Isoflavonoids Modified with Oxygen-containing Heterocycles with One Oxygen Atom

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Keywords: *3-hetarylchromones*, *O-containing heterocycles, synthesis, chemical properties, biological activity.*

This review summarizes and systematizes the data available in the literature on the synthesis of 4*H*-chromen-4-ones modified at the 3-position with *O*-containing heterocycles with one oxygen atom. Classical and modern strategies for the synthesis of natural and synthetic 3-(*O*-containing)hetarylchromones, versatile synthons used in these syntheses and chemical modifications and transformations both on the chromone ring and heterocyclic rings of different sizes with one oxygen atom of the synthesized 3-hetarylchromones are discussed. Testing data for some types of biological activity including antitumor, antimicrobial, antiviral, hypolipidemic and cardial muscle activity of a number of 3-(*O*-containing)hetarylchromones and the products of their transformation are also given.

Introduction

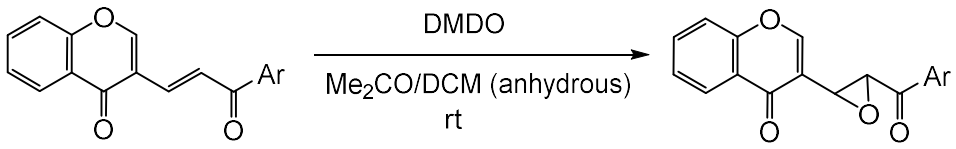
This comprehensive review covers the advances in the chemistry of polysubstituted 4*H*-chromen-4-ones modified at the 3-position of the chromone system with *O*-containing heterocycles, from the first publications in 1972 to 2024 inclusive.

The subsections of the review, structured by the size of the *O*-containing heterocycle, contain a wide range of synthetic strategies for the corresponding 3-(*O*-containing)hetarylchromones: classical and modern approaches, such as, advanced catalytic synthesis methods, environmentally friendly green chemistry approaches, multicomponent, cascade, photochemical reactions, reactions using microwave radiation, etc. (Un)substituted derivatives of 3-formyl-, 3-halo-, 3-alkynylchromone, 3-styrylchromones, benzopyranyl acrylates, 2-[3-(4-oxo-4*H*-methylene) 3-[3-(2-hydroxyaryl)-3-oxoprop-1-en-1-yl]chromones, 1-(2-hydroxyphenyl)butane-1,3-diones, α-hetaryl-2-hydroxyacetophenones, epoxides of heteroanalogues of chalcones, *o*-hydroxyarylene were used as precursors in the synthesis of 3-(*O*-containing)hetarylchromones, etc. Information on natural 3-(*O*-containing)hetarylchromones is also given in the framework of the subsections. The expansion of the structural diversity of the synthesized key 3-

(*O*-containing)hetarylchromones was facilitated by modifications and heterocyclizations carried out both on the chromone and heterocyclic fragments. For a better perception of the material, the data available in the literature on the biological activity of the described 3-(*O*-containing)hetarylchromones are given after their synthesis, and the chemical properties are described at the end of the subsections.

1. Synthesis of 3-(3-oxiran-2-yl)chromone derivatives

It is known from the literature that isolated dimethyldioxirane (DMDO) is the oxidant of choice for both the epoxidation of various chromone derivatives and α,β-unsaturated ketones. 3-(3-Oxo-3-arylpropenyl)chromen-4-ones (*E*)-**1a-h**, in whose structures both fragments of epoxidation are present, were investigated to determine which of the two electron-deficient olefinic double bonds undergoes epoxidation with dimethyldioxirane [1]. (*E*)-3-(3-oxo-3-arylpropenyl)chromen-4-ones **1a-h**, dissolved in anhydrous dichloromethane, react with isolated dimethyldioxirane (DMDO) at room temperature to form *trans*-epoxides **2a-h** as the only products detected and isolated in good yields (75-86%), which proves the fact of regioselective epoxidation of the α,β-unsaturated ketone fragment of these chromone derivatives (*E*)-**1a-h** (**Scheme 1**).



(*E*)-**1a-h** *trans*-**2a-h** (75-86 %)

