Synthesis of chromones, annulated with oxygen-containing heterocycles with two hetero atoms at C(7)-C(8) bond

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Keywords: *annulation, chromones, 6H-[1,3]dioxolo[4,5-h]chromen-6-one, 2,3-dihydro-7H-[1,4]dioxino[2,3-h]chromen-7-one, 3,4-dihydro-2H,8H-[1,4]dioxepino[2,3-h]chromen-8-one, 2,3-dihydro-1H,7H-chromeno[7,8-b][1,4]oxazin-7-one, 4H,12H-pyrano[2,3-a]phenoxazine-4-one, 9,10-dihydro-4H,8H-chromeno[8,7-e][1,3]oxazin-4-one.*

The present review represented the advanced synthetic strategies for chromones annulated at the C(7)-C(8) bond with five-membered, six-membered, and seven-membered oxygen-containing heterocycles with two heteroatoms, such as 6*H*-[1,3]dioxolo[4,5-*h*]chromen-6-one, 2,3-dihydro-7*H*-[1,4]dioxino[2,3-*h*]chromen-7-one, 3,4-dihydro-2*H*,8*H*-[1,4]dioxepino[2,3-*h*]chromen-8-one, 2,3-dihydro-1*H*,7*H*-chromeno[7,8-b][1,4]oxazin-7-one, 4*H*,12*H*-pyrano[2,3-a]phenoxazine-4-one and 9,10-dihydro-4*H*,8*H*-chromeno[8,7-e][1,3]oxazin-4-one. The biological activity of naturally occurring and modified synthetic fused hetarenochromones has been also highlighted.

Introduction

Angular hetarenochromones are of considerable interest because of their abundance in natural flavonoids and some alkaloids and promising biological activity [1]. Chromones annulated with oxygen-containing cycle occupy a significant place among them. These are first and foremost furo[2,3-*h*]chromones and pyrano[2,3-*f*]chromones. Their syntheses and biological activity have been highlited in reviews [1, 2]. Chromone derivatives annulated with oxygen-containing ring with two heteroatoms, such as dioxolane and dioxane cycles, were also isolated from various natural sources. Their *O,N*-containing analogues remain unobserved among natural products. Chromones annulated with oxazole and oxazine cycles, namely 2-methylchromeno[7,8-*d*][1,3]oxazol-6-one, chromeno[7,8-*d*][1,3]oxazol-2,6(3*H*)-dione, 4*H*-chromeno[8,7-*d*][1,2]oxazol-4-one

and 3,4-dihydrochromeno[8,7-*b*][1,4]oxazin-7(2*H*)-one are described in the review [1].

The present mini review is a continuation of the review [1] and is focused on the syntheses of chromones annulated at the C(7)-C(8) bond with five-membered, six-membered, and seven-membered oxygen-containing heterocycles with two heteroatoms, such as 6*H*-[1,3]dioxolo[4,5-*h*]chromen-6-one, 2,3-dihydro-7*H*-[1,4]dioxino[2,3-*h*]chromen-7-one, 3,4-dihydro-2*H*,8*H*-[1,4]dioxepino[2,3-*h*]chromen-8-one, 2,3-dihydro-1*H*,7*H*-chromeno[7,8-*b*][1,4]oxazin-7-one, 4*H*,12*H*-pyrano[2,3-a]phenoxazine-4-one and 9,10-dihydro-4*H*,8*H*-chromeno[8,7-e][1,3]oxazin-4-one.

1. Chromones, annulated with heterocycles containing two oxygen atoms

This section is dedicated to the progress of chromones annulated with dioxolane, dioxane and dioxepane rings.

1.1. 6*H*-[1,3]dioxolo[4,5-*h*]chromen-6-ones

The system with an annulated dioxolane cycle to the chromone nucleus at the C(7)-C(8) bond occurs in some natural flavonoids, such as granulosin **1a** from the bark of *Galipea granulosa* [3, 4], bausplendin **2a** from *Bauhinia shlendens* [5], maxima isoflavones A (**3a**) and D (**3b**) from aerial parts of *Tephrosia maxima* [6-8] and 7,8-methylenedioxy-4'-methoxyisoflavone **4** from *Indigofera linnaei* [9] (**Figure 1**).

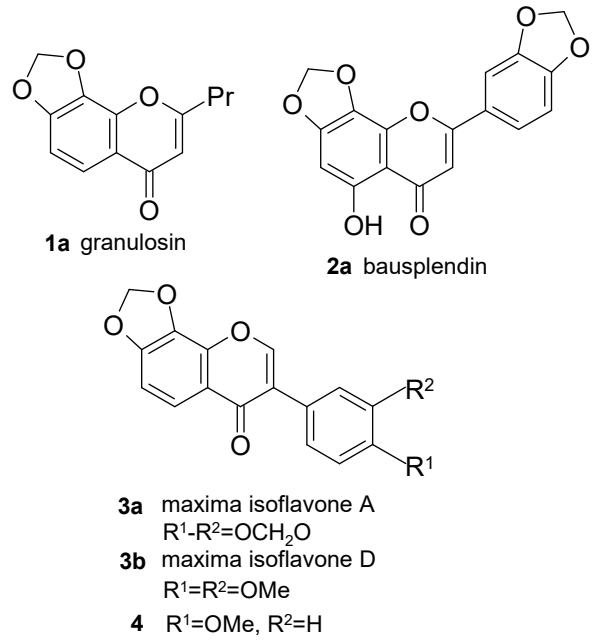
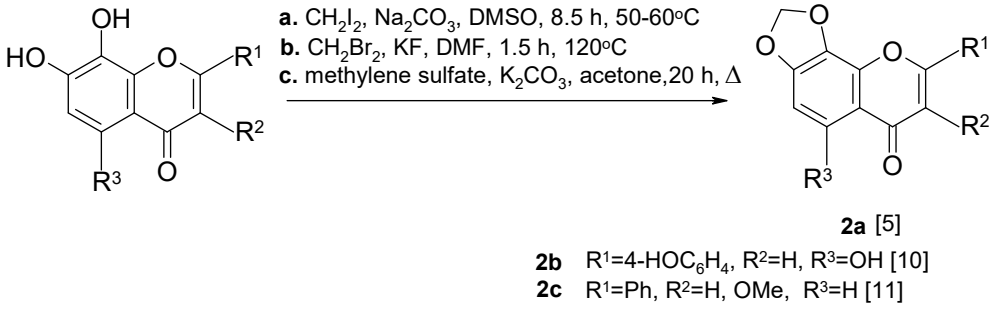


Figure 1. Natural 6*H*-[1,3]dioxolo[4,5-*h*]chromen-6-ones

Two strategies were applied for the construction of the 6*H*-[1,3]dioxolo[4,5-*h*]chromen-6-one system: the formation of the dioxolane cycle on the basis of 7,8-dihydroxychromones and the annulation of the γ-pyron ring to benzodioxole derivatives.

