3-Thienyl/benzothienylchromones. Synthesis and properties

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Keywords: *3-hetarylchromones, α-hetaryl-2-hydroxyacetophenones, chromones, thiophene and benzothiophene compounds, cyclization reactions, coupling reactions.*

This mini-review for the first time summarizes and systematizes all the data available in the literature on the synthesis and properties of 3-thienyl/benzothienylchromones, starting from 1960. Two main approaches to the formation of target structures are presented. The conditions of cyclization reactions, oxidative rearrangement, transition metals catalyzed CH activation and annulation reactions, etc. are discussed. Testing data for some types of biological activity of a number of the 3-thienyl/benzothienylchromones and the products of their transformation into the pyrazole cycle are given.

Introduction

One of the most promising ways to create new biologically active compounds for medical chemistry is certainly the synthesis of analogues of natural low molecular weight bioregulators. A synthetically realized combination of natural benzopyrone structures, such as “drug-like natural matrices”, with pharmacophores such as S-, O-, N-containing heterocycles, which are structural elements of many not only synthetic, but also endogenous biologically active compounds, has led to fundamentally new structures - the so-called “double drugs”, a potential bispharmacophore drugs.

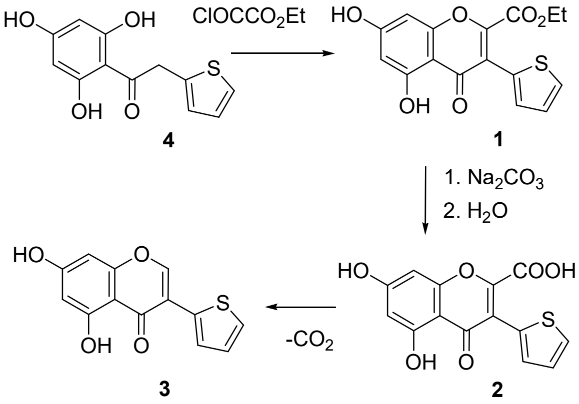
Modification of isoflavonoids by replacing the aryl substituent with a heterocyclic substituent in the classical isoflavone structure was first successfully implemented in 1960 [1]. The described thienyl analogues of estrogenic isoflavones turned out to be the first representatives of 3-hetarylchromones and stimulated the further development of synthesis methods and the study of the properties of this fundamentally new type of compounds. Against the background of a consistently high number of scientific and patent publications, review articles on 3-hetarylchromones with N- and O-containing heterocycles, there are relatively few materials on 3-hetarylchromones with S-containing heterocycles, mostly published after 2000 and, as far as is known, were not systematized.

To a certain extent, the observed increase in the publication activity of 3-hetarylchromones with S-containing heterocycles is associated with the increased use of cross-coupling reactions for the preparation of heterocyclic compounds of various structures over the past two decades [2]. Among all these reactions catalyzed by transition metals, the Suzuki-Miyaura reaction, which uses boronic acids or esters, remains the method of choice. Advances in the synthesis and study of the reactivity of new heterocyclic boronic acids make it possible to create target libraries that are now mandatory in medical chemistry [3].

This review summarizes the results of research for the synthesis and biological screening of 3-thienyl/benzothienylchromones. Two main approaches used in the synthesis of target 3-hetarylchromones, such as cyclization of S-containing ring synthons into chromone system or introduction of an S-containing heterocycle to the chromone system are highlighted. Chemical properties were represented only by a single example of a reaction with hydrazine hydrate. The range of biological action of the target 3-hetarylchromones and some their transformation products into the pyrazole cycle was determined.

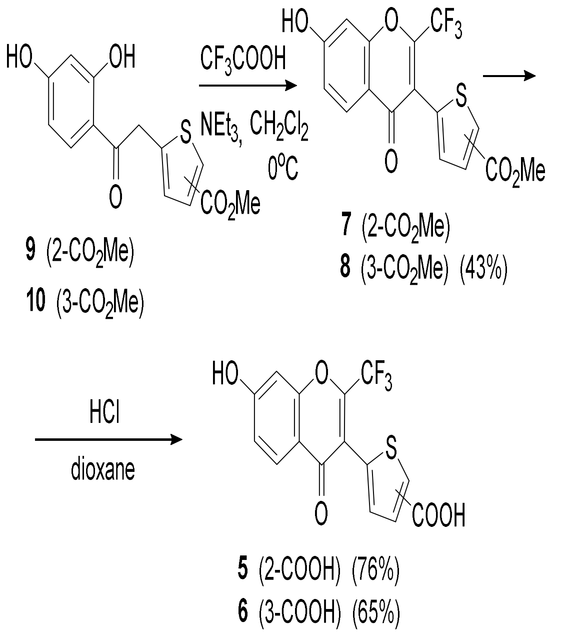
1. Synthesis of 3-thienylchromones by the formation of the pyrone cycle from synthons, including S-containing heterocycle