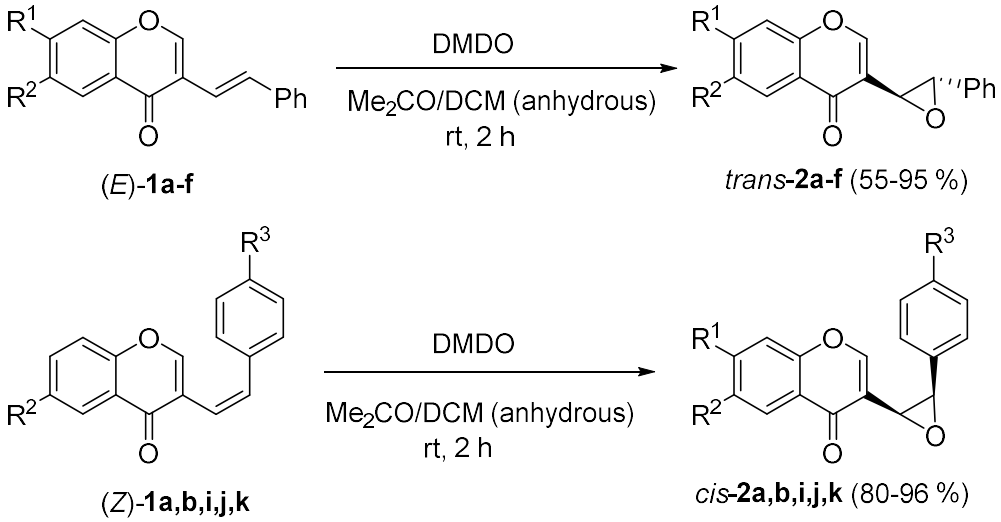
Ar= Ph (**a**), 4-MeC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**), 4-FC_6H_4 (**d**), 4-ClC_6H_4 (**e**), 4-BrC_6H_4 (**f**), 1-naphthyl (**g**), 2-naphthyl (**h**)

Scheme 1. The synthesis of *trans*-.3-(3-aroyloxiran-2-yl)chromones

Chromones with styryl groups in the 3-position represent a small and rare class of natural chromones. Some of these natural products and their synthetic analogues exhibit significant biological activity [2]. The existing methods for the synthesis of 3-styrylchromones, the microwave synthesis of (*E*)-3-styrylchromones from 3-formylchromones and phenylmalonic acid on a sodium acetate support, which proceeds without solvent in moderate to good yields and with complete diastereoselectivity, and the protocols for the epoxidation of (*E*)- and (*Z*)-3-styrylchromones, are discussed in detail in [3].

By treating solutions of styrylchromones (*E*)-**1a–f** in dichloromethane with 4 equiv. of dimethyldioxirane (DMDO) in acetone individual products (55–95%), were obtained and identified as *trans*-3-(3-phenyloxiran-2-yl)chromones - *trans*-**2a–f** with the yields of 55-

95% (**Scheme 2**). In all cases, the epoxidation occurred with complete regio- and diastereoselectivity.



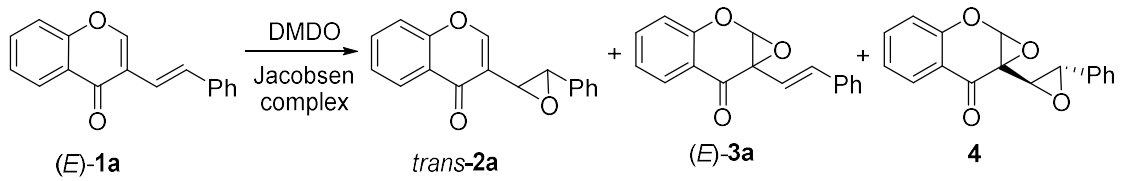
a R^1=R^2=R^3=H; **b** R^1=R^3=H, R^2=Me; **c** R^1=R^3=H, R^2=Me
d R^1=R^3=H, R^2=Cl; **e** R^1=R^3=H, R^2=Br; **f** R^1=Cl, R^3=H, R^2=R^3=H;
i R^1=R^2=H, R^3=OEt; **j** R^1=R^2=H, R^3=NO_2; k R^1=H, R^2=Me, R^3=Cl

Scheme 2. The synthesis of 3-(3-aryloxiran-2-yl)chromones

DMDO treatment of the substrates (*Z*)-**1a**, (*Z*)-**1b**, and (*Z*)-**1i–k** resulted in the formation of *cis*-3-(3-phenyloxiran-2-yl)chromones *cis*-**2a**, *cis*-**2b**, and *cis*-**2i–k** in excellent (80–96%) yields. Again, the epoxidation occurred with complete regio- and diastereoselectivity.

The relative configurations of the reported epoxides **2** were determined based on their $^3J_{2\text{-H},3\text{-H}}$ constants: values of 1.5–2.1 Hz were measured for the *trans* -isomers, whereas values of 3.9–4.3 Hz were found for the *cis*-isomers.

The DMDO/Jacobsen (salen) MnIII complex system for the epoxidation of (*E*)-3-styrylchromone - (*E*)-**1a** was also tested in [3]. Unfortunately, in this epoxidation variant, the regioselectivity observed upon treatment with DMDO in the absence of the MnIII complex was completely lost, and only a mixture of monoepoxides *trans*-**2a** and (*E*)-**3a** and two diastereomers of diepoxide **4a** were detected by ^{1}H NMR spectroscopy (**Scheme 3**). The ratio of the products depended on the amount of oxygen source used. An attempt to separate the epoxides by column chromatography on silica was unsuccessful due to the complexity of the mixtures and the lability of the diepoxides.



