Chromones Modified with 7-Membered Heterocycles: Synthesis and Biological Activity

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The present mini-review for the first time summarizes and systematizes all the data available in the literature on the synthesis and properties of chromones modified with 7-membered heterocycles throughout the chemical space around the chromone framework. Most of the 2-, 6-, 7- and 8-hetarylsubstituted chromones are represented in the patent literature and were obtained by nucleophilic substitution in the chromone core with a cyclic amine moiety. Methods for the synthesis of heterocyclic analogs of isoflavones are mainly based on 3-formylchromone, its derivatives, chromonylchalcones and by means of multicomponent reactions. The biological activity of chromones substituted with 7-membered heterocycles are also surveyed.

Introduction

In recent years, the combination of two or more pharmacophores that build up complex natural product-based compound collections is a powerful strategy to develop bioactive compounds and identifying innovative hits/leaders among them.

Chromones belong to the class of flavonoids, which are secondary metabolites that broadly occur in the plant kingdom and possess diverse biological activities. Chromone moiety is recognized as a well-identified privileged structure and a useful template for the design of novel well-diversified therapeutic molecules of potential pharmacological interest, particularly in the field of neurodegenerative disorders, i.e., Alzheimer's or Parkinson's disease [1, 2], inflammatory [3] and infectious [4] diseases as well as diabetes [5] and in anti-cancer drug discovery [6]. Natural products such as flavonoids are known to show therapeutic effects against covid-19 in reduction of hospitalization and severity of pulmonary impact by preventing the most serious forms of the infection [7].

Seven-membered-ring heterocycles with one or more heteroatoms are also recognized as privileged scaffolds, which are found in the molecular skeleton of some natural products, are good building blocks in organic synthesis and have found wide spread use in medicinal chemistry due to their
diverse biological activity in mammalian systems [8-13].

Given the fact that the combination of two pharmacophores can lead to compounds with a more pronounced biological activity inherent in such a tandem, or to a change in the activity profile, the dyads chromone-seven-membered heterocycles certainly represent an interesting motif in organic synthesis and medicinal chemistry.

As part of our ongoing interest in the chemistry of heterocyclic isoflavone analogs, we have previously summarized the literature on 3-thienyl/benzothienyl-chromones and isoflavonoids modified with azole heterocycles with three heteroatoms as shown in reviews [14, 15]. The purpose of this brief review is to highlight the design strategies of chromones modified with 7-membered heterocycles throughout the chemical space around the chromone framework.

It should be noted that publications on this topic are not numerous in comparison with publications and even reviews on the dyads of the chromone-five/six-membered heterocycles. The first work on the synthesis of an isoflavone modified with 4-aryl-2,3-dihydro-1,5-benzothiazepine appeared in 1981 (20 years after the first publication on 3-hetarylchromones [16]) and only 3 articles were published until the 21st century. Most of the 2-, 6-, 7- and 8-hetarylsubstituted chromones are represented in the patent literature and were obtained by nucleophilic substitution in the chromone core with a cyclic amine moiety. Methods for the synthesis of heterocyclic analogs of isoflavones are mainly based on 3-formylchromone, its derivatives, chromonylechalcons and by means of multicomponent reactions. Separate references to methods for the synthesis of isoflavones modified with seven-membered heterocycles are recorded in reviews on 3-hetarylchromones [17-20].

The review also attempts to determine the type of biological activity and the area of possible application of the synthesized compounds.

1. 2-Substituted chromones

Chromones modified with 7-membered heterocycles (azepane and 1,4-oxazepane) at position 2 were obtained by nucleophilic substitution in the chromone nucleus.

3-Benzoyl-2-perhydroazepinochromone (1) was obtained in 57% yield by the reaction of nucleophilic substitution of the methylthio group in 3-benzoyl-2-(methylthio)chromone 2 with azepane (Scheme 1) [21].

