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

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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 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 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 highlighted 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(3H)-dione, 4H-chromeno[8,7-d][1,2]oxazol-4-one...
and 3,4-dihydrochromeno[8,7-b][1,4]oxazino-7(2H)-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 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-pyran[2,3-a]phenoxazine-4-one and 9,10-dihydro-4H,8H-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. 6H-[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 6H-[1,3]dioxolo[4,5-h]chromen-6-ones](image)

Two strategies were applied for the construction of the 6H-[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$_2$CO$_3$
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 K₂CO₃. 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).

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

Cyclization of chalcones 11, obtained from acetophenone 8 and benzaldehydes, in TFA resulted in 7,8-methylenedioxyflavanones 12, which on oxidation with I₂ 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 I₂ [9].

\[
\begin{align*}
\text{OH} & \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{Ar} \\
\text{OH} & \quad \text{O} \quad \text{O} \quad \text{Ar} \\
\text{CF}_3 \text{COOH}, & \quad \text{I}_2, \text{DMSO}, & \quad \text{Ar} = 2-\text{MeOC}_6\text{H}_4 \quad \text{(a)}, \quad \text{4-MeOC}_6\text{H}_4 \quad \text{(b)}, \quad 3,4-(\text{MeO})_2\text{C}_6\text{H}_3 \quad \text{(c)}, \quad 3,4,5-(\text{MeO})_3\text{C}_6\text{H}_2 \quad \text{(d)}
\end{align*}
\]

**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.
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-6H-[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 boron trifluoride-diethyletherate, followed by methanesulfonylechloride addition and heating at 90°-100° for 2 h [20]. 2’-Hydroxydihydrochalcone 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 6. The synthesis of 7,8-methylenedioxyisoflavones 14 and 15 from epoxides 16

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-7H-[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-7H-[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-7H-[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 horseradish peroxidase [26] (Scheme 9).

Scheme 9. The synthesis of natural 2,3-dihydro-7H-[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$_2$CO$_3$ [8, 14, 15] (Scheme 10).

Scheme 10. The synthesis of 2,3-dihydro-7H-[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-7H-[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-7H-[1,4]dioxino[2,3-h]chromen-7-ones with substituted dioxine ring.

An alternative way to the 2,3-dihydro-7H-[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)aryl chlorides followed by rearrangement into β-diketones 32 and their cyclization in an acidic medium produced 9-(het)aryl-2,3-dihydro-7H-[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).

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).
1.3. 3,4-Dihydro-2\textit{H},8\textit{H}-[1,4]dioxepino[2,3-\textit{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\textit{H},8\textit{H}-[1,4]dioxepino[2,3-\textit{h}]chromen-8-ones \textit{36} were formed [8, 14, 15] (Scheme 14).

![Scheme 14](image)

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

2. Chromones, annulated with (benz)oxazine cycles

2,3-Dihydro-1\textit{H},7\textit{H}-chromeno[7,8-\textit{b}][1,4]oxazine-7-one is an azaanalogue of 2,3-dihydro-7\textit{H}-[1,4]dioxino[2,3-\textit{h}]chromene-7-one. 8-Nitro-7-(2-oxopropoxy)chromone \textit{37} has been selectively reduced to the amine, which spontaneously cyclizes into 2-methyl-2,3-dihydro-1\textit{H},7\textit{H}-chromeno[7,8-\textit{b}][1,4]oxazin-7-one \textit{38} [32] (Scheme 15).
Scheme 15. The synthesis of 2-methyl-2,3-dihydro-1H,7H-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-1H,7H-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-1H,7H-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 benoxazine ring to the chromone nucleus and formation of 4H,12H-pyranophenoxazine-4-ones 43 [34] (Scheme 17).
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-4H,8H-chromeno[8,7-e][1,3]oxazin-4-ones 45 [35-41] (Scheme 18).

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

Scheme 18. The synthesis of 9,10-dihydro-4H,8H-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-4H,8H-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-4H,8H-chromeno[8,7-e][1,3]oxazin-4-ones 45 were synthesized from glycine and 3-azolychromones, 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).

![Figure 3. Structures of Mannich reaction products 46 and 47](image-url)
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-4H,8H-chromeno[8,7-e][1,3]-oxazin-4-ones 45 and/or the tautomeric 7-hydroxy-8-(1,3-oxazepan-3-ylmethyl)-4H-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.

Scheme 19. Aminomethylation of 7-hydroxyisoflavones with aminoalcohols

6-Hydroxymethyl-9,10-dihydro-4H,8H-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).

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, paraformaldehyde and furfurylamine by using a microwave-assisted heating method in DMSO or PEG 400 as a solvent.[43]. The benzoxazine monomer synthesis is shown in Scheme 20.

![Scheme 20. The synthesis of the biobased benzoxazine resin (Dz-f) monomer 50](image)

Conclusions

Further search for natural substances and creating new ones among angular hetarenochromones 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.

References


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