Scheme 3. Epoxidation of (*E*)-3-styrylchromone with the DMD/Jacobsen (salen) MnIII complex system

It should also be noted that a test epoxidation of 3-styrylchromone **1a** carried out with nucleophilic oxidizers (Weitz-Schaeffer epoxidation under basic conditions with hydrogen peroxide and sodium hydroxide in various solvents (acetone, methanol, 1,4-dioxane and [bmim]PF_4 ionic liquid) and Winberg epoxidation with hydrogen peroxide in the presence of quaternary ammonium salts based on cinchona tree as an phase-transfer catalyst (PTC)) proceeded with the formation of 2,3-epoxy-3-styrylchromones [3].

2. Derivatives of 3-(furyl)- and 3-(benzofuryl)chromones

Examples of 3-(2,3-dihydrofuran-2-yl)chromone and 3-(2,3-dihydrobenzofuran-2-yl)chromone derivatives isolated from plant material are described in the literature.

A new chromone derivative (*R*)-5-hydroxy-2-methoxy-3-(2,3-dihydro-2-methoxy-carbonyl-4-methyl-3-oxo-furan-2-yl)-4*H*-1-benzopyran-4-one (**5**) together with the known oxepino[2,3-*b*]chromones, microsphaeropsones A (**6**) and B (**7**) and xanthopinone (**8**) were isolated from the wood-decomposing fungus *Rhizina. s.p*. BCC 12292 (**Figure 1**). The conversion of compound **8** to compound **5** occurred when a solution of compound **8** in MeOH was treated with *p*-TsOH or silica gel, strongly suggesting that compound **5** may be an artifact formed during the processing of the extract [4].

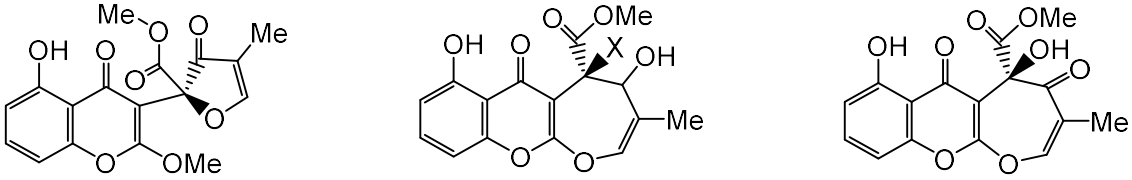


Figure 1. Compuunds **5-8**, isolated from the wood-decomposing fungus *Rhizina. s.p*. BCC 12292

Compound **5** exhibited moderate antimalarial activity against *Plasmodium falciparum* K1 with an IC_{50} of 5.1 μg/mL and cytotoxic activity against the NCI-H187 cancer cell line and non-malignant Vero cells with IC_{50} of 6.4 and 1.6 μg/mL, respectively, but was inactive against the KB and MCF-7 cancer cell lines. Tricyclic derivatives **6-8** were inactive in these assays. Compound **5** was also tested for anti-tuberculosis (*Mycobacterium tuberculosis*

H37Ra) and antifungal (*Candida albicans* and *Magnaporthe grisea* TH16) activities, but was inactive at a concentration of 50 μg/mL [4].

A number of prenylated flavonoids have been obtained from antigenotoxic extracts and fractions of the stem bark of *Erythrina latissima* E. Mey (Leguminosae) [5]. One of the compounds in this number was identified as 5,7-dihydroxy-3-(4-methoxy-2-(prop-1-en-2-yl)-2,3-dihydrobenzofuran-6-yl)-4*H*-chromen-4-one (**9**) and named erylatissin F (**Figure 2**).

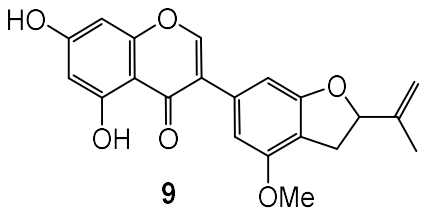


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Figure 2. The structure of erylatissin F

