* = 8.5 Hz, CH_2-$\underline{C}H_2$-N-Boc), 6.89 (1H, d, *J* = 8.5 Hz, Het-H-7), 7.68-8.00 (1H, m, Het-H-6). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 28.3 5 (O-C($\underline{C}H_3)_3$), 28.89 ($\underline{C}H_2$-CH_2-N-Boc), 46.4 (CH_2-$\underline{C}H_2$-N-Boc), 81.0 (O-$\underline{C}(CH_3)_3$), 106.5 (d, *J* = 38.9 Hz), 125.5, 125.7, 135.8 (N-$\underline{C}$(O)-C), 152.1, 159.2 (d, *J* = 231.2 Hz, C F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 80.03. LCMS, m/z: 239 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_{12}H_{16}FN_2O_2$ 239.1191; Found $C_{12}H_{16}FN_2O_2$ 239.1196.

5-fluoro-1H,2H,3H-pyrrolo[3,2-b]pyridine hydrochloride (20a)

To a solution of **19a** (30 g, 0.13 mol) in 200 ml DCM, 4M dioxane/HCl solution (100ml) was added dropwise at r.t

over 20 min. The reaction was stirred for 15 h at 40 °C. Upon completion of the reaction, the solvent was evaporated to dryness, and the crude product was crystallized from i-PrOH (200 ml), filtered, washed with i-PrOH (50 ml) and MTBE (100ml), dried to give pure HCl salt **20a**.

Yield 15.8 g (72.0%), Gray solid, M.p. 179 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 3.17 (2H, t, *J* = 8.0 Hz, $\underline{C}H_2$-CH_2-NH), 3.76 (2H, t, *J* = 8.1 Hz, CH_2-$\underline{C}H_2$-NH), 7.09 (1H, d, *J* = 8.2 Hz, Het-H-7), 7.87 (1H, t, *J* = 7.5 Hz, Het-H-6), 9.12-11.52 (2H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 30.35 ($\underline{C}H_2$-CH_2-NH), 44.8 (CH_2-$\underline{C}H_2$-NH), 108.3 (d, *J* = 38.3 Hz), 131.3, 132.4, 156.1 (d, *J* = 16.46 Hz)., 162.8 (d, *J* = 237.0 Hz, C F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 72.64. LCMS, m/z: 239 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_7H_8FN_2$ 139.0666; Found $C_7H_8FN_2$ 139.0667.

General procedure for Boc deprotection (20b-d)

To a solution of **19b-d** (0.13 mol) in 300 ml of MeOH, acetyl chloride (26.9 ml, 0.38 mol) was added dropwise at r.t over 20 min. The reaction was stirred for 15h at 40 °C. Upon completion of the reaction, the solvent was evaporated to dryness, and the crude product was crystallized with i-PrOH (200 ml), filtered, washed with i-PrOH (50 ml) and MTBE (100ml), dried to give pure HCl salts **20b-d**.

5-fluoro-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine (20b)

Yield from 3 steps 11.1 g (63.8%), Yellow solid, M.p. 231 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 3.12 (2H, t, *J* = 8.1 Hz, $\underline{C}H_2$-CH_2-NH), 3.76 (2H, t, *J* = 8.2 Hz, CH_2-$\underline{C}H_2$-NH), 7.71 (1H, dd, *J* = 7.6 Hz, *J* = 1.5 Hz, Het-H-4), 7.76 (1H, s, Het-H-6), 8.74 (1H, br s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 26.4 ($\underline{C}H_2$-CH_2-NH), 46.6 (CH_2-$\underline{C}H_2$-NH), 118.3 (d, *J* = 38.3 Hz), 127.0 (d, *J* = 26.3 Hz), 133.9, 152.6, 155.1 (d, *J* = 234.4 Hz, C F). ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 143.40. LCMS, m/z: 139 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_7H_8FN_2$ 139.0666; Found $C_7H_8FN_2$ 139.0665.

6-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]pyridine (20c)

Yield from 3 steps 13.8 g (70.3%), Beige solid, M.p. 168 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 3.18 (2H, t, *J* = 8.7 Hz, $\underline{C}H_2$-CH_2-NH), 3.64 (2H, t, *J* = 8.7 Hz, CH_2-$\underline{C}H_2$-NH), 6.68 (3H, br s, NH)7.05 (1H, d, *J* = 1.2 Hz, Het-H-4), 8.02 (1H, s, Het-H-6). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 29.3 ($\underline{C}H_2$-CH_2-NH), 45.6 (CH_2-$\underline{C}H_2$-NH), 111.2 (d, *J* = 38.3 Hz), 123.9 (q, *J* = 271.7 Hz, Het-$\underline{C}F_3$), 126.4 (q, *J* = 33.2 Hz, $\underline{C}$ CF_3), 127.7, 148.8, 156.2. ^{19}F NMR spectrum (376 MHz, DMSO-d_6) δ, ppm (*J*, Hz): - 61.60. LCMS, m/z: 189 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_8H_8F_3N_2$ 189.0634; Found $C_8H_8F_3N_2$ 189.0637.

7-methyl-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]pyridine (20d)

Yield from 3 steps 11.4 g (66.3%), Light-brown solid, M.p. 260 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.22 (3H, s, Het-$\underline{C}H_3$), 3.37 (2H, t, *J* = 8.8 Hz, $\underline{C}H_2$-CH_2-NH), 3.69 (2H, t, *J* = 8.8 Hz, CH_2-$\underline{C}H_2$-NH), 6.85 (1H, br s, NH), 7.34 (1H, d, *J* = 5.5 Hz, Het-H-6), 7.75 (1H, d, *J* = 6.0 Hz, Het-H-5), 15.92 (1H, br s, NH^+). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 17.5 (Het-$\underline{C}H_3$), 28.2 ($\underline{C}H_2$-CH_2-NH), 45.4 (CH_2-$\underline{C}H_2$-NH), 126.5 (2C), 132.7, 145.2, 149.8. LCMS, m/z: 135 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_8H_{11}N_2$ 135.0916; Found $C_8H_{11}N_2$ 135.0916.

2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridin-4-ol (20e)

19e (30 g, 0.12 mol) was added in one portion to a 200 mL of hydrochloric acid. The reaction was stirred for 15 h at 90 °C. Upon completion of the reaction, mixture was cooled to rt. and filtered, washed with i-PrOH (50 ml) and MTBE (100ml), dried to give pure HCl salt **20e**.

Yield 9.4 g (72.0%), Beige solid, M.p. 240 °C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 3.00 (2H, t, *J* = 9.4 Hz, $\underline{C}H_2$-CH_2-NH), 3.71 (2H, t, *J* = 9.4 Hz, CH_2-$\underline{C}H_2$-NH), 6.27 (1H, d, *J* = 6.8 Hz, Het-H-6), 7.56 (1H, t, *J* = 6.3 Hz, Het-H-7), 8.14 (1H, br s, NH), 12.58 (1H, br s, OH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 25.1, 47.0, 98.5, 105.6, 138.4, 154.2, 164.9. LCMS, m/z: 137 $[M+H]^+$. HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_7H_9N_2O$ 139.0709; Found $C_7H_9N_2O$ 137.0712.

Supplementary information file containing ^{1}H and ^{13}C NMR spectra and mass spectra of the synthesized compounds is available at the journal website http://hgs.osi.lv.

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