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 posses 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.

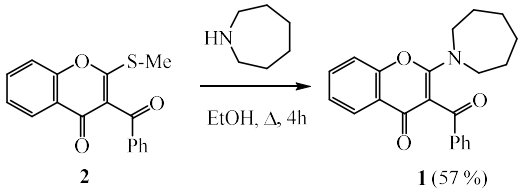
It should be noted that publications on this topic are not numerous in comparison with publications and even reviews on the dyads of the chromone-five/six-membered heterocycles. The first work on the synthesis of an isoflavone modified with 4-aryl-2,3-dihydro-1,5-benzothiazepine appeared in 1981 (20 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, chromonylchalcones 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.

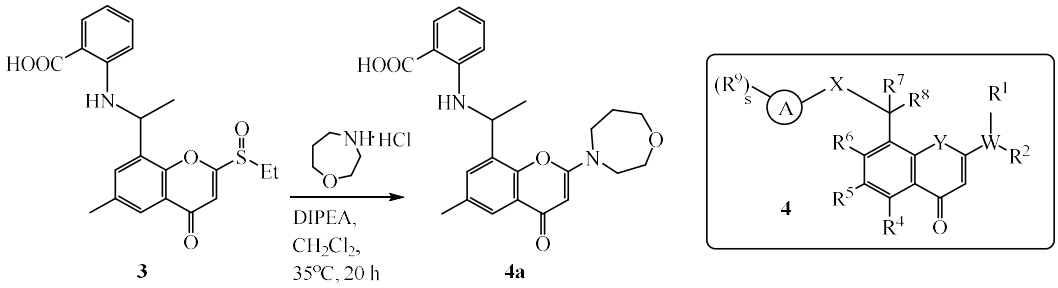
3-Benzoyl-2-perhydroazepino-chromone (**1**) was obtained in 57% yield by the reaction of nucleophilic substitution of the methylthio group in 3-benzoyl-2-(methylthio)chromone **2** with azepane (**Scheme 1**) [21].



2 **1** (57 %)

Scheme 1. The synthesis of 3-benzoyl-2-perhydro-azepinochromone (**1**)

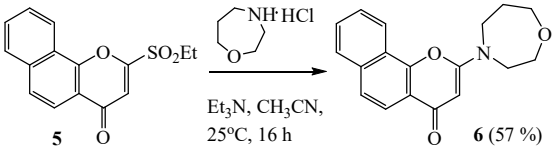
The ethylsulfinyl group could also be easily substituted with secondary amines, and 2-[1-(2-ethylsulfinyl-6-methyl-4-oxo-chromen-8-yl)ethylamino]benzoic acid (**3**) was successfully transformed to 2-(1,4-oxazepan-4-yl) derivative **4a** when treated with 1,4-oxazepan hydrochloride (**Scheme 2**) [22].



Scheme 2. The synthesis of 2-((1-(6-methyl-2-(1,4-oxazepan-4-yl-4-oxo-4*H*-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)-4*H*-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].

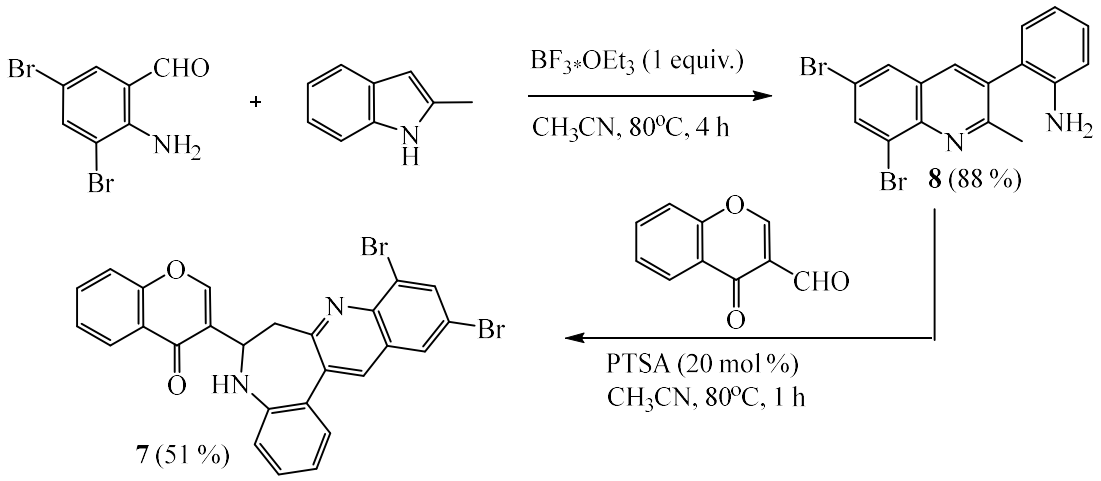


Scheme 3. The synthesis of 2-(1,4-oxazepan-4-yl)-4*H*- benzo[*h*]chromen-4-one (**6**)

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].

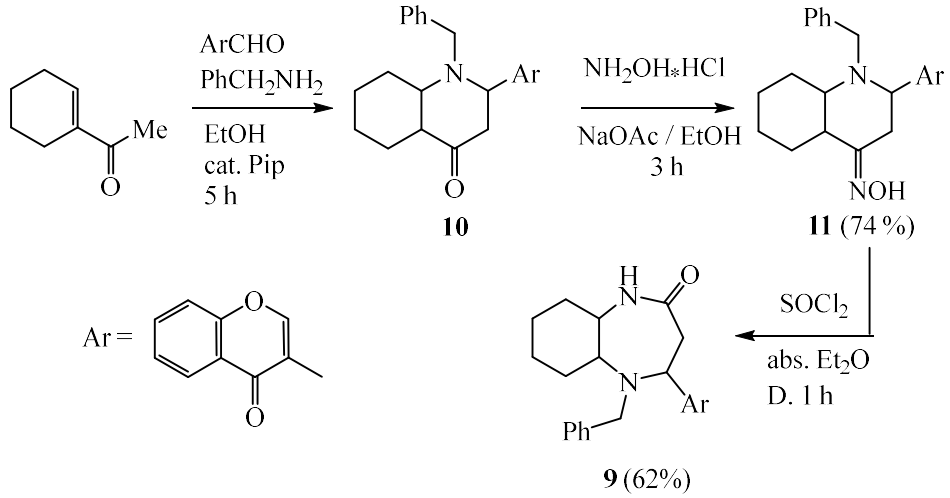
2. 3-Substituted chromones

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-5*H*-benzo[6,7]azepino[4,5-*b*]quinolin-6-yl)-4*H*-chromen-4-one (**7**)