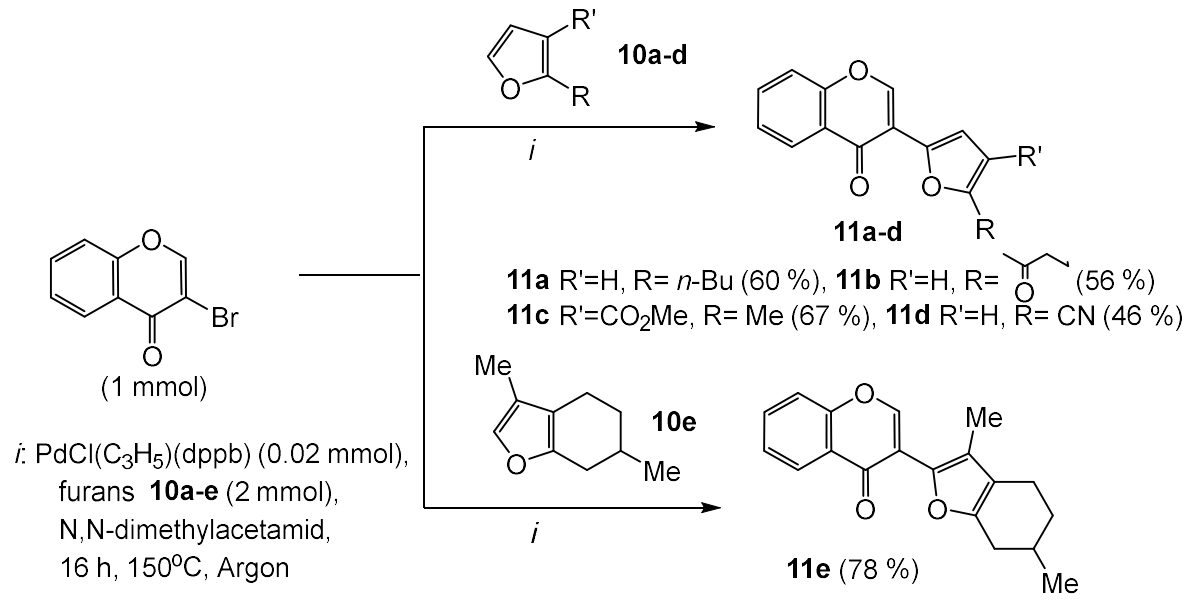
Evaluation of antigenotoxic properties (against genotoxicity induced by aflatoxin B1, metabolically activated) in the Vitotox assay showed that compound **9** has activity with an IC_{50} value of 68.7 μg/mL, compared to curcumin with an IC_{50} of 18.4 mg/mL, which was used as a reference antigenotoxic compound [5].

2.1. Synthesis of 3-(furyl/benzofuryl)chromones

The synthesis of 3-(furyl/benzofuryl)chromones was carried out both by adding a heterocycle to the chromone system and by building a chromone system by cyclization of precursor substrates.

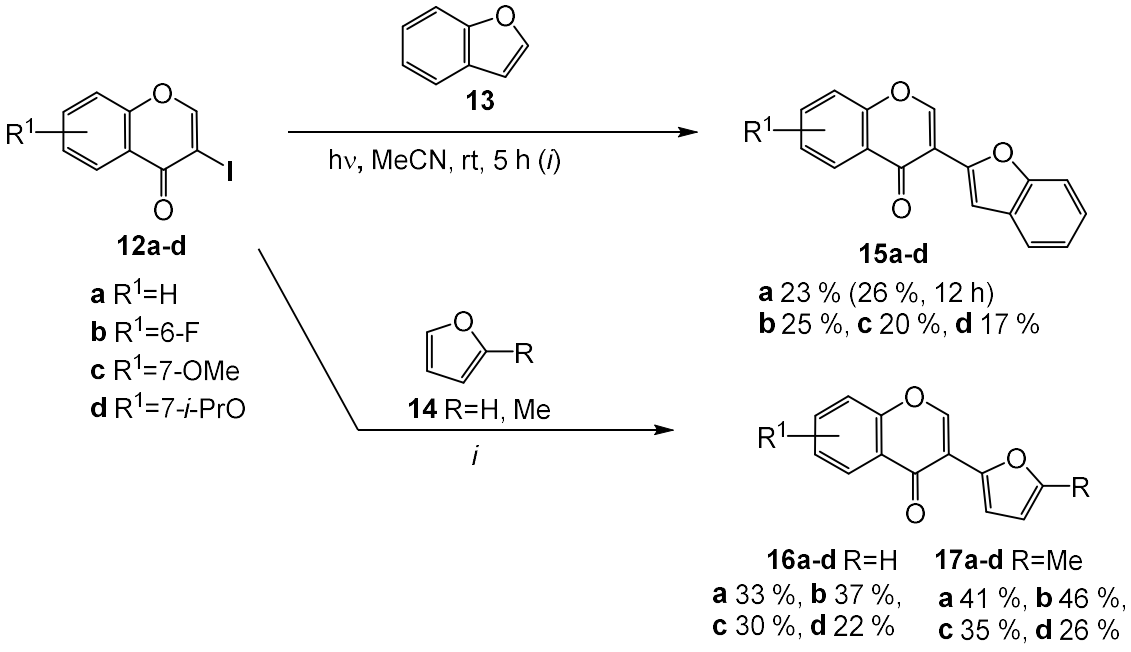
2.1.1. Synthesis by adding a heterocycle to the chromone system

The direct coupling reaction of furan derivatives **10a-d** and 3-bromochromone using 2 mol.% $PdCl(C_3H_5)$(dppb) (1,4-bis(diphenyl-phosphino)butane) as a catalyst and KOAc as a base afforded 3-furanylchromones **11a-d** (**Scheme 4**). Menthofuran **10e**, a natural product present in peppermint oil, was also found to be reactive for direct coupling with 3-bromochromone and the target chromone **11e** was obtained in 78% yield [6].