Scheme 1. The synthesis of 3-benzoyl-2-perhydroazepinochromone (1)
The ethylsulfinyl group could also be easily substituted with secondary amines, and 2-[1-(2-ethylsulfinyl-6-methyl-4-oxo-chromen-8-yl)ethylamino]benzoic acid (3) was successfully transformed to 2-(1,4-oxazepan-4-yl) derivative 4a when treated with 1,4-oxazepan hydrochloride (Scheme 2) [22].

Scheme 2. The synthesis of 2-((1-(6-methyl-2-(1,4-oxazepan-4-yl-4-oxo-4H-chromen-8-yl)ethylamino)benzoic acid (4a)

Compound 4a, as one of the variants of implementation compounds of general formula 4, is declared as allosteric chromenone inhibitor of phosphoinositide 3-kinase (PI3K) useful in the treatment of diseases or disorders associated with modulating PI3K, wherein the diseases associated with modulating PI3K are cancer, CLOVES syndrome or PIK3CA-related overgrowth syndromes (PROS) [22].

Nucleophilic substitution of ethylsulfonyl group in 2-(ethylsulfonyl)-4H-benzo[h]chromen-4-one (5) in the reaction with 1,4-oxazepane hydrochloride enabled introduction of 1,4-oxazepane cycle at the 2-position in 57 % yield under ambient conditions (Scheme 3) [23].

Scheme 3. The synthesis of 2-(1,4-oxazepan-4-yl)-4H-benzo[h]chromen-4-one (6)

Compound 6 was evaluated for inhibitory activity against the DNA repair enzyme DNA dependent protein kinase (DNA-PK). Its IC$_{50}$ value is 2.01 μM [23, 24].

2. 3-Substituted chromones

The isoflavone modified by the quinoline-fused 1-benzazepine derivative 7 was synthesized by a Mannich-type cyclization reaction from 3-formylchromone as an electrophilic component and a new C,N-1,6-bisnucleophile 8 generated from 2-aminobenzaldehyde and 2-methylindole by transformation of the indole cycle into the quinoline cycle under the conditions indicated in Scheme 4 [25].
Scheme 4. The synthesis of 3-(9,11-dibromo-6,7-dihydro-5H-benzo[6,7]azepino[4,5-b]quinolin-6-yl)-4H-chromen-4-one (7)

The general pathway for the synthesis of octahydro-1H-benzo[b][1,5]diazepin-2-ones 9 is presented in Scheme 5. As a result of the reaction of 1-benzyl-2-aryldecahydroquinolin-4-ones 10 with hydroxylamine hydrochloride, intermediate oximes 11 are formed, which served as useful precursors in the selective thionyl chloride-induced Beckman rearrangement to construct the desired products. According to this protocol, 5-benzyl-4-(4-oxo-4H-chromen-3-yl)octahydro-1H-benzo[b][1,5]diazepin-2-(3H)-one (9) was obtained with a yield of 62 % [26].

Scheme 5. The synthesis of 5-benzyl-4-(4-oxo-4H-chromen-3-yl)octahydro-1H-benzo[b][1,5]diazepin-2-(3H)-one 9

Screening of 5-benzyl-4-(4-oxo-4H-chromen-3-yl)octahydro-1H-benzo-[b][1,5]diazepin-2-(3H)-one (9) in vitro for antidepressant activity by forced swim test
(FST), using clomipramine as a reference standard, at a dose level of 20 mg/kg i.p. showed significant antidepressant potential of the compound. This can be seen from the reduction of immobility duration values in seconds: 39.4±2.39 with compound 9 against 18.68±2.25 with clomipramine and 112.4 ± 2.88 in the control group, a high percentage of reduction of immobility duration values (% DID) -83.56 with compound 9 against -92.21 with clomipramine and in the absence of neurotoxicity.