The general pathway for the synthesis of octahydro-1*H*-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-4*H*-chromen-3-yl)octahydro-1*H*-benzo[*b*][1,5]diazepin-2-(3*H*)-one (**9**) was obtained with a yield of 62 % [26].



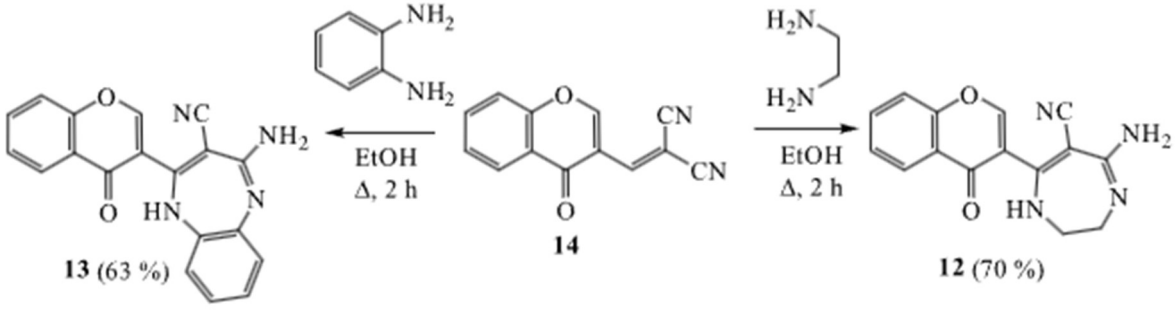
Scheme 5. The synthesis of 5-benzyl-4-(4-oxo-4*H*-chromen-3-yl)octahydro-1*H*-benzo[*b*][1,5]diazepin-2-(3*H*)-one **9**

Screening of 5-benzyl-4-(4-oxo-4*H*-chromen-3-yl)octahydro-1*H*-benzo-[*b*][1,5]diazepin-2-(3*H*)-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-4*H*-chromen-3-yl)octahydro-1*H*-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.

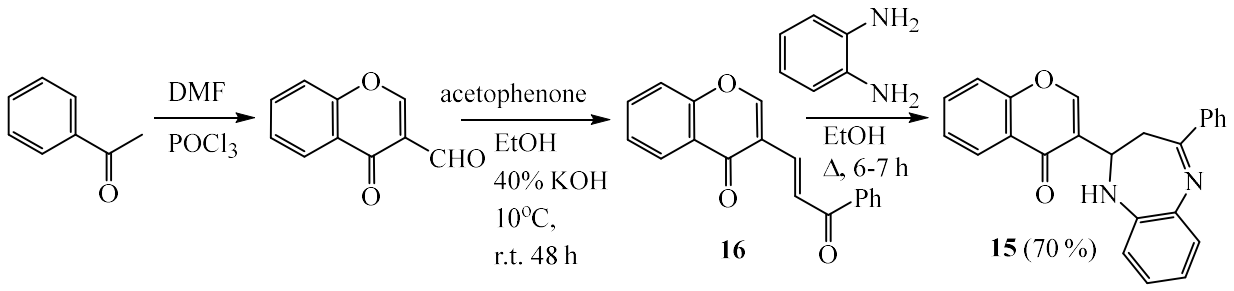
Synthesis of 5-amino-7-(4-oxo-4*H*-chromen-3-yl)-2,3-dihydro-1*H*-1,4-diazepine-6-carbonitrile (**12**) and 4-amino-2-(4-oxo-4*H*-chromen-3-yl)-1*H*-1,5-benzodiazepine-3-carbonitrile (**13**) was implemented in [27]. The reaction of [(4-oxo-4*H*-chromen-3-yl)methylidene]propandinitrile (**14**), obtained 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-4*H*-chromen-3-yl)-2,3-dihydro-1*H*-1,4-diazepine-6-carbonitrile (**12**) and 4-amino-2-(4-oxo-4*H*-chromen-3-yl)-1*H*-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].