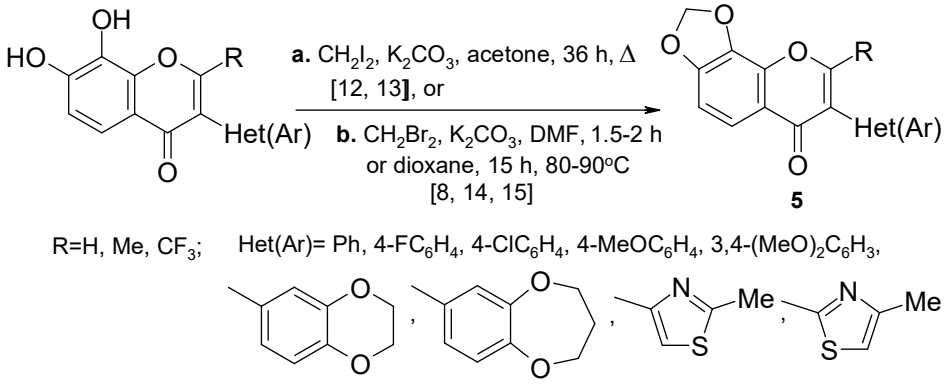
The first one was realized in the synthesis of bausplendin **2a** and its analogues **2b,c**, which were synthesized from the corresponding 7,8-dihydroxyflavones by alkylation with diiodomethane [5], dibromomethane [10] or methylene sulfate [11] in DMSO [5], DMF [10] or acetone [11] in the presence of an inorganic base: Na_2CO_3

[5], K_2CO_3 [11] or KF [10] (**Scheme 1**).



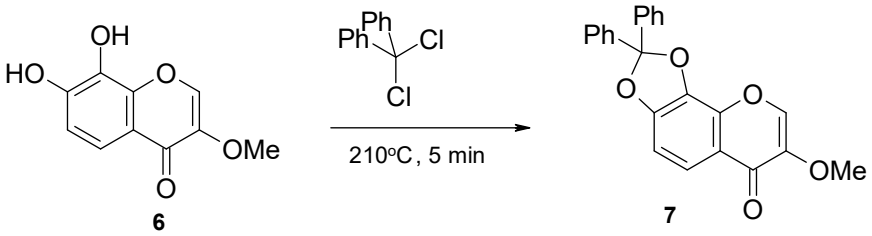
Scheme 1. The synthesis of bausplendin **2a** and its analogues **2b,c**

7,8-Methylenedioxyisoflavones and their thiazole analogues of formula **5**, were prepared via the alkylation of the corresponding 7,8-dihydroxychromones by diiodo [12, 13] and dibromomethane [8, 14, 15] in the presence of K_2CO_3. When heated in acetone or dioxane, the reaction was completed in 36 [12] and 15 hours [8], respectively. When DMF [8, 14, 15] or its mixture with acetone [13] has been used as a solvent, the reaction time was reduced to 1,5-2 h and yield of target products was increased (**Scheme 2**).



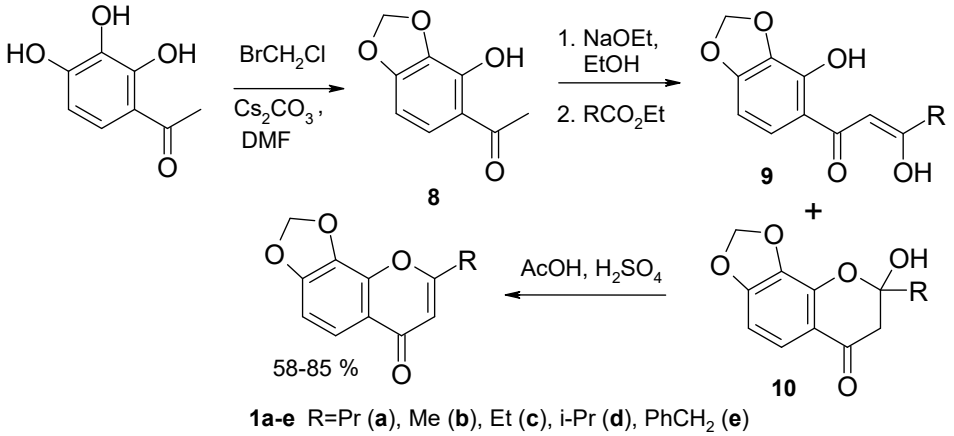
Scheme 2. The synthesis of 7,8-methylenedioxyisoflavones and their thiazole analogues **5**

Alkylation of the natural chromone retusin **6**, with α-dichlorodiphenylmethane upon heating in an oil bath to 210°C until the evolution of HCI gas ceased (5 min) resulted in the diphenylmethylene derivative **7** [16] (**Scheme 3**).



Scheme 3. Alkylation of the natural chromone retusin **6** with α-dichlorodiphenylmethane

Granulosin **1a** and its analogues **1b-e**, all of which exhibit toxicity to the brine shrimp *Artemia salina*, have been prepared from 2',3',4'-trihydroxyacetophenone using a second approach. The first step of the synthesis involved the formation of the benzodioxole derivative **8** via the regioselective acetalisation of 2',3',4'-trihydroxyacetophenone (**Scheme 4**) using 1 equivalent of bromochloromethane in the presence of cesium carbonate. Treatment of 2'-hydroxy-3',4'-methylendioxy)acetophenone **8** with two equivalents of sodium ethoxide in ethanol afforded the enolate which, on reaction with a series of ethyl carboxylate esters gave mixtures of the corresponding enols **9** and their cyclic derivatives **10**, according to NMR spectroscopy. Treatment of these mixtures with a mixture of acetic and sulfuric acids afforded 7,8-methylenedioxychromones **1a-e** in 58-85% yields [4].

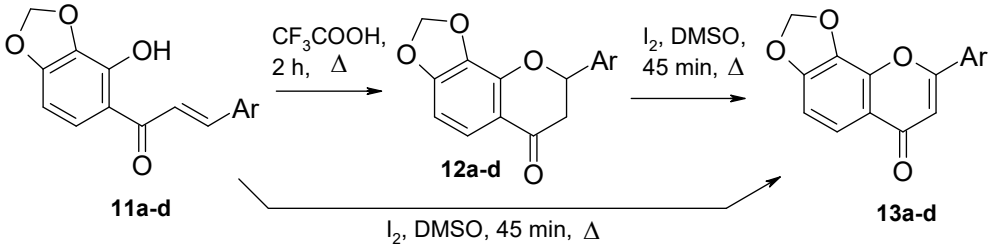


1a-e R=Pr (**a**), Me (**b**), Et (**c**), i-Pr (**d**), $PhCH_2$ (**e**)

Scheme 4. The synthesis of Granulosin **1a** and its analogues **1b-e**

Cyclization of chalcones **11**, obtained from acetophenone **8** and benzaldehydes, in TFA resulted in 7,8-methylenedioxyflavanones **12,** which on oxidation with I_2 in DMSO gave 7,8-methylenedioxyflavones **13** [9, 17, 18] (**Scheme 5**). Finally, the flavone **13b** was also prepared in 95% yield by simply heating chalcone **11b** under reflux in DMSO

containing a crystal of I_2 [9].