Antibacterial activity of 5-benzyl-4-(4-oxo-4H-chromen-3-yl)octahydro-1H-benzo[b][1,5]diazepin-2-(3H)-one (9) in vitro was studied against four strains of bacteria (gram-negative bacteria: Pseudomonas aeruginosa ATCC 9027, Escherichia coli ATCC 35218; gram-positive bacteria: Staphylococcus aureus ATCC 6538 and Bacillus subtilis ATCC 6631) by the disk diffusion method using Muller-Hinton medium and ciprofloxacin (an antibacterial drug) as a reference standard. Compound 9 showed good antibacterial activity against Gram-negative bacteria and moderate activity against Gram-positive bacteria compared to the standard as assessed by inhibition zone values in mm at 10 µg/ml.

Synthesis of 5-amino-7-(4-oxo-4H-chromen-3-yl)-2,3-dihydro-1H-1,4-diazepine-6-carbonitrile (12) and 4-amino-2-(4-oxo-4H-chromen-3-yl)-1H-1,5-benzodiazepine-3-carbonitrile (13) was implemented in [27]. The reaction of [(4-oxo-4H-chromen-3-yl)methylidene]propandinitrile (14), obtained by condensation of 3-formylchromone with malononitrile, with ethylenediamine or o-phenylenediamine in absolute ethanol proceeded through the nucleophilic addition of one amino group to the exocyclic vinyl carbon with subsequent cycloaddition of another amino group to the nitrile function with accompanying dehydrogenation (Scheme 6).

Scheme 6. The synthesis of 5-amino-7-(4-oxo-4H-chromen-3-yl)-2,3-dihydro-1H-1,4-diazepine-6-carbonitrile (12) and 4-amino-2-(4-oxo-4H-chromen-3-yl)-1H-1,5-benzodiazepine-3-carbonitrile (13)
Isoflavone analogs with seven-membered heterocycles can be synthesized by reacting of chromone derivatives bearing an enone fragment with binucleophiles.

Thus, the synthesis of 3-(4-phenyl-2,3-dihydro-1,5-benzodiazepin-2-yl)chromone (15) was realized by the interaction of 1-phenyl-3-(chromon-3-yl)-2-propene-1-one (chromonylchalcone) (16) with o-phenylenediamine. The reaction took place in 6-7 hours when boiling in alcohol. The key chalcone 16 was obtained according to Scheme 7 [28].

![Scheme 7](image-url)

Scheme 7. The synthesis of 3-(4-phenyl-2,3-dihydro-1,5-benzodiazepin-2-yl)chromone (15)

7-hydroxy-3-(4-R-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-yl)-4H-chromen-4-ones 17a,b were obtained by condensation of chalcones 18a,b with o-phenylenediamine in the presence of a catalytic amount of glacial acetic acid in DMF. Under normal conditions, the reaction turned out to be too sluggish, so the reaction was carried out by irradiating the mixture in a Catalyst microwave oven for 15 minutes at a power of 160 W (Scheme 8) [29].

In studies on antioxidant activity, 7-hydroxy-3-(4-R-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-yl)-4H-chromen-4-ones 17a,b were found to be inactive.
Examples of the application of multicomponent reactions (MCR), which are resource-saving and contribute to the implementation of the concept of "green" chemistry, in the molecular design of new 3-(1,5-benzodiazepin-4-yl)chromones are presented in works [30, 31].

The method for the synthesis of 3-[2,3-dihydro-2-(6-R-4-oxo-4H-chromen-3-yl)-1H-1,5-benzodiazepin-4-yl]-4-hydroxy-2H-1-benzopyran-2-ones 19a,b by three-component condensation of 3-formylchromones, o-phenylenediamine and 3-acetyl-4-hydroxycoumarin under the influence of microwave radiation using heterogeneous catalysis and water as an economically available solvent is an environmentally friendly [30]. The NSBNPSA (N-propyl sulfamic acid, nanosilica based) catalyst enables rapid chemical conversion with high product yield (~90%) in minimal time and can be reused with nearly the same activity for up to eight cycles. According to the protocol, reagents are taken in the amount of 1 mmol in 10 ml of water in the presence of 30 mg of NSBNPSA (Scheme 9).
3,3-Dimethyl-2,3,4,5,10,11-hexahydro-11-[6-R-4-oxo-4H-chromen-3-yl]-1H-dibenzo-[b,e][1,4]diazepin-1-ones 20a-c were synthesized by the three-component condensation of 3-formylchromones, \( o \)-phenylenediamine and dimedone, as the CH acid component, which took place using a heterogeneous Fe(OTs)\(_3\)/SiO\(_2\) catalyst in the absence of a solvent at 80°C. According to the protocol, when adding 5 mmol of each of the reagents, 0.5 g of Fe(OTs)\(_3\)/SiO\(_2\) is taken. Excellent yields (> 90%) in a short reaction time, the possibility of reusing the catalyst, and environmental friendliness emphasize the advantages of the developed method (Scheme 10) [31].