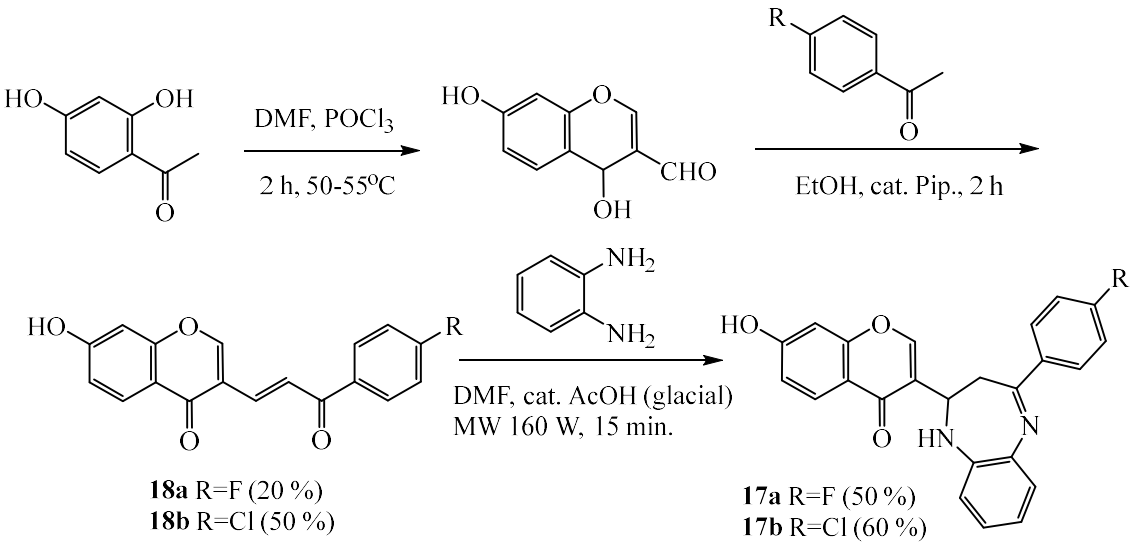


Scheme 7. The synthesis of 3-(4-phenyl-2,3-dihydro-1,5-benzodiazepin-2-yl)chromone (**15**)

3-(4-Phenyl-2,3-dihydro-1,5-benzodiazepin-2-yl)chromone (**15**) has been found to exhibit antibacterial activity against *Bacillus bacteria*, some of which cause food poisoning, anthrax (malignant furuncle) etc., with 100 % growth inhibition at 1 % concentration (w/v) in DMF.

The synthesis of substituted analogues of compound **15** 7-hydroxy-3-(4-R-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl)-4*H*-chromen-4-ones **17a,b** was carried out according to the following protocol: 7-hydroxy-3-formylchromone was obtained from rezacetophenone by the Vilsmeyer-Haack reaction, from which chalcones **18a,b** were formed in the piperidine-catalyzed aldol condensation with substituted acetophenones. The target 7-hydroxy-3-(4-R-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl)-4*H*-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].

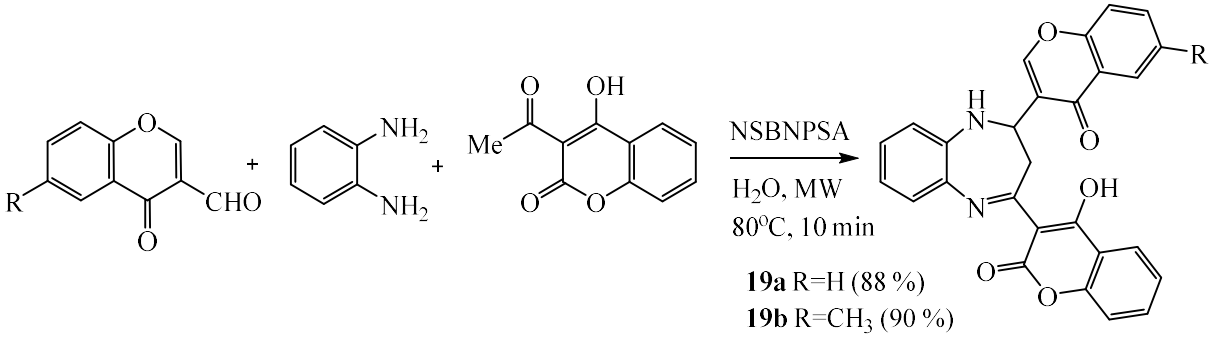
In studies on antioxidant activity, 7-hydroxy-3-(4-R-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl)-4*H*-chromen-4-ones **17a,b** were found to be inactive.



Scheme 8. The synthesis of 7-hydroxy-3-(4-R-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-yl)-4*H*-chromen-4-ones

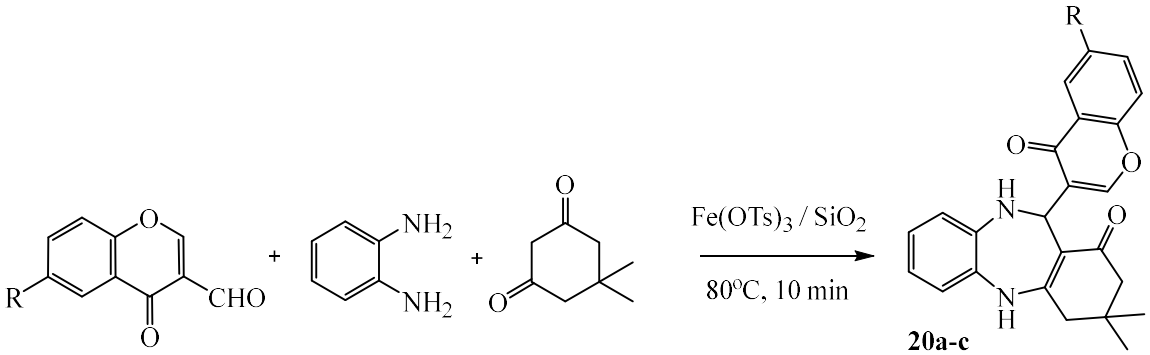
Examples of the application of multicomponent reactions (MCR), which are resource-saving and contribute to the implementation of the concept of "green" chemistry, in the molecular design of new 3-(1,5-benzodiazepin-4-yl)chromones are presented in works [30, 31].

The method for the synthesis of 3-[2,3-dihydro-2-(6-R-4-oxo-4*H*-chromen-3-yl)-1*H*-1,5-benzodiazepin-4-yl]-4-hydroxy-2*H*-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, nano-silica 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**).