Scheme 4. The direct coupling of furans **10a-d** and 3-bromochromone

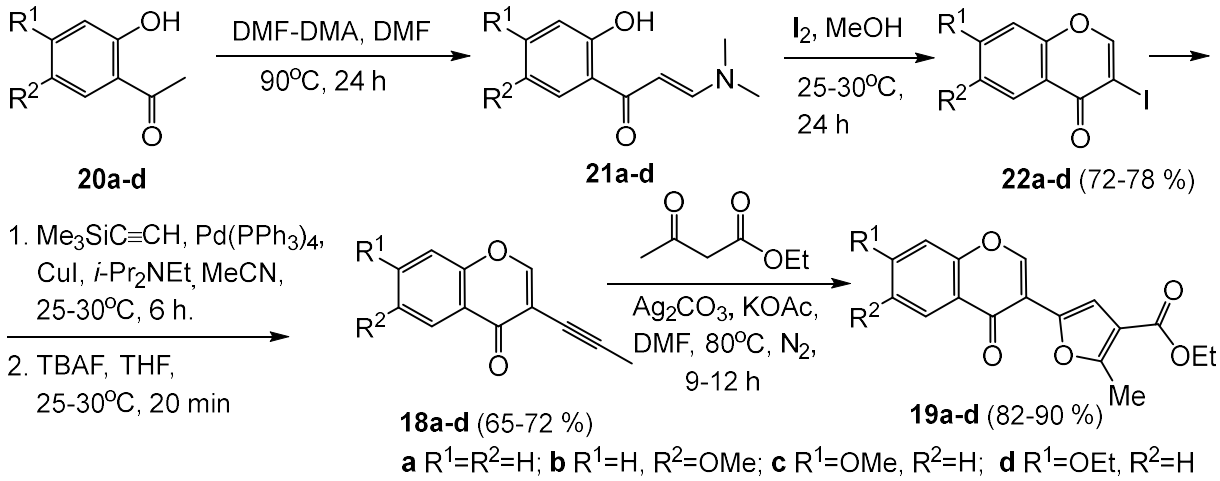
By direct coupling of (un)substituted 3-iodochromone **12a-d** with benzofuran (**13**) and furan derivatives **14** by photochemical reaction in acetonitrile under a high-pressure mercury lamp without any catalysts and bases, 3-(benzofuran-2-yl)chromones **15a-d** and 3-(furan-2-yl)chromones **16a-d** and **17a–d** were obtained (**Scheme 5**) [7, 8]



Scheme 5. The direct coupling of (benzo)furans and 3-iodochromones via photochemical reaction

Silver-mediated oxidative C–H/C–H functionalization of the *sp*-hybridized carbon of the acetylene moiety in chromones and the sp^3-hybridized carbon in ethyl acetoacetate was carried out on 3-ethynylchromones **18a–d** using ethyl acetoacetate in the presence of silver

carbonate and potassium acetate in DMF to synthesize new 3-furanochromones **19a–d** (**Scheme 6**).



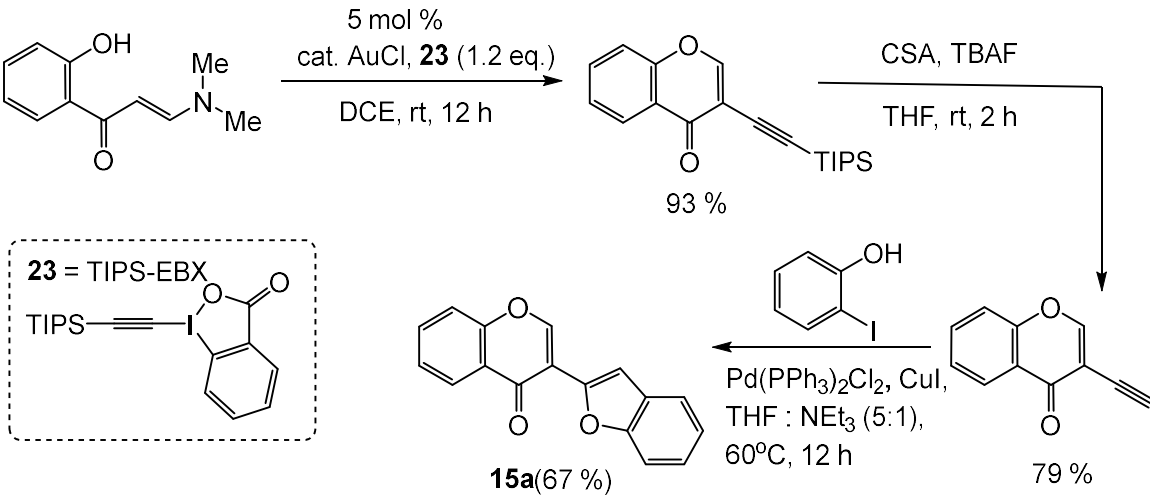
Scheme 6. Silver-mediated synthesis of 3-furanochromones based on 3-ethynylchromones