![Scheme 10](image)

Scheme 10. The synthesis of 3,3-dimethyl-2,3,4,5,10,11-hexahydro-11-[6-R-4-oxo-4H-chromen-3-yl]-1H-dibenzo-[b,e][1,4]diazepin-1-ones 20a-c

As an alternative way for the synthesis of structural analogues of benzodiazepine compounds 20, the two-stage approach described in patent [32] according to Scheme 11 may be used.

![Scheme 11](image)

Scheme 11. The two-stage approach for the synthesis of structural analogues of benzodiazepine compounds 20
Compounds 20d-f are claimed as inhibitors of hepatitis C virus replication [32]. The patent also discloses variants of pharmaceutical compositions based on these compounds, combinations with other anti-HCV agents and the possibility of their use as drugs for the treatment of HCV infection. Compounds 20d-f were tested for anti-HCV activity by testing their activity against NS5b polymerase (IC$_{50}$ (μM) 20d $> 42.667$; IC$_{50}$ (μM) 20e $> 42.667$; IC$_{50}$ (μM) 20f $> 42.678$) and in the analysis of HCV replicons (EC$_{50}$ (μM) 20d $= 17.821$; EC$_{50}$ (μM) 20e $= 3.692$; EC$_{50}$ (μM) 20f $= 13.195$).

The synthesis of 3-(4-R-2,3-dihydro-1,5-benzothiazepin-2-yl)chromones (R=phenanthrenyl) 21 by the interaction of 1-R-3-(chromone-3-yl)-2-propen-1-ones (chromonylchalcones) 22 with 2-aminothiophenol followed by intramolecular cyclization of the formed Michael adduct 23 in the presence of acetic acid was implemented in [33].

![Scheme 12](image)

Scheme 12. The synthesis of 3-(4-phenanthrenyl-2,3-dihydro-1,5-benzothiazepin-2-yl)chromones 21

The synthesis of 3-(4-aryl-2,3-dihydro-1,5-benzothiazepin-2-yl)chromones 21 described in [34, 35] was carried out in a similar way to [33] by the interaction of the corresponding chromonylchalcones 22 with 2-aminothiophenol under conditions indicated in Scheme 13, without the separation of the intermediate Michael adduct. Acetic acid catalyzes ring closure of the Michael adduct and, therefore, proved to be a convenient catalyst for the one-step synthesis of 3-(4-aryl-2,3-dihydro-1,5-benzothiazepin-2-yl)chromones 21. It should be noted that the yields among the same in both works 3-(4-aryl-2,3-dihydro-1,5-benzothiazepin-2-yl)chromones 21b-d are higher by 13-15% for those synthesized under the conditions proposed in [35].
Scheme 13. The synthesis of 3-(4-aryl-2,3-dihydro-1,5-benzothiazepin-2-yl)chromones 21

Antimicrobial activity of 3-(3-aryl-2,3-dihydro-1,5-benzothiazepin-2-yl)-4H-1-benzopyran-4-ones 21a-d was tested in [34]. According to the results of screening for the antibacterial activity against *Bacillus megaterium* and *Proteus vulgaris* at concentrations of 400 and 600 μg/ml, the compounds 21a-d showed weak activity against *B. megaterium* and were practically inactive against *P. vulgaris*. Testing for the antifungal activity was performed against *Dreschlera speciferum* and *Fusarium solani* at concentrations of 360, 600 and 840 μg/ml and the activity is measured as the percentage inhibition of spore germination. The lack of fungicidal activity of compounds 21a-d was established.