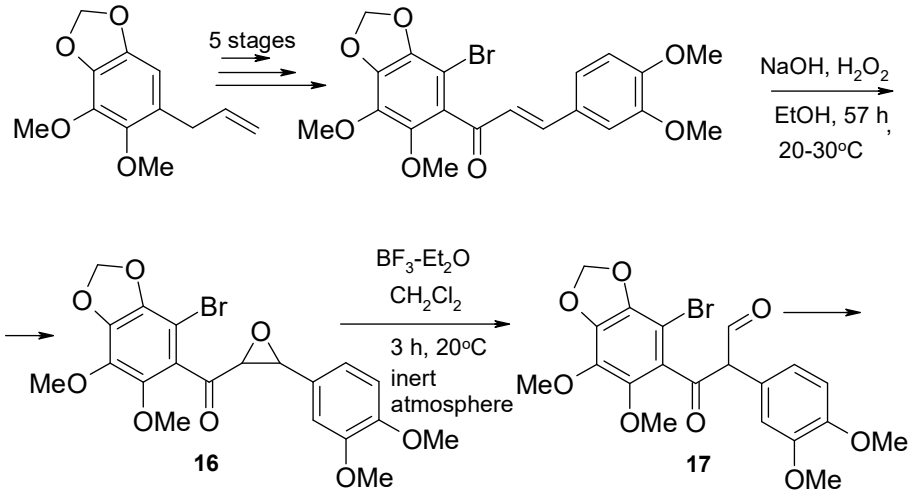


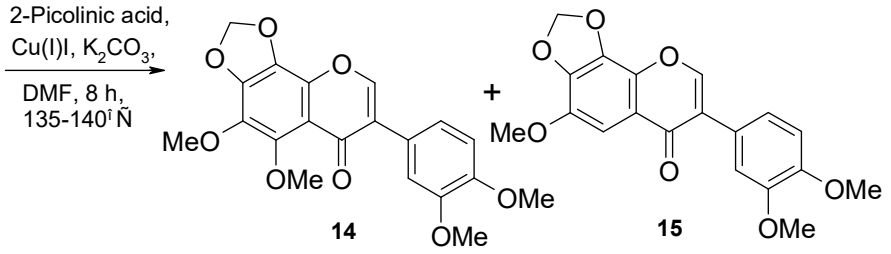
Ar = 2-MeOC$_6$H$_4$ (**a**), (b)4-MeOC$_6$H$_4$ (**b**), 3,4-(MeO)$_2$C$_6$H$_3$ (**c**), 3,4,5-(MeO)$_3$C$_6$H$_2$ (**d**)

Scheme 5. Oxidative cyclization of chalcones **11**

This new series of chalcones **11**, flavanones **12** and flavones **13** have been assessed for their effect on proliferation, cytotoxic potential and apoptosis in human leukemia cells. Among the tested compounds, the chalcone series showed the best activity and chalcone **11a** showed a significant effect on down-regulation of cancer cell proliferation and viability in three different leukemia cell lines (K562, Jurkat, U937) [17].

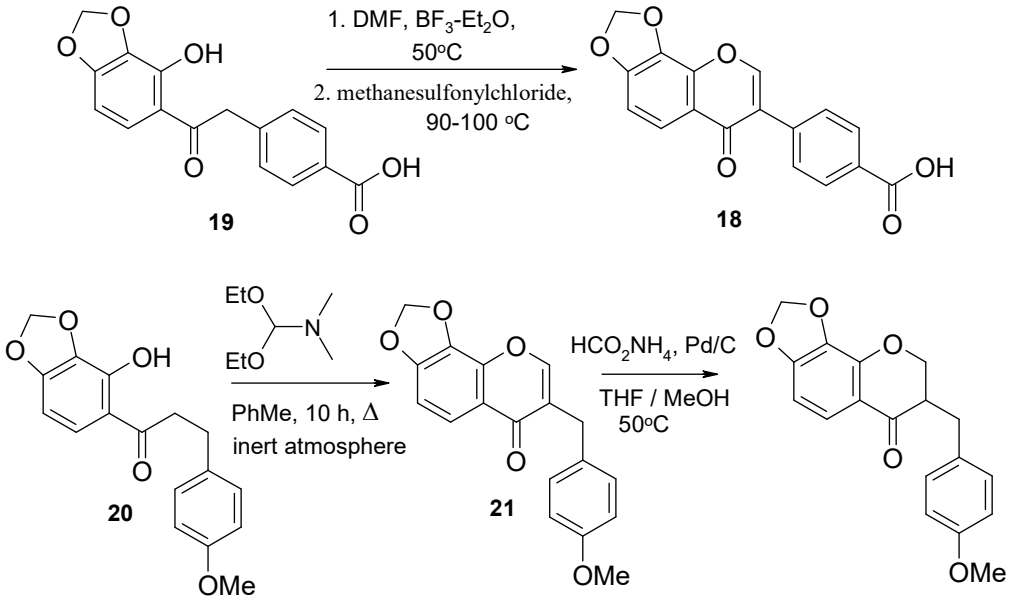
A mixture of 7,8-methylenedioxyisoflavones **14** and **15** (13:10 ratio, respectively) was obtained starting with readily available plant metabolite from dill and parsley seeds [19] (**Scheme 6**). The reaction sequence involved an efficient conversion of the key intermediate epoxide **16** into the respective β-ketoaldehyde **17** followed by its Cu(I)-mediated cyclization into the target 7,8-methylenedioxyisoflavone **14** and its 5-unsubstituted derivative **15**, obtained due to the instability of the 5-OMe group under experimental conditions (overall yield 22%). The latter compound **15** was successfully isolated from the reaction mixture via chromatography.





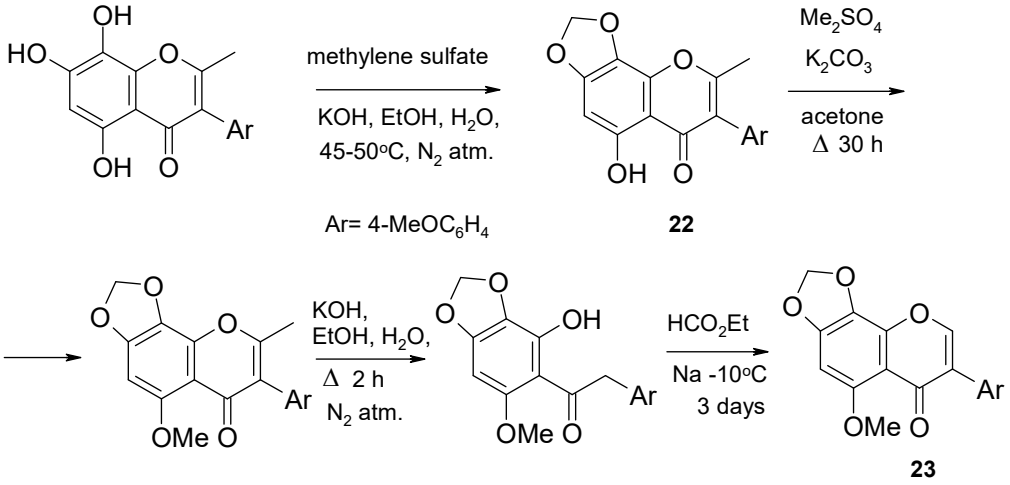
Scheme 6. The synthesis of 7,8-methylenedioxyisoflavones **14** and **15** from epoxides **16**

7,8-Methylenedioxyisoflavones and their homoanalogs can also be obtained via formylation of deoxybenzoines and their homo-analogs followed by the γ-pyron ring closure, as shown in **Scheme 7**. Thus, 4-(6-oxo-6*H*-[1,3]dioxolo[4,5-*h*]chromen-7-yl)benzoic acid **18**, patented as useful for treating vascular diseases, was obtained from deoxybenzoine **19** upon treatment with DMF and borontrifluoride-diethyletherate, followed by methanesulfonylchloride addition and heating at 90°-100° for 2 h [20]. 2'-Hydroxy-dihydrochalcone **20** was subjected to cyclization by treatment with N,N-dimethylformamide diethyl acetal to give homoisoflavone **21**, which on reduction and deracemization resulted in homoisoflavonone, isolated from *Chlorophytum Inornatum* [21].