The synthesis of 3-ethynylchromones **18a–d**, in turn, was carried out from the corresponding 2-hydroxyacetophenones **20a–d** in four steps. Thus, the reaction of hydroxyacetophenones **20a–d** with N,N-dimethylformamide dimethyl acetal (DMF-DMA) in DMF led to the formation of 3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-ones **21a–d** in 89–92% yield, which, when reacted with iodine in methanol, gave 3-iodochromones **22a–d** in 72–78% yield. The Sonogashira reaction of 3-iodochromones **22a–d** with trimethylsilylacetylene followed by desilylation of the resulting 3-trimethylsilylethynylchromones led to the formation of 3-ethynylchromones **18a–d** [9].

The synthesized furanochromones **19a-d** were evaluated for antituberculosis activity against the susceptible H37Rv strain of *M. tuberculosis* by measuring their ability to inhibit the growth of the virulent strain. The minimum inhibitory concentrations (MICs) of the test compounds and the first-line drugs, ethambutol and streptomycin, taken as reference standards, were determined using the Alamar Blue (MABA) microplate assay. Compounds **19a-d** were found to be moderate antituberculosis agents with MICs in the range of 10 to 12 μg/mL (ethambutol MIC 0.25-2 μg/mL and streptomycin MIC 2 μg/mL).

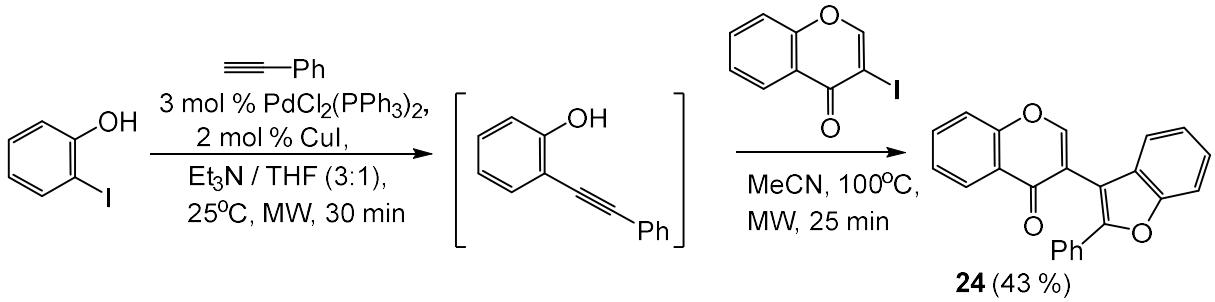
The synthesis of 3-(benzofuran-2-yl)chromone **15a** was also realized by the Sonogashira reaction/intramolecular hydroalkoxylation of 3-ethynylchromone, obtained, in turn, by gold-catalyzed hypervalent iodine reagent **23** (I-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX)) alkynylation/cyclization of *o*-hydroxyaryl-enaminones with subsequent deprotection of the TIPS group using a combination of TBAF

(Tetrabutylammonium fluoride) and camphorsulfonic acid (CSA) (**Scheme 7**) [10].



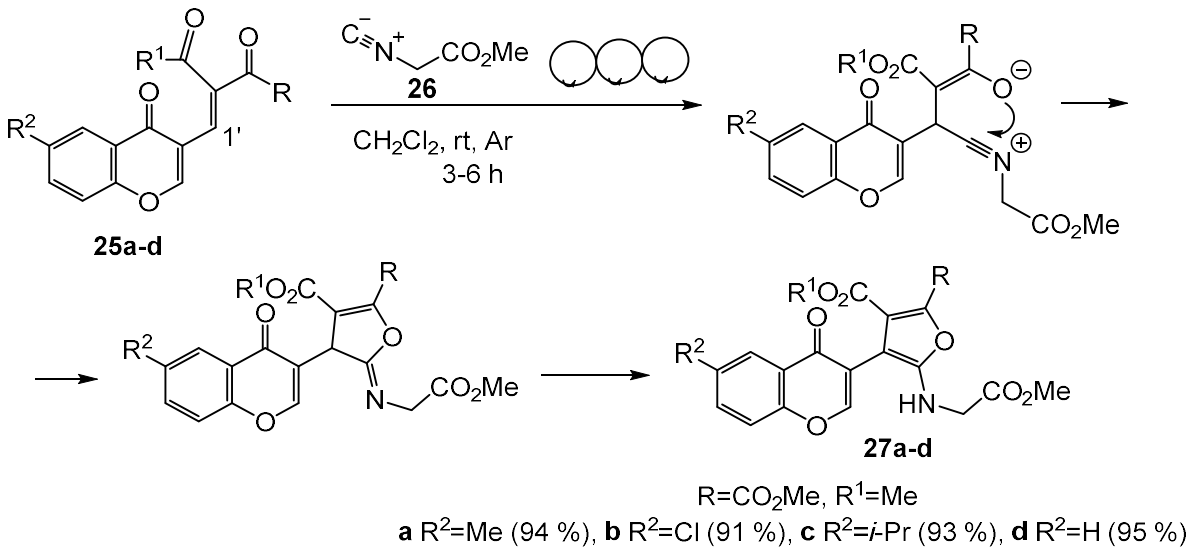
Scheme 7. The synthesis of 3-(benzofuran-2-yl)chromone **15a** by the Sonogashira reaction/intramolecular hydroalkoxylation of 3-ethynylchromone