Scheme 9. The synthesis of 3-[2,3-dihydro-2-(6-R-4-oxo-4*H*-chromen-3-yl)-1*H*-1,5-benzodiazepin-4-yl]-4-hydroxy-2*H*-1-benzopyran-2-ones **19a,b**

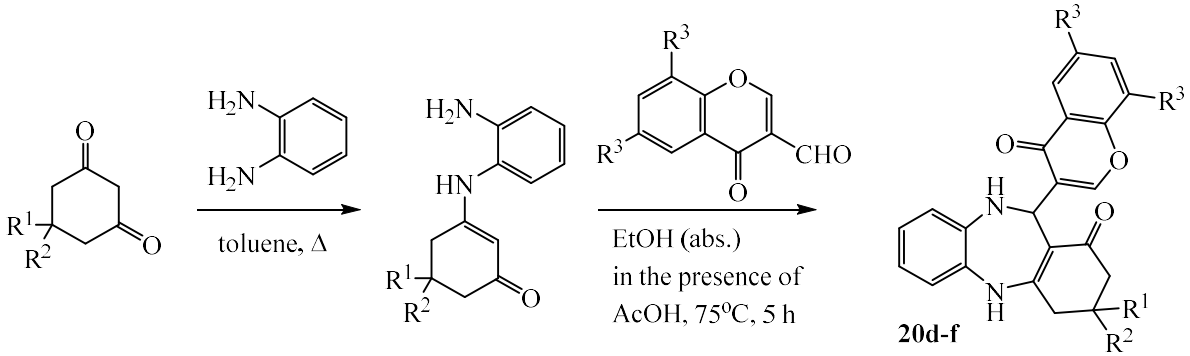
3,3-Dimethyl-2,3,4,5,10,11-hexahydro-11-[6-R-4-oxo-4*H*-chromen-3-yl]-1*H*-dibenzo-[*b,e*][1,4]diazepin-1-ones **20a-c** were synthesized by the three-component condensation of 3-formylchromones, *o*-phenylenediamine and dimedone, as the CH acid component, which took place using a heterogeneous $Fe(OTs)_3/SiO_2$ 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].



R= H (93 %) (**a**), Me (93 %) (**b**), Cl (92 %) (**c**)

Scheme 10. The synthesis of 3,3-dimethyl-2,3,4,5,10,11-hexahydro-11-[6-R-4-oxo-4*H*-chromen-3-yl]-1*H*-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.



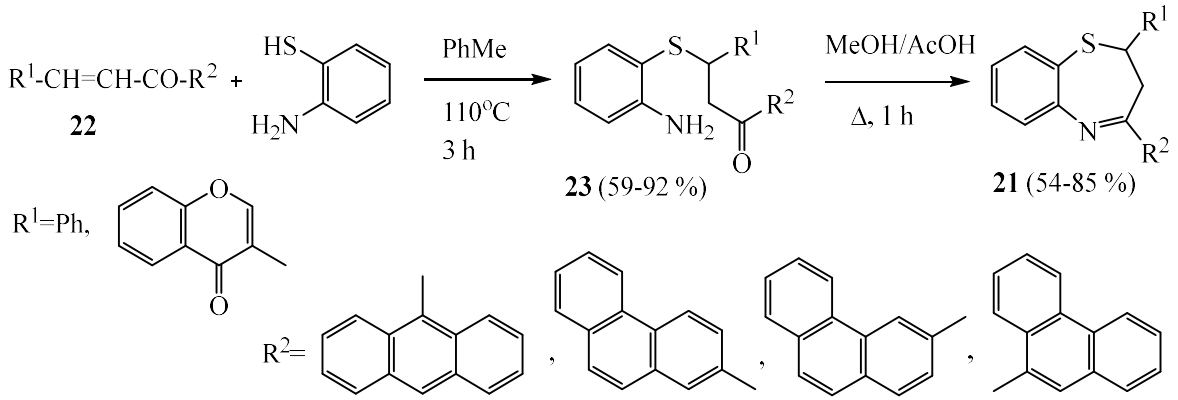
d $R^1=R^3=$ H, $R^2=$Ph; **e** $R^1=R^3=$ H, $R^2=$3,4-$(MeO)_2C_6H_3$; **f** $R^1=R^2=$ Me, $R^3=$Cl

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.

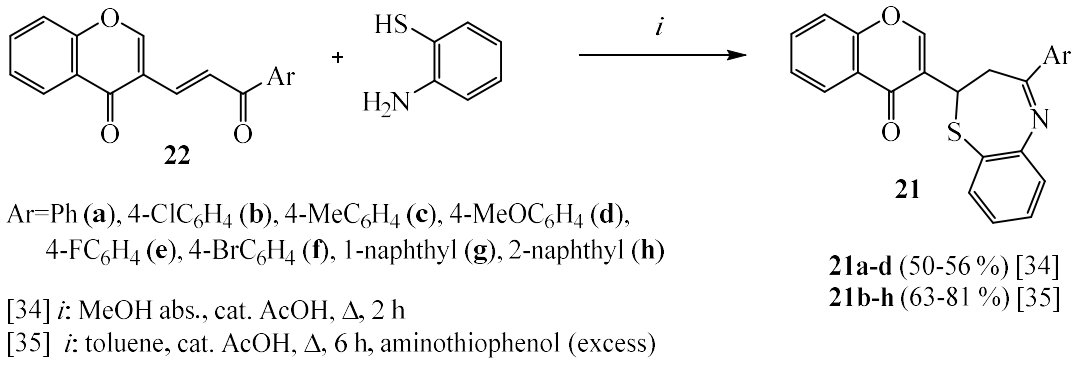
Compounds **20d-f** were tested for anti-HCV activity by testing their activity against NS5b polymerase (IC_{50} (μM) **20d** > 42.667; IC_{50} (μM) **20e** > 42.667; IC_{50} (μM) **20f** > 42.678) and in the analysis of HCV replicons (EC_{50} (μM) **20d** = 17.821; EC_{50} (μM) **20e** = 3.692; EC_{50} (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. 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].