The first synthesized heteroanalogs of isoflavones were thienyl derivatives **1**–**3** obtained upon cyclization of α-(2-thienyl)-2,4,6-trihydroxyacetophenone **4** with ethyl oxalyl chloride and subsequent transformations of 2-ethoxycarbonyl-3-(2-thienyl)-5,7-dihydroxychromone **1** on the ethoxycarbonyl group (hydrolysis and decarboxylation) [1] (**Scheme 1**).



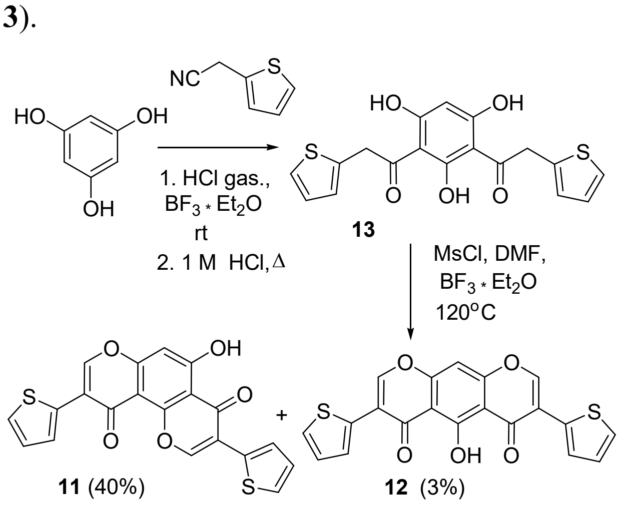
Scheme 1. The synthesis of 2-(un)substituted-3-(2-thienyl)-5,7-dihydroxychromones

The patent [4] discloses the synthesis of 5-(7-hydroxy-4-oxo-2-trifluoromethyl-4*H*-chromen-3-yl)thiophen-2- and thiophene-3-carboxylic acids **5**, **6** and their methyl esters **7**, **8** by cyclization of the corresponding α-(2-thienyl)-2,4-dihydroxyacetophenones **9**, **10** with trifluoroacetic acid in the presence of triethylamine in dichloromethane at 0 °C (**Scheme 2**).



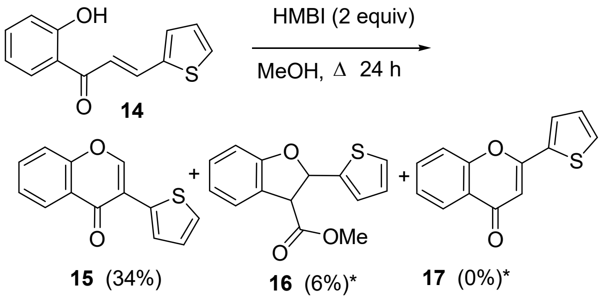
Scheme 2. The synthesis of 5-(7-hydroxy-4-oxo-2-trifluoromethyl)-4H-chromen-3-yl)thiophen-2- and thiophene-3-carboxylic acids and their methyl esters

The thienyl derivatives of benzodipyranone of an asymmetric and symmetrical structure - benzodipyrano-4,10-dione **11** and benzodipyrano-4,6-dione **12** were obtained by the Vilsmeier-Haack reaction from the condensation product of phloroglucinol and 2-thienylacetonitrile **13** with methanesulfonyl chloride and N, N-dimethylformamide in boron trifluoride etherate at 120 °C [5] (**Scheme 3**).