Using the Sonogashira reaction conditions, an efficient one-pot method was developed for the synthesis of 2,3-disubstituted benzo[*b*]furans from commercially available 2-iodophenols, terminal acetylenes, and aryl iodides. After the initial Sonogashira coupling of the 2-iodophenol with a terminal alkyne, cyclization with the aryl iodide/(3-I-chromone) affords the 2,3-disubstituted benzo[*b*]furan. The use of microwave irradiation shortens the reaction time and minimizes by-products. This methodology has also been shown to be useful for the synthesis of 3-(2-phenylbenzofuran-3-yl)chromone (**24**) (**Scheme 8**) [11].



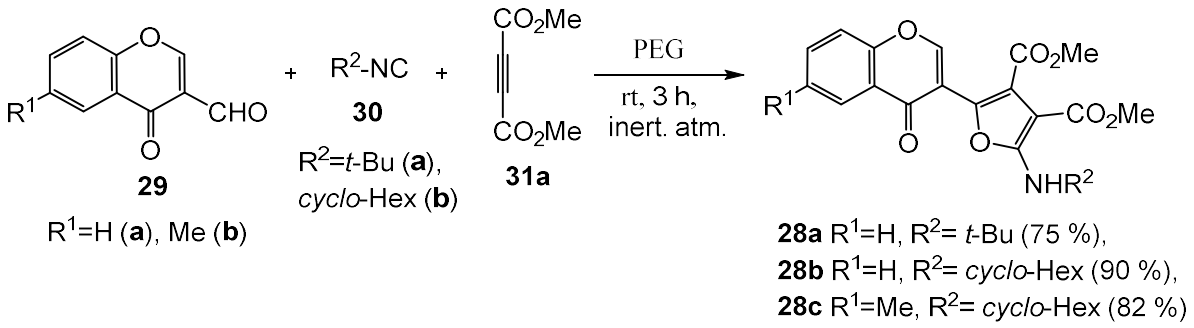
Scheme 8. The synthesis of 3-(2-phenylbenzofuran-3-yl)chromone (**24**) by the Sonogashira coupling

According to the "branched cascade" strategy, treatment of ketoester substrate **25** (1 mmol) with methyl isocyanoacetate zwitterion **26** (1.1 mmol) in dichloromethane under argon affords substituted 3-(furan-3-yl)-4*H*-chromen-4-ones **27a-d** in 91-95% yields within 3-6 hours (**Scheme 9**). According to the authors, the initial addition of zwitterion **26** to C1' of substrate **25** leads to the formation of an oxanion, which adds to the nearest iminium cation to give the product, the isomerization/aromatization of which provides the final product **27** [12].