Ar=Ph (**a**), 4-ClC_6H_4 (**b**), 4-MeC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**), 4-FC_6H_4 (**e**), 4-BrC_6H_4 (**f**), 1-naphthyl (**g**), 2-naphthyl (**h**)

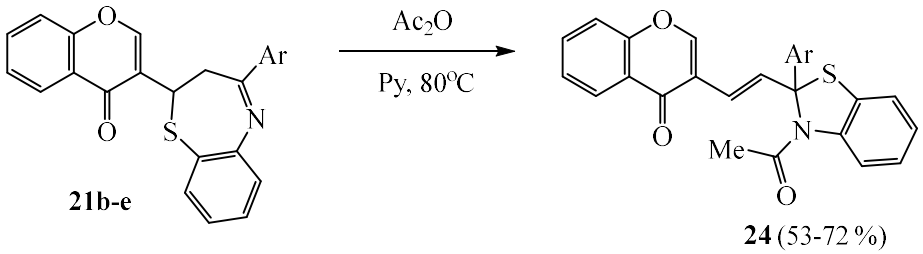
[34] *i*: MeOH abs., cat. AcOH, Δ, 2 h
[35] *i*: toluene, cat. AcOH, Δ, 6 h, aminothiophenol (excess)

21a-d (50-56 %) [34]
21b-h (63-81 %) [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)-4*H*-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.

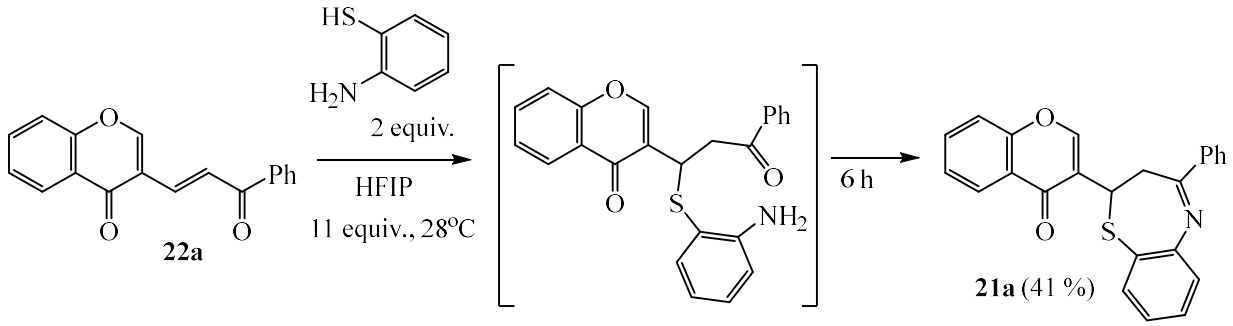
It was found that 3-(4-aryl-2,3-dihydro-1,5-benzothiazepin-2-yl)chromones **21** (R = 4-Me, 4-MeO, 4-F, 4-Cl-C_6H_4) when heated to 80°C in a mixture of anhydrous pyridine and acetic anhydride undergo ring reduction under acetylation conditions, forming 3-acetyl-2,3-dihydrobenzothiazole **24** with a yield of 53-72 % (**Scheme 14**) [35].



Ar= 4-ClC_6H_4 (**b**), 4-MeC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**), 4-FC_6H_4 (**e**)

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**).

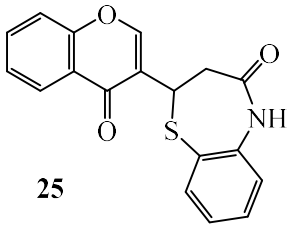


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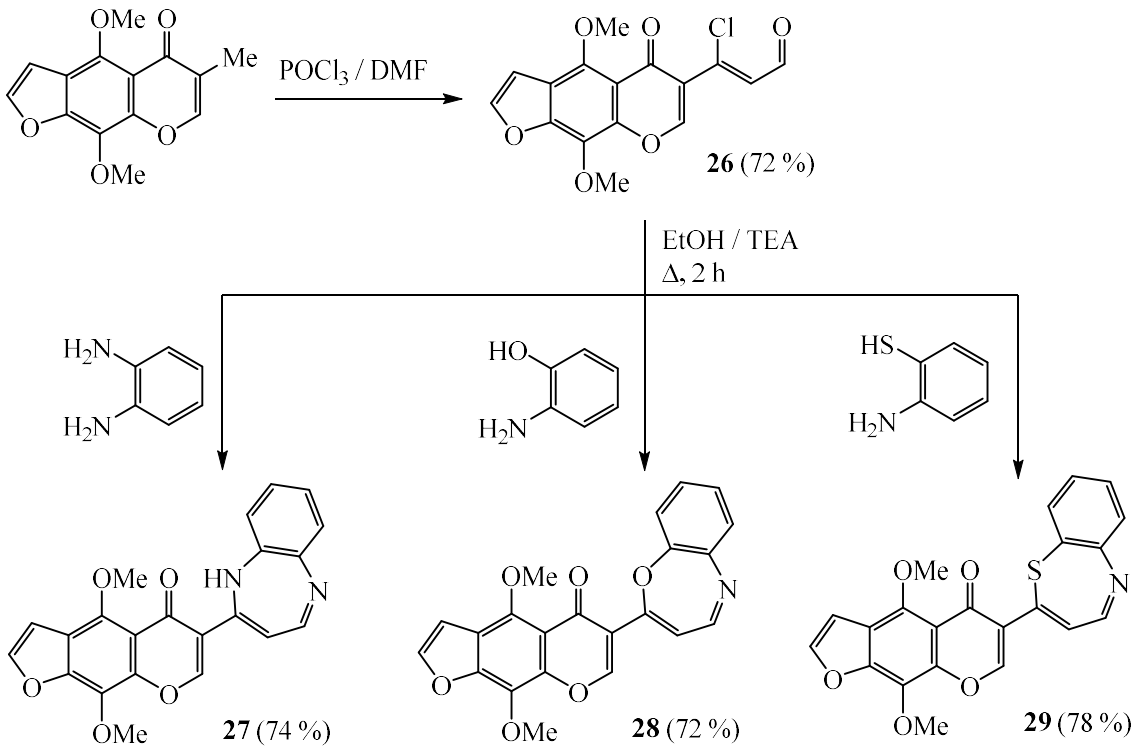
Figure 1. Bioactive 2-(chromon-3-yl)-2,3-dihydro-1,5-benzothiazepin-4-one (**25**)