It was found that 3-(4-aryl-2,3-dihydro-1,5-benzothiazepin-2-yl)chromones 21 (R = 4-Me, 4-MeO, 4-F, 4-Cl-C₆H₄) when heated to 80°C in a mixture of anhydrous pyridine and acetic anhydride undergo ring reduction under acetylation conditions, forming 3-acetyl-2,3-dihydrobenzothiazole 24 with a yield of 53-72% (Scheme 14) [35].

Scheme 14. The synthesis of 3-acetyl-2,3-dihydrobenzothiazoles 24
Derivatives of 2,3-dihydro-1,5-benzothiazepines have been obtained through a domino process involving a Michael addition of 2-aminothiophenols to chalcones, followed by in situ cyclization. Carrying out the reaction under optimized conditions at room temperature in practically neutral conditions with the use of hexafluoro-2-propanol (HFIP) as an effective medium and the ratio of chalcone: aminothiophenol: HFIP 1:2:11 contributed to a significant increase in the yield of the desired 2,3-dihydro-1,5-benzothiazepines [36]. The authors believe that due to its high acidity, hexafluoropropan-2-ol can activate both carbonyl and thiol groups through hydrogen bonding and behave as a proton shuttle. However, 3-(4-phenyl-2,3-dihydro-1,5-benzothiazepin-2-yl)chromone (21a) under these conditions was obtained in only 41% yield, which is lower than 52% in [34] (Scheme 15).

Scheme 15. The synthesis of 3-(4-phenyl-2,3-dihydro-1,5-benzothiazepin-2-yl)chromone (21a)

Among the compounds that modulate the transcription factor, 2-(chromon-3-yl)-2,3-dihydro-1,5-benzothiazepin-4-one (25) is mentioned in patent [37] without providing the synthesis protocol. Such compounds may be useful as anti-infectives that reduce resistance, virulence, or prevent growth of microbes and help reduce virulence and infectivity, inhibit biofilms, and treat bacterial infections. Compound 25 inhibits the MarA family, is an inhibitor of MarA, Rob and/or SoxS, and modulates luciferase expression in a luciferase assay (Figure 1).

Figure 1. Bioactive 2-(chromon-3-yl)-2,3-dihydro-1,5-benzothiazepin-4-one (25)

Heterocyclic systems bearing the function of β-chloroenaldehyde are key precursors for the construction of various heterocyclic compounds by reactions with nucleophilic reagents. Condensation of 3-chloro-3-(4,9-dimethoxy-5-oxo-5H-
furo[3,2-g]chromen-6-yl)prop-2-enal (26) with β-chloroenaldehyde function in position 6 with 1,4-binucleophiles such as o-phenylenediamine, 2-aminophenol and 2-aminothiophenol in boiling ethanol containing TEA afforded 6-(1,5-benzodiazepin-2-yl)/1,5-benzoxazepin-2-yl/1,5-benzothiazepin-2-yl)furo[3,2-g]chromen-5-ones 27-29, respectively [38] (Scheme 16).

![Scheme 16](image)

Scheme 16. The synthesis of 6-(1,5-benzodiazepin-2-yl)/1,5-benzoxazepin-2-yl/1,5-benzothiazepin-2-yl)furo[3,2-g]chromen-5-ones 27-29

6-(1,5-Benzodiazepin-2-yl)/1,5-benzoxazepin-2-yl/1,5-benzothiazepin-2-yl)furo[3,2-g]chromen-5-ones 27-29 were investigated in vitro for antimicrobial activity at 500 and 1000 μg/ml against gram-positive bacteria, namely Staphylococcus aureus (ATCC25923) and Bacillus subtilis (ATCC6635), as well as gram-negative bacteria, namely Salmonella typhimurium (ATCC 14028) and E. coli (ATCC 25922). They were also tested against yeast (Candida albicans ATCC 10231) and fungi (Asperigillus fumigatus). Antimicrobial activity was determined by measuring the zones of inhibition, including the disc diameter (6 mm). Compounds 27-29 showed a high level of antimicrobial activity against all types of microorganisms compared to the standard drug, such as chloramphenicol in the case of gram-positive bacteria, cephalothinin
in the case of gram-negative bacteria, and cycloheximide in the case of yeasts and fungi.