Scheme 3. The synthesis of thienyl derivatives of benzodipyrano-4,10-dione and benzodipyrano-4,6-dione

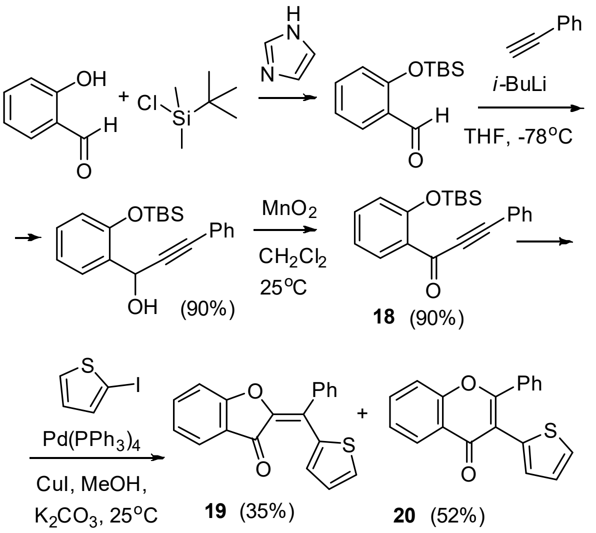
The work [6] described examples of the oxidative rearrangement of a 2′-hydrochalcone with various substituents (R) in ring B using 1H-1-hydroxy-5-methyl-1,2,3-benzodioxathiol 3,3-dioxide (HMBI). Direct conversion took place by boiling in methanol, without the need for preliminary protection of the 2’-hydroxy group of the chalcone. Derivatives of terminal isoflavones are formed as the main product, and 2,3-dihydro-2-R-3-benzofurancarboxylic acid methyl esters and the corresponding flavone derivatives are formed in low yields. In the case of a 2'-hydroxychalcone with a thienyl substituent in ring B **14**, 3-(2-thienyl) chromone **15** was obtained in 34% yield, and the yields of 2,3-dihydro-2-(2-thienyl)-3-benzofurancarboxylic acid methyl ester **16** and 2-(2-thienyl)chromone **17** were determined to be 6% and 0%, respectively, based on ^{1}H NMR spectroscopy data, using the internal standard in a separate experiment (**Scheme 4**).



Scheme 4. The synthesis of 3-(2-thienyl)chromone

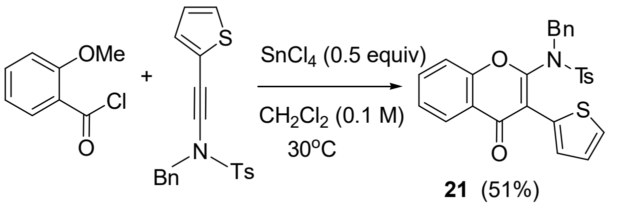
The catalyzed by transition metals reactions of CH-activation and annulation are an effective tool for the synthesis of 3-hetarylchromone derivatives. The role of the catalyst/catalytic complex is not only to accelerate the speed of the process, but can also affect the selectivity of the chemical reaction.

In the coupling reaction of 1-(2-*tert*-butyldimethylsilyloxy)phenyl-3-phenyl-2-propyn-1-one **18** with 2-iodothiophene in absolute methanol in the presence of catalytic amounts of $Pd(PPh_3)_4$ and CuI and K_2CO_3 as base 2-(1-thienyl-1-phenylmethylene) benzofuranone **19** and 2-phenyl-3-thienylchromone **20** were obtained [7] (**Scheme 5**).



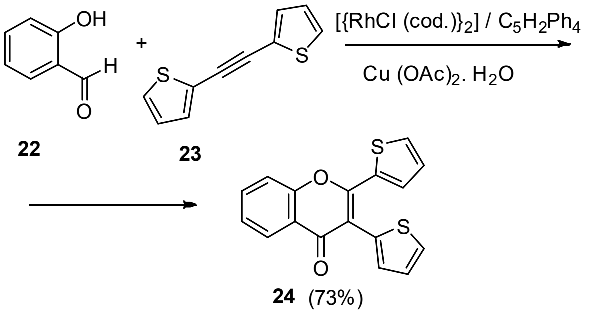
Scheme 5. The synthesis of 2-phenyl-3-(2-thienyl)chromone

A new effective method for the synthesis of 3-substituted 2-aminochromones promoted by Sn(IV) annulation of ynamides with 2-methoxy aroyl chlorides under mild conditions was used to obtain 3-(2-thienyl)chromone having substituted amino group at C-2 **21**. This method provides concomitant construction of C-C and C-O bonds between ynamides and 2-methoxy aroyl chlorides according to the tandem Friedel-Crafts acylation/Michael addition/ elimination strategy [8] (**Scheme 6**).