Scheme 7. The synthesis of 7,8-methylenedioxyisoflavones and their homoanalogs via formylation of deoxybenzoines and their homo-analogs

Synthesis of 5-hydroxy-2-methyl-7,8-methylenedioxy-4'-methoxyisoflavone **22** by the first approach and its conversion to 5-methoxy-7,8-methylenedioxy-4'-methoxyisoflavone **23** using the second strategy is reported in [22] (**Scheme 8**).



Scheme 8. The synthesis of 7,8-methylenedioxyisoflavones **22** and **23**

1.2. 2,3-Dihydro-7*H*-[1,4]dioxino[2,3-*h*]chromen-7-ones

Annulation of the 1,4-dioxane heterocycle to the chromone system at C(7)-C(8) bond leads to the formation of 2,3-dihydro-7*H*-[1,4]dioxino[2,3-*h*]chromen-7-ones.

This system is the basis of the molecules of scutellasprostins A, B, C **24a-c** [23] and xanthocercines A and B **25a,b** [24] - flavolignans isolated from the plants *Scutellaria prostrata* and *Xanthocercis zambesia*, respectively (**Figure 2**).

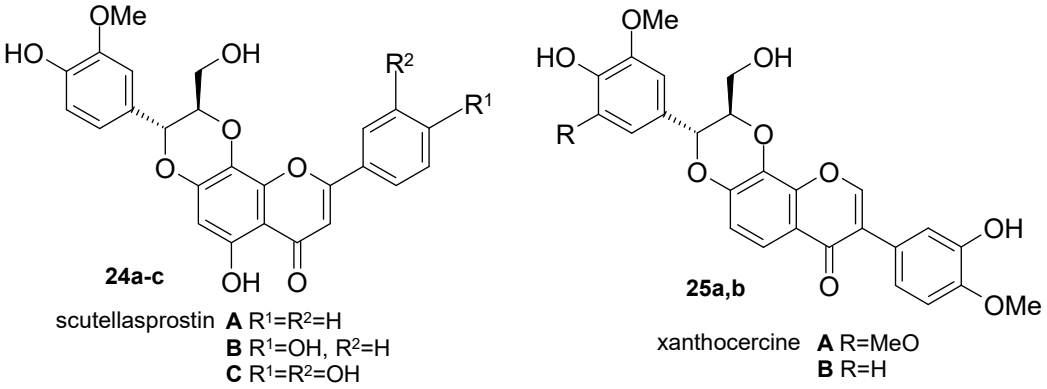
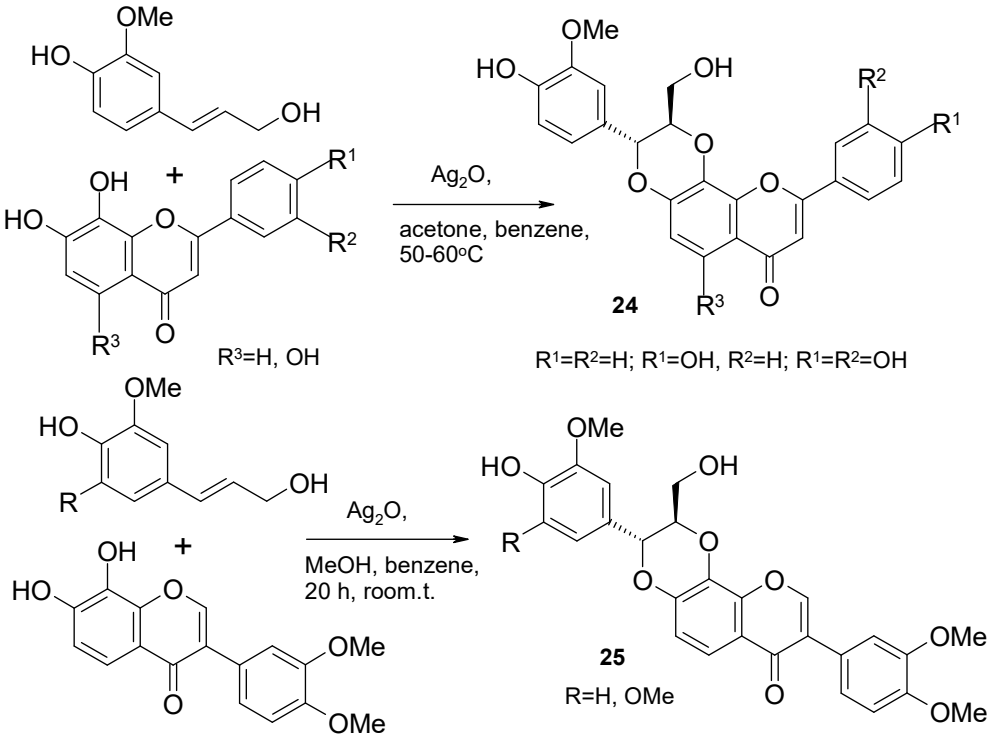


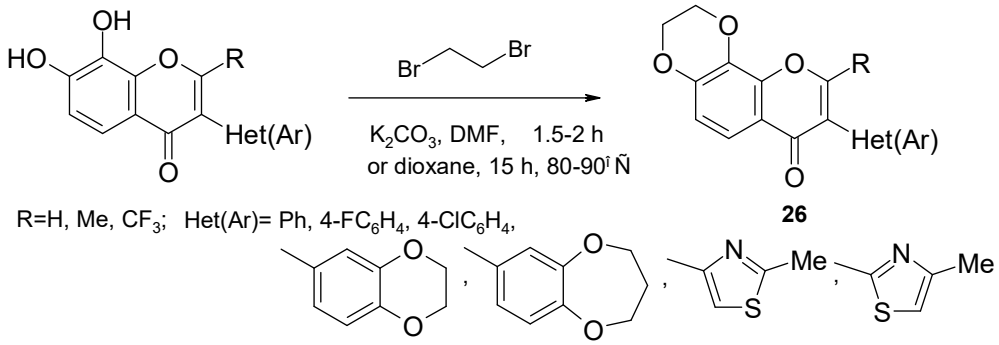
Figure 2. Natural 2,3-dihydro-7*H*-[1,4]dioxino[2,3-*h*]chromen-7-ones

Synthesis of these compounds and their analogues was realized by oxidative coupling of the coniferyl or synapic alcohol with the corresponding natural flavones and isoflavones in the presence of silver oxide [23-25] or horsradish peroxidase [26] (**Scheme 9**).