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-5*H*-

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. 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**

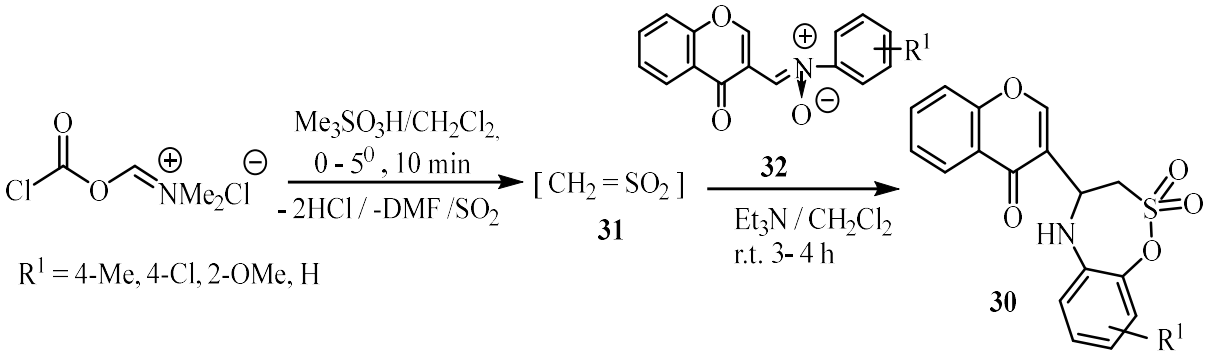
6-(1,5-Benzodiazepin-2-yl)/1,5-benzoxazepin-2-yl/1,5-benzothiazepin-2-yl)furo[3,2-*g*]chromen-5-ones **27-29**, were investigated *in vitro* for antimicrobial activity at 500 and 1000 μg/ml against gram-positive bacteria, namely *Staphylococcus aureus* (ATCC25923) and *Bacillus subtilis* (ATCC6635), 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 *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_{50} = 54.91-77.06 μg/ml) compared to the standard anticancer drug doxorubicin (IC_{50} =–4.58 μg/ml). Compound **27** showed weak cytotoxic activity against the HCT-116 cell line panel (IC_{50} =–68.71 μg/ml) compared to the standard anticancer drug doxorubicin (IC_{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_{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** with the yields of 80-85 % were obtained by the cycloaddition of sulfene **31**, which was formed *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_2 atmosphere), compounds **30** were obtained with low yields (for example, **30** (R^1 = 4-Me) – 25 %) **(Scheme 17**) [39].

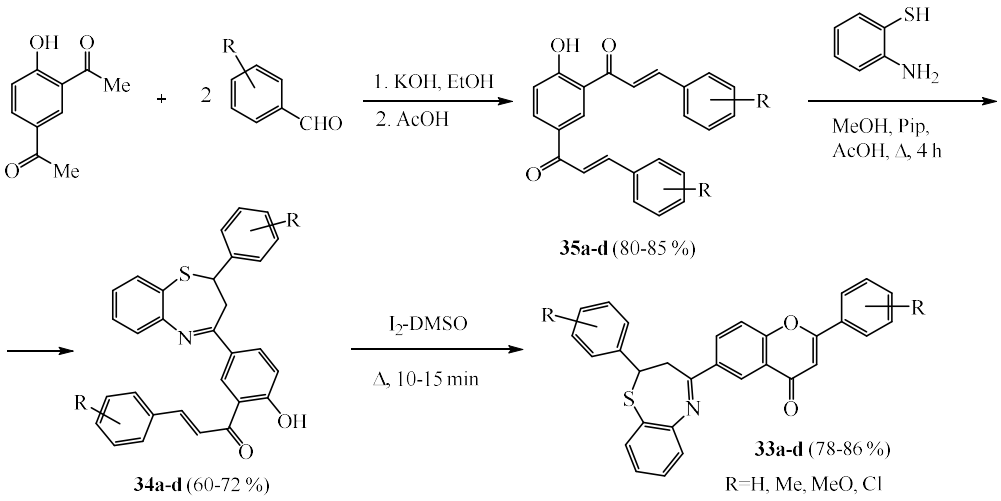


Scheme 17. The synthesis of 4,5-dihydro-4-(4-oxo-4*H*-1-benzopyran-3-yl)-3*H*-1,2,5-benzoxathiazepine-2,2-dioxides **30**

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-benzothiazepinylchalcones **34a-d** in I_2-DMSO, which, in turn, were obtained by