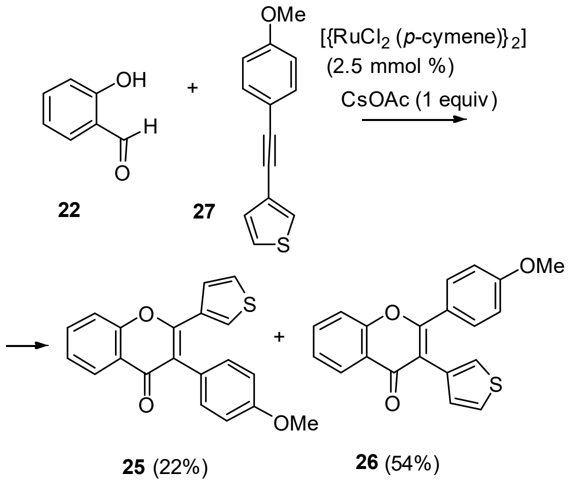
Scheme 6. The synthesis of 3-(2-thienyl)chromone having substituted amino group at C-2

By direct oxidative coupling of salicylic aldehyde **22** with bis(2-thienyl)acetylene **23** in the presence of a rhodium catalyst, cyclopentadiene ligand and copper(II) acetate in *o*-xylene at 140 °C in nitrogen atmosphere within 4 hours, 2,3-bis(2-thienyl)chromone **24** was obtained [9] (**Scheme 7**).



Scheme 7. The synthesis of 2,3-bis(2-thienyl)chromone

The isomeric thienyl derivatives of chromone **25** and **26** were obtained by the annulation reaction of salicylic aldehyde **22** with disubstituted alkyne **27** using the newly developed Ru(II) catalyst system in *tert*-amyl alcohol at 80 °C in air within 12 hours and were separated by column chromatography on silica gel [10] (**Scheme 8**).

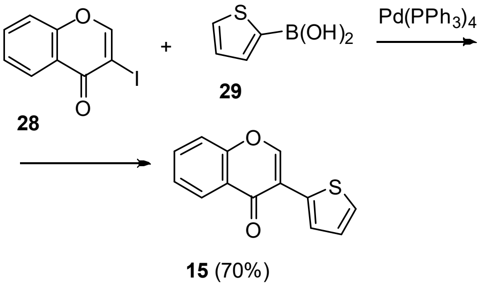


Scheme 8. The synthesis of 2-aryl-3-(3-thienyl)chromone

2. Synthesis of 3-thienyl/benzothienyl chromones by introduction of an S-containing heterocycle to the chromone system

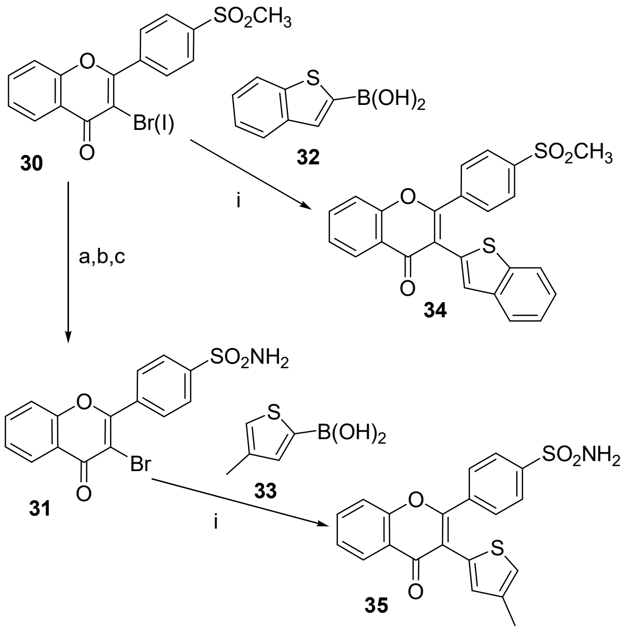
The classic way to obtain derivatives of 3-hetarylchromones is the reaction of the interaction of 3-halochromone with derivatives of heteroarylboronic acid using a palladium catalyst.

The synthesis of the thienyl analogue of isoflavone **15** by the cross-coupling reaction of 3-iodochromone **28** with thiophenboronic acid **29** using tetrakis(triphenylphosphine) palladium as a catalyst in an argon atmosphere at room temperature was described in [11] (**Scheme 9**).