Scheme 9. The synthesis of natural 2,3-dihydro-7*H*-[1,4]dioxino[2,3-*h*]chromen-7-ones

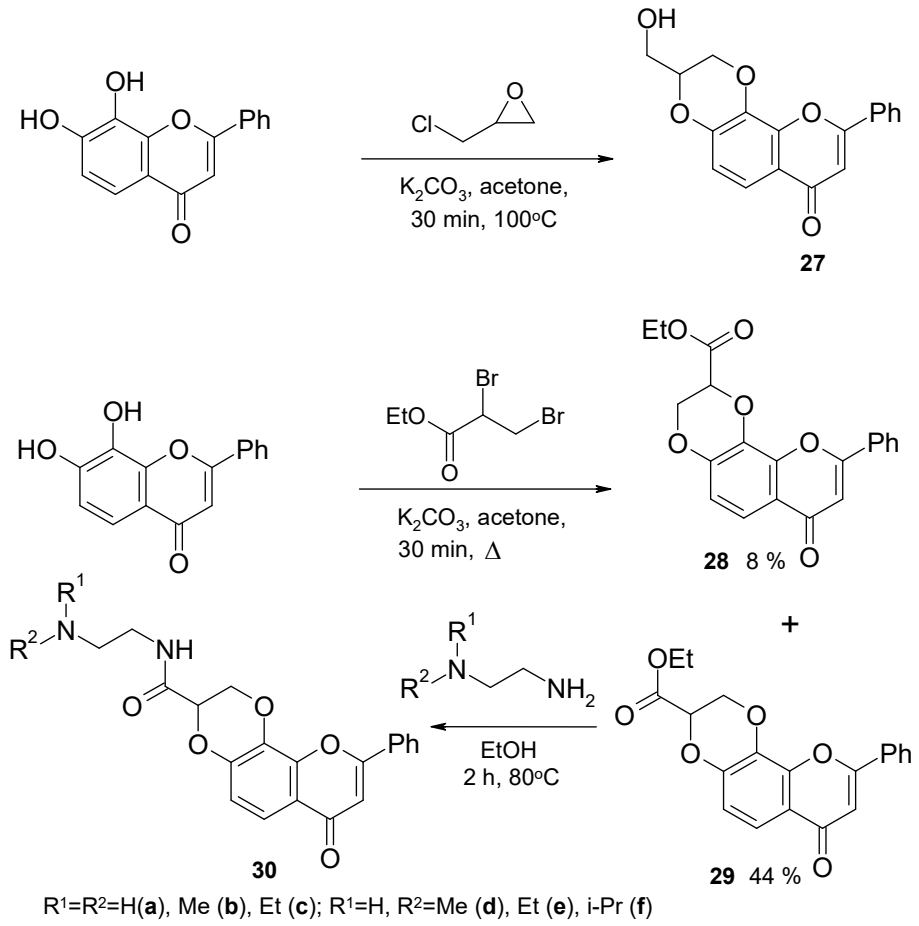
Synthetic analogues of xanthocercin with unsubstituted dioxane ring **26**, were prepared from 7,8-dihydroxyisoflavones and their 3-hetaryl analogues via the alkylation with 1,2-dibromoethane in dioxane or DMF in the presence of K_2CO_3 [8, 14, 15] (**Scheme 10**).



Scheme 10. The synthesis of 2,3-dihydro-7*H*-[1,4]dioxino[2,3-*h*]chromen-7-ones via the alkylation of 7,8-dihydroxychromones with 1,2-dibromoethane

Upon alkylation of 7,8-dihydroxyflavone with 2-chloromethyloxirane 3-hydroxymethyl-2,3-dihydro-7*H*-[1,4]dioxino[2,3-*h*]chromen-7-one **27** [27] was obtained, while the reaction

with ethyl 2,3-dibromopropanoate resulted in a mixture of the regio isomers **28** and **29**, which was separated by fractional crystallisation. Selective group transformation in compound **29** using various ethylenediamine derivatives is furnished in a series of amides **30a-f** in 40-73% yields [28] (**Scheme 11**). In the spasmolysis test, **30b** showed significant antagonistic effect towards the acetylcholine agonists, barium chloride and histamine [28].

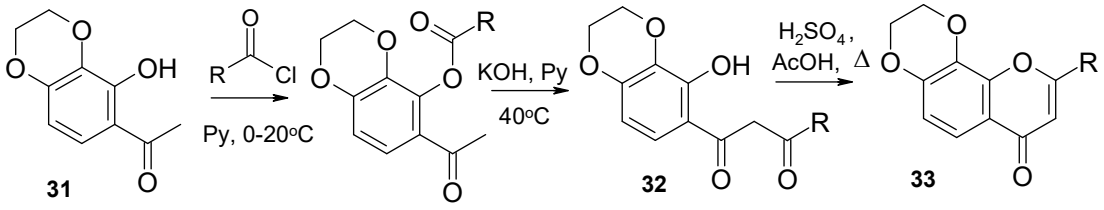


Scheme 11. The synthesis of 2,3-dihydro-7*H*-[1,4]dioxino[2,3-*h*]chromen-7-ones with substituted dioxine ring

An alternative way to the 2,3-dihydro-7*H*-[1,4]dioxino [2,3-*h*]chromene-7-one system is the construction of γ-pyron ring based on benzodioxane derivatives.

Acetylation of 5-hydroxy-6-acetylbenzodioxane **31** with (het)aroyl chlorides followed by rearrangement into β-diketones **32** and their cyclization in an acidic medium produced 9-(het)aryl-2,3-dihydro-7*H*-[1,4]dioxino[2.3-*h*]chromen-7-ones **33**, which were tested for the ability to activate the cystic fibrosis transmembrane conductance regulator

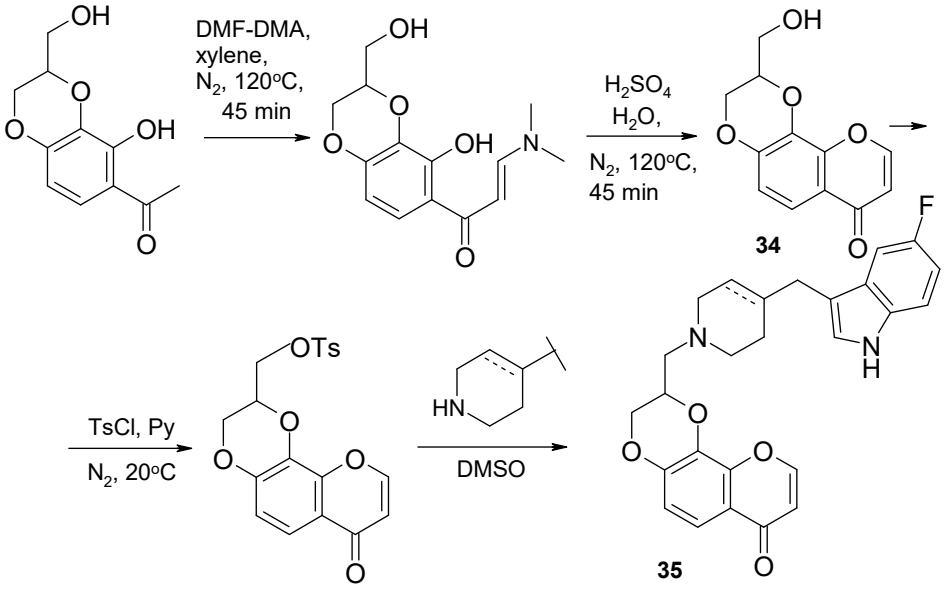
(CFTR) of both wild type CFTR and a mutant CFTR (G551D-CFTR) that causes cystic fibrosis in some human subjects [29] (**Scheme 12**).