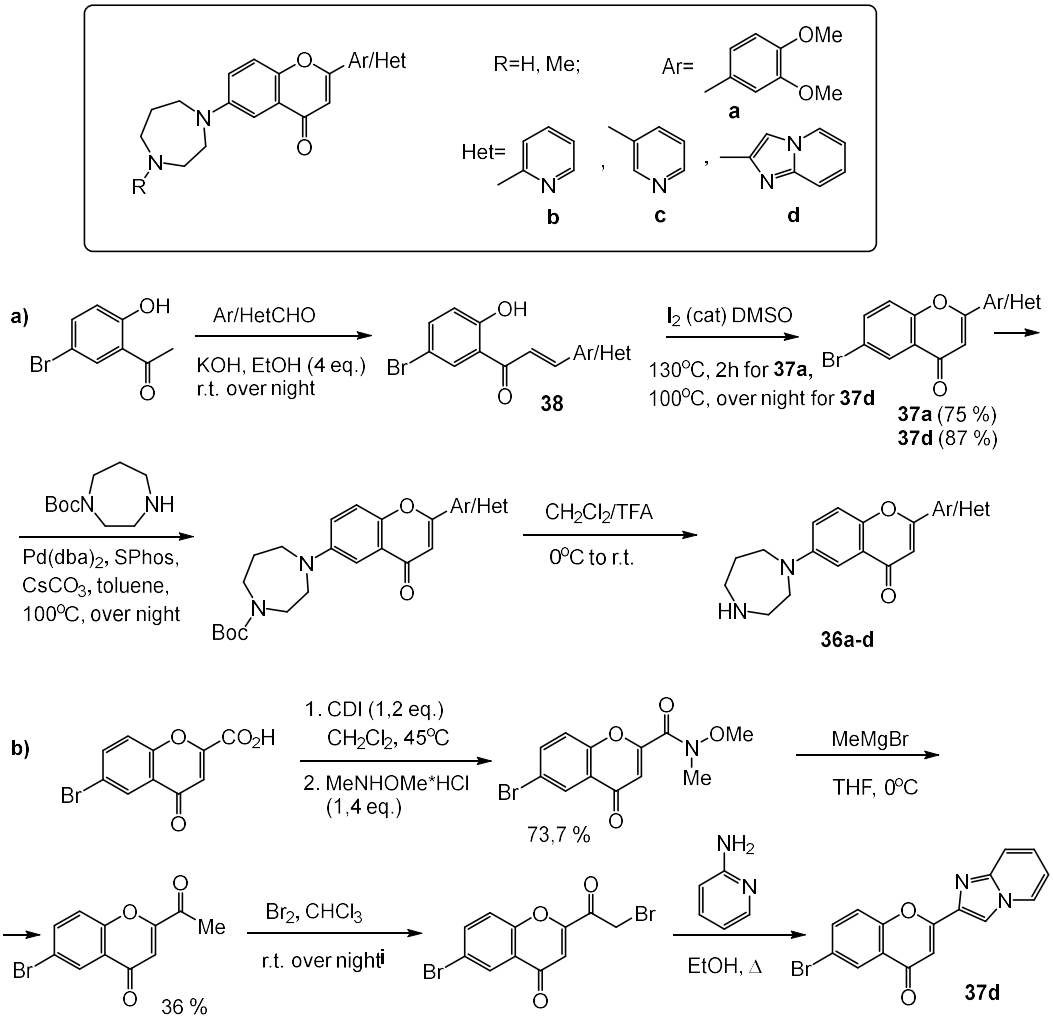
cyclocondensation of 2,4-di-(3'-aryl-acrylo)phenol (bis-chalcone) **35a-d** with 2-aminothiophenol (**Scheme 18**) [40].



Scheme 18. 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-4*H*-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-4*H*-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 J_2-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].

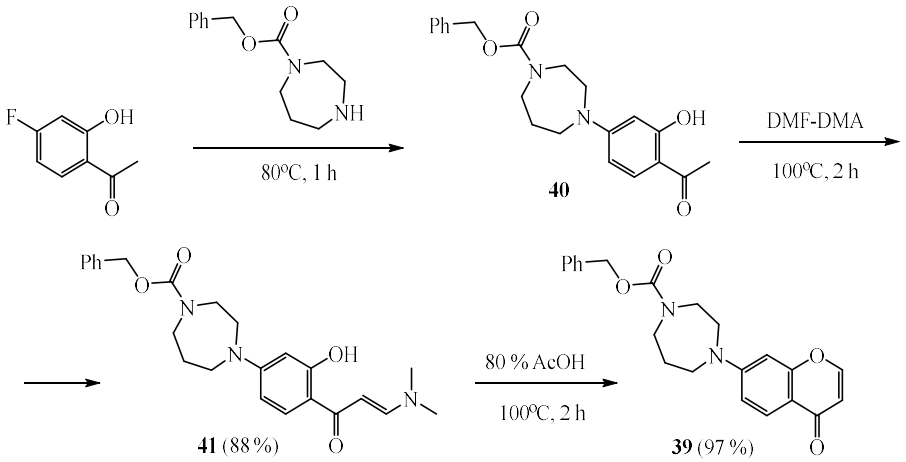


Scheme 19 The synthesis of 6-(1,4-diazepan-1-yl)chromones **36a-d**

2-Ar/Het-6-(4-R-1,4-diazepan-1-yl)-4*H*-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].

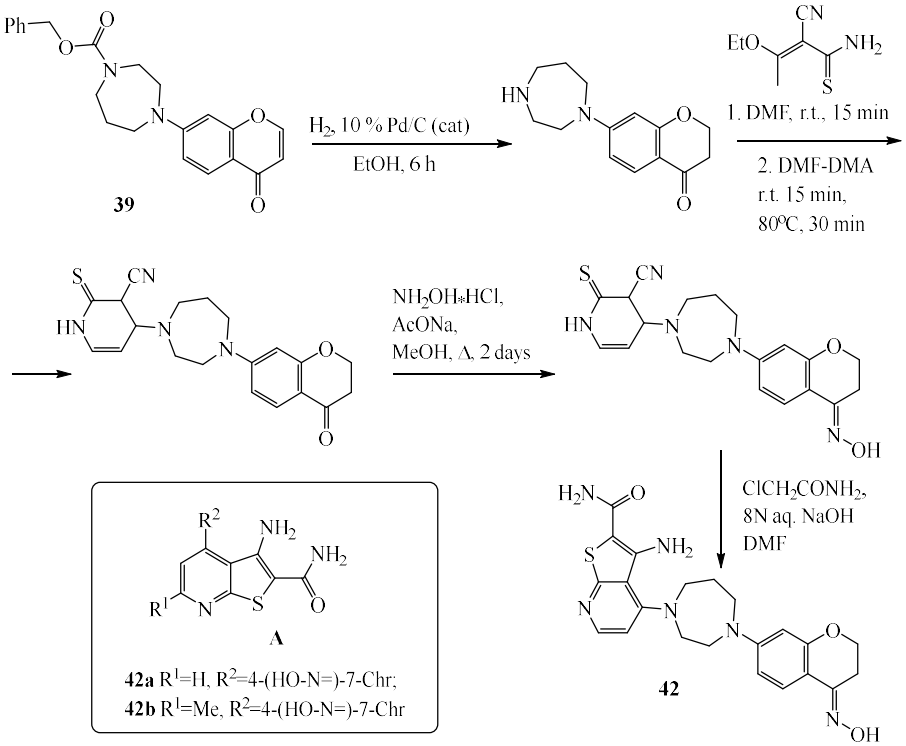
4. 7-Substituted chromones

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-4*H*-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-[(2*E*)-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-4*H*-chromen-7-yl)-1,4-diazepane-1-carboxylate (**39**)