Scheme 9. The synthesis of 3-(2-thienyl)chromone

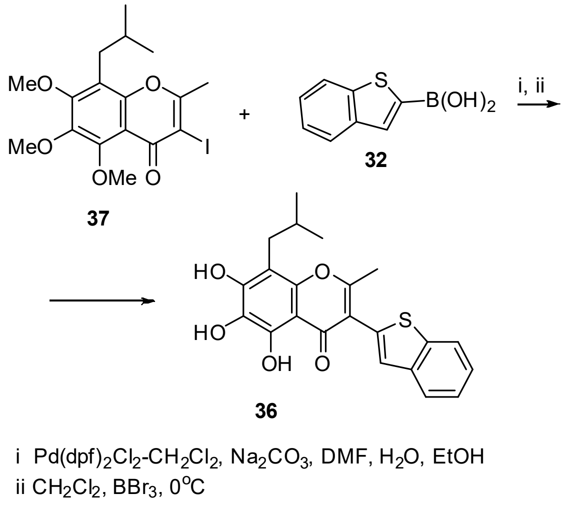
Using the Suzuki coupling reaction of 3-halogenflavones **30** and **31** with heteroarylboronic acids **32** and **33** made it possible to obtain 2-aryl-3-(2-benzothienyl)chromone **34** and 2-aryl-3-(2-thienyl)chromone **35** with pharmacophore groups [12] (**Scheme 10**).



a: $(CF_3CO)_2O$, reflux , b: Cl_2, AcOH; c: NH_4OH
i: $Pd(PPh_3)_4$, 2 M Na_2CO_3, EtOH-H_2O-toluene

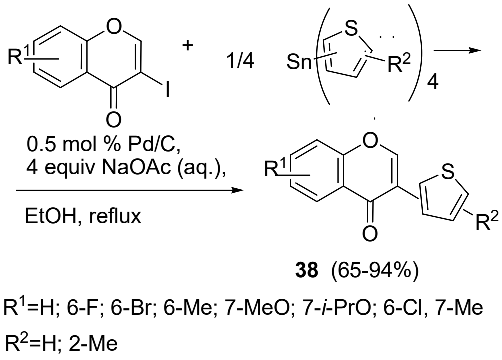
Scheme 10. The synthesis of 2-aryl-3(2-thienyl/benzothienyl)chromones with pharmacophore groups

Claimed in the patent [13] 2-methyl-5,6,7-trihydroxy-8-isobutyl-3-(2-benzothienyl)chromone **36** was also obtained by the Suzuki reaction from a derivative of 3-iodochromone **37** and benzothiophenboronic acid **32** when using the $Pd(dpf)_2Cl_2$-CH_2Cl_2 catalyst system and subsequent demethylation (**Scheme 11**).



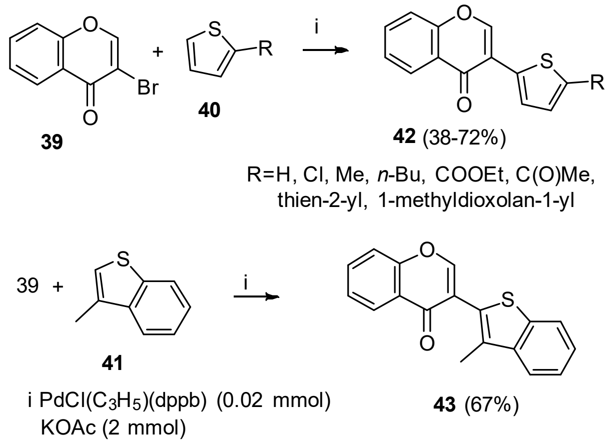
Scheme 11. The synthesis of 2-methyl-5,6,7-trihydroxy-8-isobutyl-3-(2-benzothienyl)chromone

According to the Stille reaction, as a variant of the cross-coupling reaction, the interaction of (un)substituted 3-iodochromone and tetratiophenstannins in the presence of palladium on charcoal under mild conditions yielded (un)substituted derivatives of 3-(2-thienyl)- and 3-(3-thienyl)chromones **38** [14] (**Scheme 12**).