R=Ph, 2-FC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 3-FC_6H_4, 4-IC_6H_4, pyridin-4-yl

Scheme 12. The synthesis of 2,3-dihydro-7*H*-[1,4]dioxino[2,3-*h*]chromen-7-ones starting from 5-hydroxy-6-acetylbenzodioxane

Condensation of 3-hydroxymethyl-5-hydroxy-6-acetylbenzodioxane with N,N-dimethylformamide dimethylacetal and subsequent cyclization in the presence of sulfuric acid results in 2-hydroxymethyl derivative **34**, which was further modified by the hydroxyl group into compounds **35,** patented as useful for the treatment of depressive disorders [30, 31] (**Scheme 13)**.

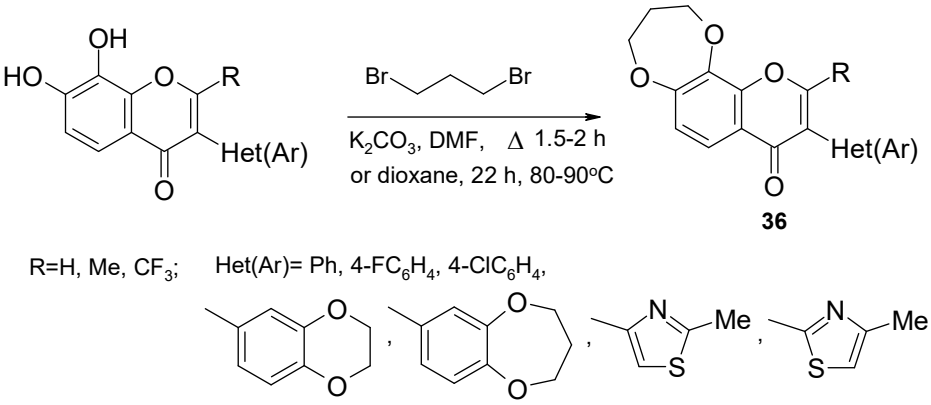


Scheme 13. The synthesis of 2,3-dihydro-7*H*-[1,4]dioxino[2,3-*h*]chromen-7-ones starting from 3-hydroxymethyl-5-hydroxy-6-acetylbenzodioxane

1.3. 3,4-Dihydro-2*H*,8*H*-[1,4]dioxepino[2,3-*h*]chromen-8-ones

Annulation of dioxepane cycle to chromone system was carried out using the same starting 7,8-dihydroxychromones, on the basis of which chromones condensed with dioxolane and dioxane cycles were synthesized.

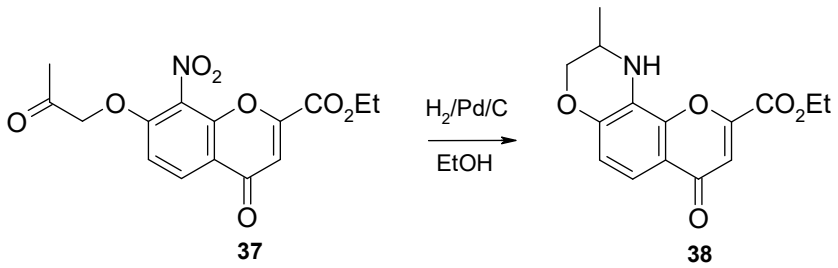
Thus, upon the alkylation of 7,8-dihydroxyisoflavones and their analogues with benzodioxane, benzodioxepane and thiazole substituents with 1,3-dibromopropane in DMF (1,5-2 h) or dioxane (22 h), products of the dioxepane cycle annulation to the chromone nucleus, namely 3,4-dihydro-2*H*,8*H*-[1,4]dioxepino[2,3-*h*]chromen-8-ones **36** were formed [8, 14, 15] (**Scheme 14**).



Scheme 14. The synthesis of 3,4-dihydro-2*H*,8*H*-[1,4]dioxepino[2,3-*h*]chromen-8-ones

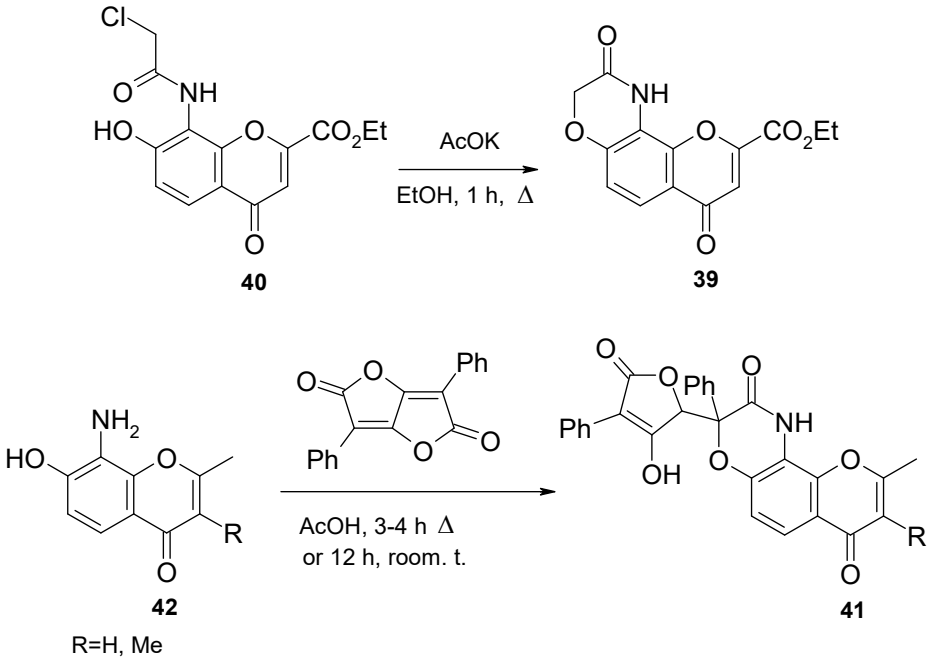
2. Chromones, annulated with (benz)oxazine cycles

2,3-Dihydro-1*H*,7*H*-chromeno[7,8-*b*][1,4]oxazine-7-one is an аzaanalogue of 2,3-dihydro-7*H*-[1,4]dioxino[2,3-*h*]chromene-7-one. 8-Nitro-7-(2-oxopropoxy)chromone **37** has been selectively reduced to the amine, which spontaneously cyclizes into 2-methyl-2,3-dihydro-1*H*,7*H*-chromeno[7,8-*b*][1,4]oxazin-7-one **38** [32] (**Scheme 15**).