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

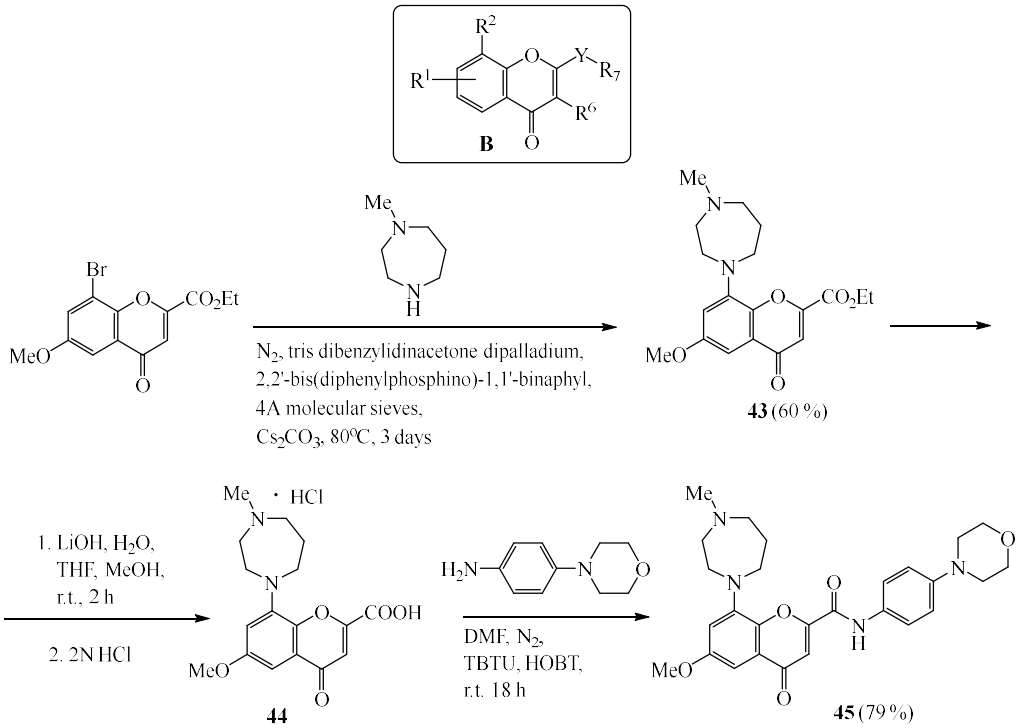


Scheme 21. The synthesis of osteogenesis-promoting thienopyridine derivative **42**

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**).



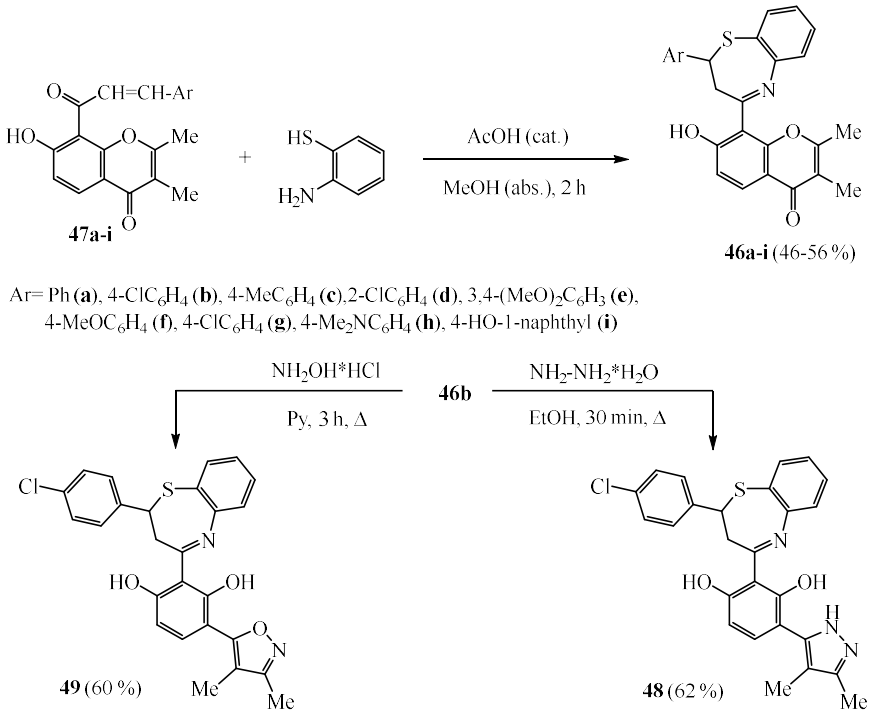
Scheme 22. The synthesis of 6-methoxy-8-(4-methyl-[1,4]diazepan-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid derivatives **43-45**

6-Methoxy-8-(4-methyl-[1,4]diazepan-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid ethyl ester (**43**) was synthesyzed 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_2O 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 chromonylchalcones **47a-i** with 2-aminothiophenol in dry methanol containing catalytic amount of glacial acetic acid (**Scheme 23**).



Scheme 23. The synthesis of 8-(2-aryl-2,3-dihydro-1,5-benzothiazepin-4-yl)-7-hydroxy-2,3-dimethyl-4*H*-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-y1]-4-(3,4-dimethyl-1*H*-pyrazol-5-yl)-l,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-yI]-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

concentrations of 400 and 600 μg/ml, all tested compounds **46**, registered a feeble activity against *B. megaterium*, but were virtually inactive against *P. vulgaris*. Testing for 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. 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, chromonylchalcones 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.

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