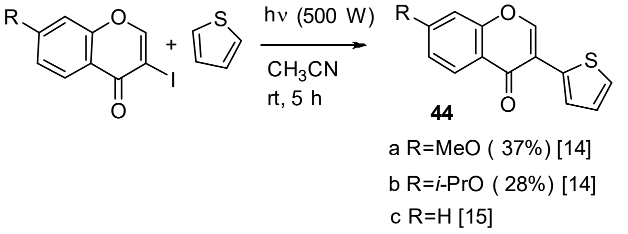
Scheme 12. The synthesis of 3-(2-thienyl)- and 3-(3-thienyl)chromones

In the direct coupling reaction of 3-bromochromone **39** with (un)substituted thiophene **40** and 3-methylbenzothiophene **41** catalyzed by palladium, (un)substituted 3-(2-thienyl)chromones **42** and 3-[2-(3-methylbenzothienyl)]chromone **43** were obtained [15] (**Scheme 13**).



Scheme 13. The synthesis of (un)substituted 3-(2-thienyl)chromones and 3-[2-(3-methylbenzothienyl)]chromone

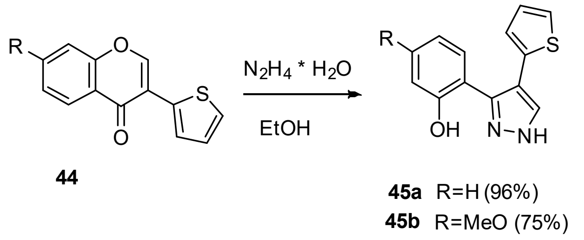
The synthesis of 3-(2-thienyl)chromones **44a-c** by direct coupling of (un)substituted 3-iodochromone with thiophene under the conditions of the photochemical reaction in acetonitrile under a high-pressure mercury lamp without any catalysts and bases was proposed in the works [16, 17] (**Scheme 14**).



Scheme 14. The synthesis of 3-(2-thienyl)chromones

3. Chemical properties of 3-hetarylchromones with S-containing heterocycles

Chemical properties are represented by a single example of the interaction of 3-(2-thienyl)chromones **44a,b** with hydrazine hydrate [17]. The reaction was carried out at a ratio of the reagents chromone : hydrazine hydrate 1:2 in boiling alcohol to obtain 3-aryl-4-(2-thienyl)-1H-pyrazoles **45a, b** (**Scheme 15**).



Scheme 15. The synthesis of 3-aryl-4-(2-thienyl)-1H-pyrazoles

4. The biological activity of 3-thienyl/benzothienylchromones and their transformation products

When searching for drugs with a higher therapeutic index and less toxic side effects, considerable attention has been paid to compounds of the thiophene series, which have a wide spectrum of biological effects, namely, analgesic, antimicrobial, antihistamine, antispasmodic, anticonvulsant, antiviral, anticancer, diuretic, pesticidal and others [18].

Recently, there have been many patent publications in which compounds of the thiophene and benzothiophene series are claimed to be selective modulators of estrogen receptors.

As for the thiophene analogues of isoflavones, according to the patents [19, 20], 5,7-dihydroxy-3-(2-thienyl)chromone (**3**) and 5,7-dihydroxy-3-(3-thienyl)chromone are ER-ß selective ligands having better selectivity compared to estrogen relative to estrogen-ß receptor compared to estrogen-α receptor and can be used in the treatment of diseases associated with the estrogen receptor-ß, in particular, Alzheimer's disease, anxious disorders, depressive disorders, osteoporosis, cardiovascular disease, rheumatoid arthritis or prostate cancer. It should be noted that in an early review, the absence of estrogenic activity of 5,7-dihydroxy-3-(2-thienyl)chromon was reported [21].

In the extended patent family [4, 22] 5-(7-hydroxy-4-oxo-2-(trifluoromethyl)-4*H*-chromen-3-yl)thiophene-2-carboxylic acid (**5**) (IC_{50} < 0.1 μM) and 5-(7-hydroxy-4-oxo-2-(trifluoromethyl)-4*H*-chromen-3-yl)thiophene-3-carboxylic acid (**6**) (IC_{50} <1 μM) are claimed to be inhibitors of S-nitrosoglutathione reductase and may be used in the treatment of diseases and pathological conditions associated with impaired NO balance, such as pulmonary hypertension, ARDS, asthma, pneumonia, pulmonary fibrosis, cystic fibrosis, chronic obstructive pulmonary disease (COPD), hypertension, ischemic radar syndromes, gastrointestinal disorders, inflammatory diseases, degenerative neurological disorders.