6-(1,5-Benzodiazepin-2-yl)/1,5-benzoxazepin-2-yl/1,5-benzothiazepin-2-yl)furo[3,2-\(g\)]chromen-5-ones 27-29 were tested \textit{in vitro} for cytotoxic activity against a panel of two human tumor cell lines, namely: hepatocellular carcinoma (liver) HepG2 and colon cancer HCT-116.

Cytotoxic activity was assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) colorimetric assay. Compounds 27-29 showed weak cytotoxic activity against the HepG2 line panel (IC\textsubscript{50} = 54.91-77.06 μg/ml) compared to the standard anticancer drug doxorubicin (IC\textsubscript{50} = 4.58 μg/ml). Compound 27 showed weak cytotoxic activity against the HCT-116 cell line panel (IC\textsubscript{50} = 68.71 μg/ml) compared to the standard anticancer drug doxorubicin (IC\textsubscript{50} = 4.22 μg/ml), while compounds 28 and 29 did not show cytotoxic activity at all against panel of the HCT-116 line (IC\textsubscript{50} => 100 μg/ml).

4,5-Dihydro-4-(4-oxo-4\(H\)-1-benzopyran-3-yl)-3\(H\)-1,2,5-benzoxathiazepine-2,2-dioxides 30 were obtained by the cycloaddition of sulfene 31, which was formed \textit{in situ} from the corresponding sulfonic acid and [(chlorosulfonyl)methylene]dimethylammonium chloride, with nitrones of chromone 32. If methanesulfonyl chloride and trimethylamine were used to form the sulfene (conditions: -10°C, N\textsubscript{2} atmosphere), compounds 30 were obtained with low yields (for example, 30 (R\textsubscript{1} = 4-Me) - 25 %) (Scheme 17) [39].

![Scheme 17](image)

**Scheme 17.** The synthesis of 4,5-dihydro-4-(4-oxo-4\(H\)-1-benzopyran-3-yl)-3\(H\)-1,2,5-benzoxathiazepine-2,2-dioxides 30

3. **6-Substituted chromones**

Chromones 33a-d, containing a 1,5-benzothiazepinyl fragment in the 6-position, were synthesized by oxidative cyclization of 1,5-benzothiazepinyllchalones 34a-d in I\textsubscript{2}-DMSO, which, in turn, were obtained by
cyclocondensation of 2,4-di-(3'-aryl-acrylo)phenol (bis-chalcone) 35a-d with 2-aminothiophenol (Scheme 18) [40].

![Scheme 18](image)

Scheme 18. The synthesis of 2-aryl-2,3-dihydro-4-[2-aryl-chromon-6-yl)-1,5-benzothiazepenes 33a-d

Synthesized compounds 33a-d were tested for antimicrobial activity using the filter paper disc method. The antimicrobial activity of the compounds in two concentrations of 250 ppm and 500 ppm was evaluated against various bacteria and fungi. Carbendazim (Bavastin) and streptomycin sulfate were used as a standard for Aspergillus flavus, Helminthosporium oryzaeta, Xanthomonas compestris, Bacillus subtilis, respectively. The compounds showed a moderate degree of antimicrobial activity (antibacterial and antifungal activity), and compound 33d was the most active against all microorganisms.