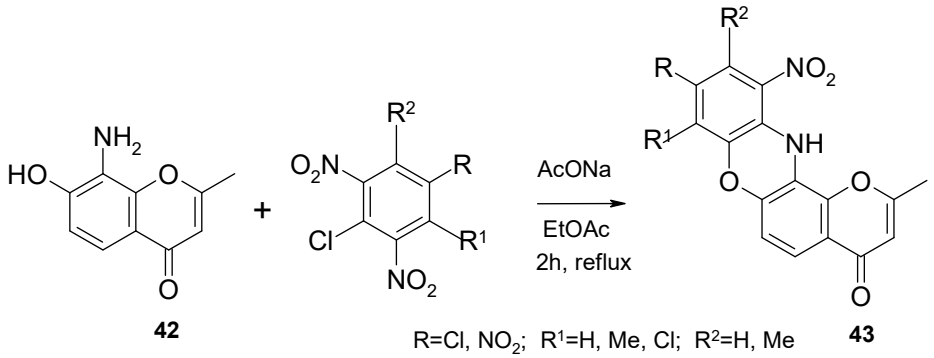
Scheme 15. The synthesis of 2-methyl-2,3-dihydro-1*H*,7*H*-chromeno[7,8-*b*][1,4]oxazin-7-one **38**

Its 2-oxo analogue **39** was obtained upon cyclization of 7-hydroxy-8-chloroacetylaminochromone **40** in the presence of AcOK [32] (**Scheme 16**). 2,3-Dihydro-1*H*,7*H*-chromeno[7,8-*b*][1,4]oxazin-2,7-diones **41,** synthesized on the basis of 7-hydroxy-8-aminochromones **42** and pulvinic acid dilactone, were tested for antimicrobial activity [33] (**Scheme 16**).



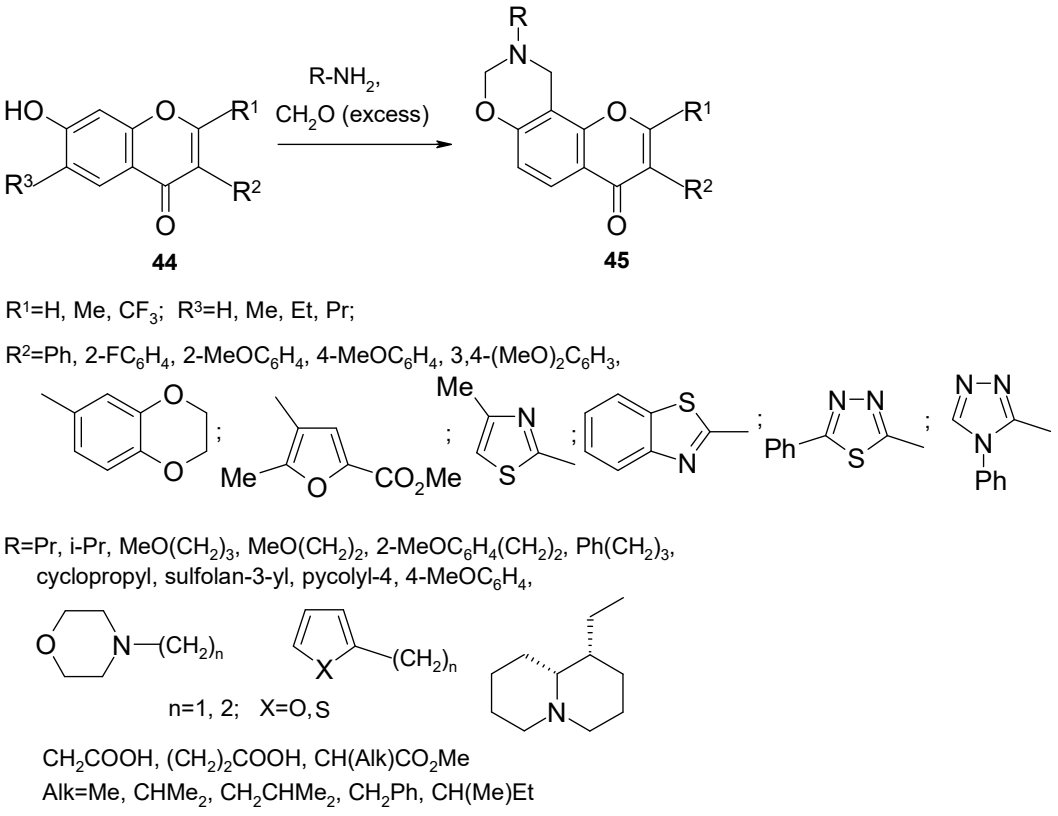
Scheme 16. The synthesis of 2,3-dihydro-1*H*,7*H*-chromeno[7,8-*b*][1,4]oxazin-2,7-diones **39** and **41**

The interaction of 7-hydroxy-8-aminochromone **42** with a number of ortho-nitrochlorobenzenes resulted in annulation of the benzoxazine ring to the chromone nucleus and formation of 4*H*,12*H*-pyrano[2,3-a]phenoxazine-4-ones **43** [34] (**Scheme 17**) .



Scheme 17. The synthesis of 4*H*,12*H*-pyrano[2,3-a]phenoxazine-4-ones **43**

Upon the interaction of 7-hydroxychromones **44** with amines and the excess (2 equiv.) of formalin under the Mannich reaction conditions simultaneous *C*- and *O*-aminomethylation of the benzopyran-4-one nucleus took place leading to the annulation of the 3,4-dihydro-1,3-oxazine ring to the chromone core and the formation of 9,10-dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-ones **45** [35-41] (**Scheme 18**).



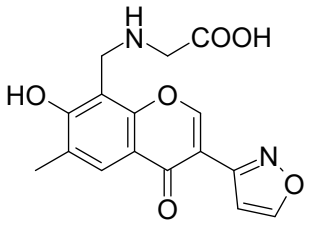
Scheme 18. The synthesis of 9,10-dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-ones **45**

As a substrate, natural flavones [35], isoflavones [36, 37], their synthetic analogues [37-39] and 3-hetaryl derivatives [40] were used. Primary aliphatic [36, 37], aromatic [36], heterocyclic amines [35], amino acids [40] and their esters [39], amino alcohols [41] and alkaloids [38] served as an amine component.

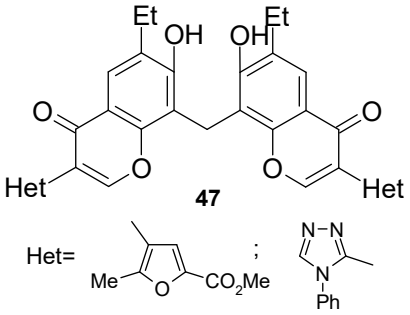
For the first time, the **45** system was obtained in 31% yield from 7-hydroxyflavone and 2-amino-4-phenylthiazole, when boiling in acetic acid with an excess of 40% formalin and paraform followed by ammonia treatment, after removal of the solvent [35].