Current knowledge of the antiapoptotic Bcl-2 family role in cancer cells determine the targeting of this subfamily of proteins for therapeutic intervention in hyperproliferative diseases and malignant tumors. According to patent [13] in one embodiment 2-methyl-5,6,7-trihydroxy-8-isobutyl-3-(2-benzothienyl)chromone (**36**) is declared as compound that is an inhibitor of the anti-apoptotic family Bcl-2 and enhances cell sensitivity to apoptosis inducers, such as chemotherapy and radiation therapy, in animals.

To solve the problem of overcoming the multidrug resistance of tumor cells a series of asymmetric and symmetric benzodipyranones was tested in vitro as P-glycoprotein inhibitors [5] (**Figure 1**).

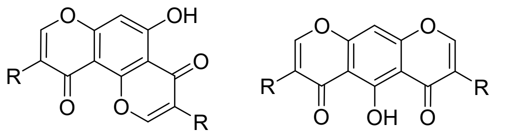


Figure 1. General formula of asymmetric and symmetric benzodipyranones

The test results revealed the structure-activity relationship of a series of P-gp inhibitors and compound-leader. The symmetric benzodipyranones proved to be inactive. Asymmetric benzodipyranones with electron-donating substituents proved to be the most active (leader compound R = 3-methylphenyl), inhibition of P-gp activity was observed in compounds with electron-withdrawing substituents, compounds having thiophen-2-yl substituents (compound **11**), 1-naphthyl, phenyl, cyclopropyl lost activity.

Currently, topical search for new classes of biologically active compounds COX-2 inhibitors, which are analogues coxibs in structure and action. Celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl)pyrazol-1-yl] benzenesulfonamide) and rofecoxib (4-(4-methylsulfonylphenyl)-3-phenyl-5H-furan-2-one) have sufficiently high clinical efficacy comparable to the therapeutic (anti-inflammatory and analgesic) effect of traditional NSAIDs, however, due to the high specificity of the inhibitory effect on COX-2 and the absence of influence on the COX-1 isoenzyme (responsible for the development of side effects when using NSAIDs) they have low gastrointestinal toxicity and lack of effect on platelet activity. Flavone derivatives with the necessary pharmacophore groups and (hetero)aryl substituents at the ~~3-rd~~ position 3 of the benzopyrone backbone, which can conditionally be considered as coxib analogues in structure, were tested for the inhibitory effect on COX-2 [12]. The results of testing of compounds of this series made it possible to draw certain conclusions about the structure-activity relationship, and although some of the compounds (for example, compounds with a thienyl substituent **35** and a benzothienyl substituent **34**) are practically inactive, and the highest activity was shown by the studied 2,3-diarylchromones, although with significantly lower activity compared to coxibs, the search for COX-2 inhibitors among this class of compounds has a future.

Tests of 3-(2-thienyl)chromone **44** transformation products under the action of a nucleophilic reagent - pyrazole compounds **45** *in vitro*, on antifungal activity against five phytopathogenic fungi (*Cytospora sp., Colletotrichum gloeosporioides, Botrytis cinerea, Alternaria solani and Fusarium solani*) showed that compounds **45a,b** exhibit higher antifungal activity than the positive control of gimexazole against *Cytospora sp., Colletotrichum gloeosporioides, Alternaria solani* and *Fusarium solani*, however, they were almost inactive against *Botrytis cinerea*. The studied 3-aryl-4-(2-thienyl)-1H-pyrazoles **45a,b** selectively inhibit the growth of *Cytospora sp., Colletotrichum gloeosporioides*. Thus, the growth inhibition rate of *Colletotrichum gloeosporioides* with an IC_{50} value of 12.86 μg/ml of pyrazole **45a** is much higher than the positive control of gimexazole (IC_{50} > 100 μg/ml).

Conclusions

The considered methods for the synthesis of 3-thienyl/benzothienylchromones are quite simple and effective. The target products are mainly obtained with good and sometimes quite high yields. The directed functionalization of 3-hetarylchromones by introducing pharmacophore groups, such as CF_3-, SO_2CH_3-, SO_2NH_2-, etc., as well as transforming into other heterocyclic systems, opens up wide possibilities for obtaining new substances, the spectrum of biological activity of which is significantly expanded and modified while maintaining a low toxicity level.

Due to the great importance of benzopyrones and thiophene in nature, medical chemistry and chemistry of materials, one hopes that the appearance of practically significant derivatives of 3-hetarylchromones with S-containing heterocycles is only a matter of time.

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