The synthesis of 2-Ar/Het-4H-chromen-4-ones modified at position 6 with 1,4-diazepane heterocycle 36a-d was carried out by nucleophilic substitution of the bromine atom in 2-Ar/Het-6-Br-4H-chromen-4-ones 37 with Boc-1,4-diazepan followed by deprotection. Various known approaches can be used for the synthesis of key chromones 37. Thus, Scheme 19 a) shows a general approach involving the condensation of 1-(5-bromo-2-hydroxyphenyl)ethanone with the corresponding aryl/hetarylaldehyde followed by cyclization of the resulting chalcone 38 in the presence of J2-DMSO. An approach involving completion of the heterocyclic ring at the second position of the finished chromone system is shown in Scheme 19 b) using chromone 37d as an example [41].
2-Ar/Het-6-(4-R-1,4-diazepan-1-yl)-4H-chromen-4-ones 36 enhance the inclusion of SMN2 exon 7 in mRNA transcribed from the SMN2 gene and increase the level of Smn protein, produced from the SMN2 gene and, therefore, can be used to treat spinal muscular atrophy (SMA) in humans [41].

4. **7-Substituted chromones**

An example of a chromone modified with a 7-membered heterocycle at position 7 has been found in the literature [42]. Benzyl-4-(4-oxo-4H-chromen-7-yl)-1,4-diazepan-1-carboxylate (39) was synthesized in three stages: nucleophilic substitution of a fluorine atom in 4'-fluoro-2'-hydroxyacetophenone with benzyl-1-homopiperazinecarboxylate to give benzyl 4-(4-acetyl-3-hydroxyphenyl)-1,4-diazepan-1-carboxylate (40); treatment of the latter with N,N-dimethylformamide dimethylacetal to obtain benzyl-4-{4-[4-(2E)-3-(dimethylamino)prop-2-enoyl]-3-hydroxyphenyl}-1,4-diazepan-1-carboxylate (41); subsequent cyclization in acetic acid (Scheme 20).
Scheme 20. The synthesis of benzyl 4-(4-oxo-4H-chromen-7-yl)-1,4-diazepane-1-carboxylate (39)

Chromone 39 was used as an intermediate in the synthesis of 3-amino-4-{4-[4E)-(4-hydroxyimino-3,4-dihydro-2H-chromen-7-yl)-1,4-diazepan-1-yl]thieno[2,3-b]pyridine-2-carboxamide (42) according to the Scheme 21.

Scheme 21. The synthesis of osteogenesis-promoting thienopyridine derivative 42

Compounds 42, representing thienopyridine derivatives of the general formula (A), promote osteogenesis, inhibition of bone resorption and/or increase bone density, they are useful as a pharmaceutical composition for the prevention or treatment of osteopathy, for example, osteoporosis, osteopenia or bone destruction associated with rheumatoid arthritis, Paget's disease of the bone, bone fracture, or osteoarthritis.
5. 8-Substituted chromones

Among the therapeutic chromone compounds of the general formula B, 6-
methoxy-8-(4-methyl-[1,4]diazepan-1-yl)-4-oxo-4\(H\)-chromene-2-carboxylic acid and its derivatives are also mentioned in patent family [43] (Scheme 22).

Scheme 22. The synthesis of 6-methoxy-8-(4-methyl-[1,4]diazepan-1-yl)-4-oxo-4\(H\)-chromene-2-carboxylic acid derivatives 43-45

6-Methoxy-8-(4-methyl-[1,4]diazepan-1-yl)-4-oxo-4\(H\)-chromene-2-carboxylic acid ethyl ester (43) was synthesized from 8-bromo-6-methoxy-4-oxo-4\(H\)-chromene-2-carboxylic acid ethyl ester and 1-methylhomopiperazine in dry toluene in the presence of tris dibenzylidineacetone dipalladium, racemic 2,2'-bis(diphenylphosphino)-1,1'-binapthyl and cesium carbonate under nitrogen at 80°C for 3 days. Ester 43 was hydrolyzed with LiOH in THF-MeOH-H\(2\)O to the acid and treated with 2N HCl to give the product as the hydrochloride salt 44 in the quantitative yield. Condensation of 44 with 4-morpholinoaniline in DMF in the presence of 1-[bis(dimethylamino)methylene]-1\(H\)-benzotriazolium 3-oxide tetrafluoroborate (TBTU) and hydroxybenzotriazole (HOBT) in DMF for 18 h afforded amide 45.