The reaction of isoflavones with amines was carried out by refluxing in propanol-2 in the presence of a catalytic amount of N,N-dimethylaminopyridine (DMAP). With aliphatic amines, as well as benzyl- or hetarylalkylamines and alkaloid lupine derivative, 9,10-dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-ones **45** are formed in 65-84% yields. In the case of aromatic amines, *p*-methoxyaniline formed the product **45** in a satisfactory yield, while the reaction with *o*-substituted anilines have not resulted in the desired polycyclic system [36].

The reaction with amino acids and their esters was carried out in aqueous-alcoholic solution without a catalyst with the excess (2 equiv.) of amino acid. While the interaction of isoflavones with amino acid esters runs smoothly and derivatives **45** [39] form in high yields, the reaction products of 7-hydroxy-3-hetarylchromones and amino acids depend on the type of heterocycle and amino acid [40]. 9,10-Dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-ones **45** were synthesized from glycine and 3-azolylchromones, except 3-isoxazolylchromone [40]. In this case, the Mannich base **46** was isolated (**Figure 3**). The reaction with β-alanine is similar to the reaction with glycine, while proline did not participate in the reaction and bis(6-ethyl-3-hetaryl-7-hydroxychromon-8-yl)methanes **47** were isolated **47** [40] (**Figure 3**).



46



47

Het=

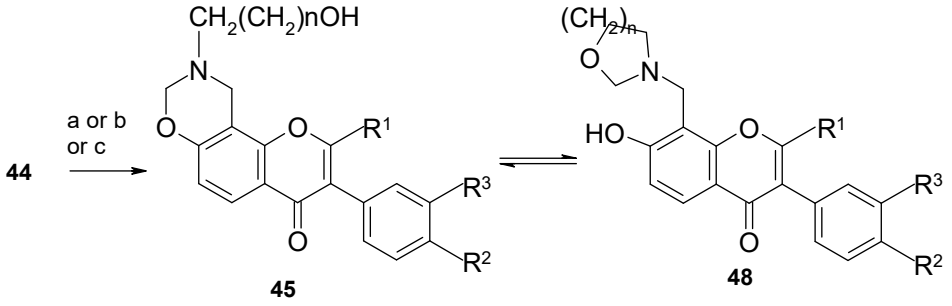
;

Figure 3. Structures of Mannich reaction products **46** and **47**

In the case of 3-azinylchromones, (3-pyridyl- and 3-quinolylchromones) complex mixtures of unidentifiable products were obtained [40].

An attempt of receiving a linear system isomeric to **45** from 8-substituted-7-hydroxychromones and glycine under above mentioned conditions [40] failed.

The aminomethylation of 7-hydroxyisoflavones with 2-aminoethanol, 3-amino-1-propanol, 4-amino-1-butanol and 5-amino-1-pentanol in the presence of excess formaldehyde led principally to 9-(2-hydroalkyl)-9,10-dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]-oxazin-4-ones **45** and/or the tautomeric 7-hydroxy-8-(1,3-oxazepan-3-ylmethyl)-4*H*-chromen-4-ones **48** [41] (**Scheme 19**). The ratio of these tautomers was dependent on solvent polarity, electronic effects of aryl substituents in the isoflavone and the structure of the amino alcohol. NMR studies confirmed the interconversion of tautomeric forms.

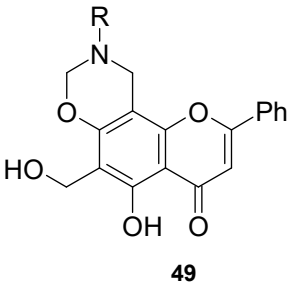


R^1=H, Me, CF_3; R^2=F, OMe; R^3=H, OMe

(a) $HOCH_2(CH_2)_nNH_2$, where n = 1-4, CH_2O, EtOH or *i*-PrOH, DMAP, 80^{O}C, 4–6 h;
(b) bis(1,3-oxazolidin-3-yl)methan, dioxane, 100 ^{O}C, 2-4 h;
(c) 3-butoxymethyl-1,3-oxazolidin, dioxane, 100 ^{O}C, 2-4 h.

Scheme 19. Aminomethylation of 7-hydroxyisoflavones with aminoalcohols

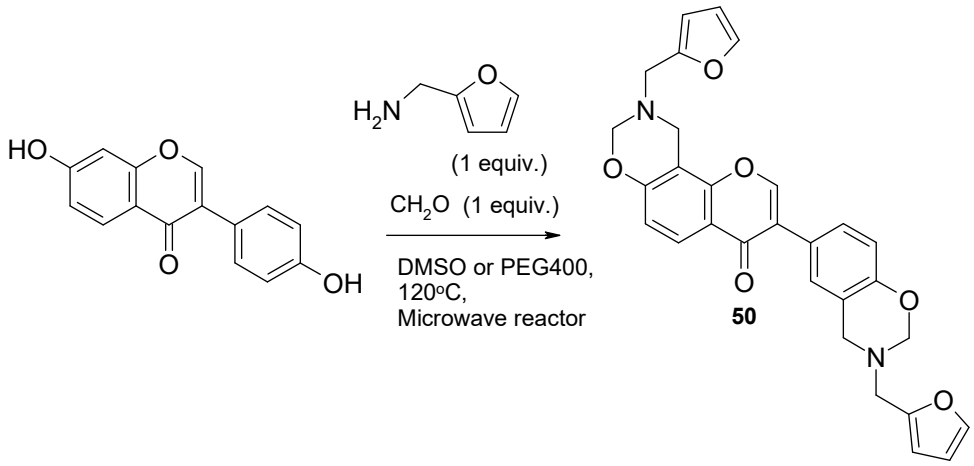
6-Hydroxymethyl-9,10-dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-ones **49** (**Figure 4**), synthesized from natural flavone chrysin, fluoroanilines and an excess (12 equiv.) of formalin in MeOH were patented as useful in treating hyperuricemia [42] (**Figure 4**).



R = 4-FC_6H_4, 2,4-$F_2C_6H_3$, 4-$CF_3C_6H_4$

Figure 4. Structures of Mannich reaction products **49**

In recent years, with the rapid development of biobased materials, using renewable phenolic or amine derivatives to replace the petroleum-based raw materials for the synthesis of benzoxazine monomers has attracted considerable attention. A biobased benzoxazine resin (Dz-f) demonstrating excellent thermal properties was synthesized from daidzein, paraformaldehide and furfurylamine by using a microwave-assisted heating method in DMSO or PEG 400 as a solvent.[43]. The benzoxazine monomer **50** synthesis is shown in **Scheme 20**.



Scheme 20. The synthesis of the biobased benzoxazine resin (Dz-f) monomer **50**

Conclusions

Further search for natural substances and creating new ones among angular hetarenochomones as well as development of the new methods of their syntheses opens up broad prospects in order to create new highly effective materials for medicine and agriculture.

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