6-Methoxy-8-(4-methyl-[1,4]diazepan-1-yl)-4-oxo-4\(H\)-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide 45 is 5 HT1B antagonist and is useful for the treatment of psychiatric disorders including but not limited to depression, generalized anxiety,
eating disorders, dementia, panic disorder, and sleep disorders and may also be useful in the treatment of gastrointestinal disorders, cardiovascular regulation, motor disorders, endocrine disorders, vasospasm and sexual dysfunction.

The synthesis of 8-(2-aryl-2,3-dihydro-1,5-benzothiazepin-4-yl)-7-hydroxy-2,3-dimethyl-4H-1-benzopyran-4-ones 46a-i described in [34] was carried out by the interaction of the corresponding chromonylechalcones 47a-i with 2-aminothiophenol in dry methanol containing catalytic amount of glacial acetic acid (Scheme 23).

![Scheme 23](image)

**Scheme 23.** The synthesis of 8-(2-aryl-2,3-dihydro-1,5-benzothiazepin-4-yl)-7-hydroxy-2,3-dimethyl-4H-1-benzopyran-4-ones 46a-i and their recyclizations under binucleophyles.

To know the nature and reactivity of chromonyl benzothiazepines 46 one representative compound 46b has been reacted with hydrazine hydrate in alcohol. It is interesting to note that the pyrone ring is cleaved at ethereal oxygen to form 2-[2-(4-chlorophenyl)-2,3-dihydro-1,5-benzothiazepin-4-yl]-4-(3,4-dimethyl-1H-pyrazol-5-yl)-1,3-benzenediol (48). The same type of cleavage is observed when 46b is treated with hydroxylamine hydrochloride in pyridine to afford 2-[2-(4-chlorophenyl)-2,3-dihydro-1,5-benzothiazepin-4-yl]-4-(3,4-dimethyl-5-isoxazolyl)-1,3-benzenediol (49) (Scheme 23).

According to the results of screening for antibacterial activity against *Bacillus megaterium* and *Proteus vulgaris* at hydroxy-2,3-dimethyl-4H-1-benzopyran-4-ones 46a-i described in [34] was carried out by the interaction of the corresponding chromonylechalcones 47a-i with 2-aminothiophenol in dry methanol containing catalytic amount of glacial acetic acid (Scheme 23).
concentrations of 400 and 600 μg/ml, all tested compounds 46, registered a feeble activity against \textit{B. megaterium}, but were virtually inactive against \textit{P. vulgaris}. Testing for antifungal activity was performed against \textit{Dreschlera speciferum} and \textit{Fusarium solani} at concentrations of 360, 600 and 840 µg/ml and the activity is measured as the percentage inhibition of spore germination. Compound 46a is highly toxic to both the fungi and hence can be exploited for the fungicidal formulation, while 46b registered a moderate toxicity towards both the fungi.

Conclusions

In conclusion, it should be noted that chromones modified with 7-membered heterocycles were practically unknown until the 21st century. Most of the 2-, 6-, 7- and 8-substituted compounds were obtained by nucleophilic substitution in the chromone core with a cyclic amine moiety. Chromones modified with 7-membered heterocycles on the benzene ring are represented mostly in the patent literature. 5-Substituted ones are unknown. More attention was paid to the study of isoflavone analogues with 7-membered heterocycles. Methods for their synthesis are mainly based on 3-formylchromone, its derivatives, chromonylchalones and by means of multicomponent reactions.

Taking into account positive pharmacological profile of chromones modified with 7-membered heterocycles including various types of biological activity (antibacterial, antifungal, anti-HCV, antidepressant anticancer activity, inhibitory activity against the DNA repair enzyme DNA dependent protein kinase (DNA-PK), inhibitory activity against the phosphoinositide 3-kinase (PI3K)) further study of dyads chromone-seven-membered heterocycles, expanding the range of introduced 7-membered heterocycles and development of new modern methods for their synthesis is promising.

References


[39] Prajapati D, Singh S, Mahajan A, Sandhu J.