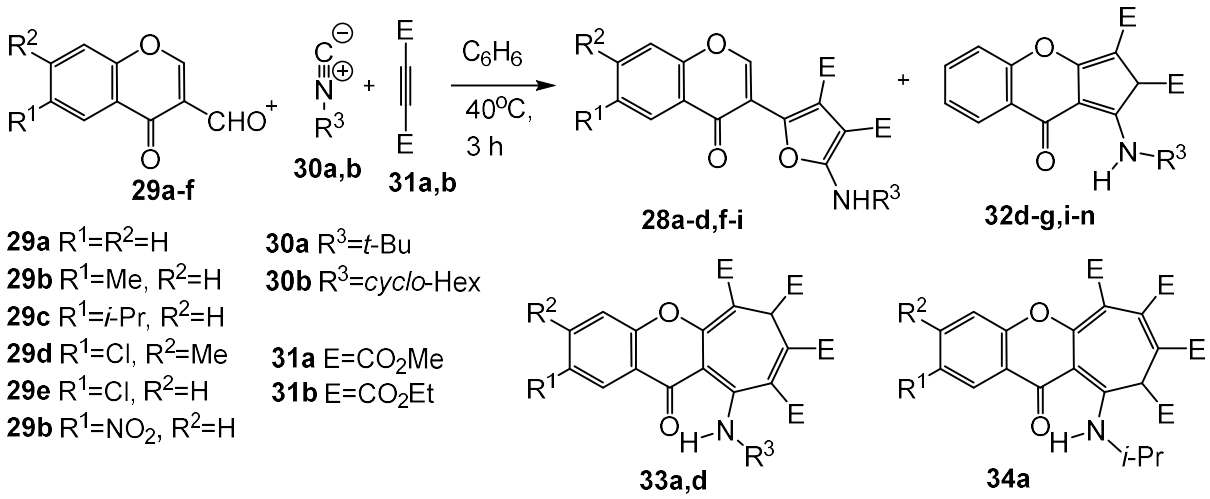


Scheme 9. The synthesis of 3-(furan-3-yl)-4*H*-chromen-4-ones **27a-d** via the "branched cascade" strategy

A rapid and highly productive method for the synthesis of 3-(furan-2-yl)chromones **28** via the three-component reaction of 3-formylchromones **29a-b** with zwitterionic intermediates formed *in situ* from *tert*-butylisocyanide **30a** or cyclohexylisocyanide **30b** and dimethylacetylenedicarboxylate **31a** in a polyethylene glycol (PEG 400) solvent at room temperature in an inert atmosphere is described in [13] (**Scheme 10**).



Scheme 10. The reaction of 3-formylchromones with isocyanides and dimethylacetylenedicarboxylate in PEG



Scheme 11. The reaction of 3-formylchromones with isocyanides and dimethylacetylenedicarboxylate in benzene

In benzene, this three-component reaction proceeds non-selectively (**Scheme 11**) [14]. Depending on the substituents in 3-formylchromones, isocyanides and dialkylacetylenedicarboxylates, the ratio of reactants, the amount of solvent and the temperature regime, the reaction product is a mono-product - derivatives of 3-(furan-2-yl)chromones **28** or derivatives of cyclopentachromendicarboxylates **32**; two-component mixtures of derivatives of 3-(furan-2-yl)chromones **28** with cyclohepta-chromentetracarboxylates **33** or with cyclopentachromendicarboxylates **32**; or three-component mixtures of derivatives **28**, **32** and **33**, or **28**, **33** and **34** (**Table 1**). The reactions were carried out at a ratio of reactants **29**:**30**:**31**=1:1.2:1.2. The use of 2 molar amounts of DMAD (Dimethyl acetylenedicarboxylate) did not facilitate the reaction, which became unclear and complex, most likely as a result of the prolonged polymerization of DMAD and the formation of many minor products.

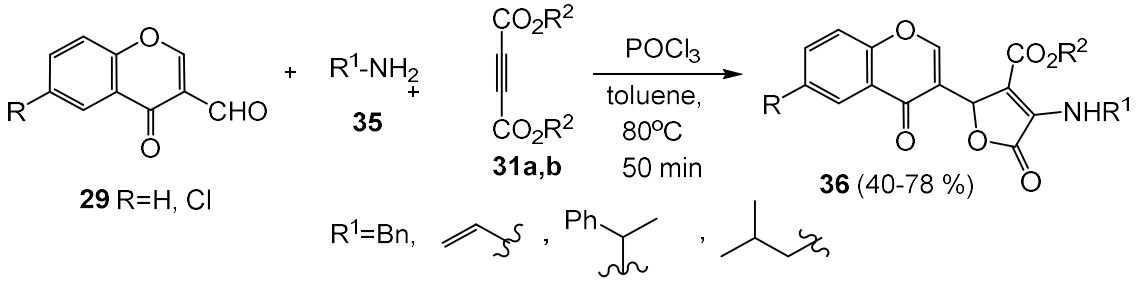
Table 1. Products of the three-component reaction when carried out in benzene

№	**29**	**30**	**31**	Product	T°C	**28** (%)	**32** (%)	**33** (%)	**34** (%)
1	**29a**	**30a**	**31a**	**a**	40	42		`12	
2	**29a**	**30a**	**31a**	**a**	40	6*		51*	5*
3	**29b**	**30a**	**31a**	**b**	40 55	28 35			
4	**29c**	**30a**	**31a**	**c**	40	45			
5	**29d**	**30a**	**31a**	**d**	40	16	31	7	
6	**29e**	**30a**	**31a**	**e**	40		52		
7	**29f**	**30a**	**31a**	**f**	40	4	38		

					55	9	43		
8	**29a**	**30b**	**31a**	**g**	40	27	44		
9	**29c**	**30b**	**31a**	**h**	40	48			
10	**29e**	**30b**	**31a**	**i**	40 55	3	48 46		
11	**29a**	**30a**	**31b**	**j**	40		48		
12	**29c**	**30a**	**31b**	**k**	40 55		38 32		
13	**29e**	**30a**	**31b**	**l**	40		60		
14	**29a**	**30b**	**31b**	**m**	55		48		
15	**29b**	**30b**	**31b**	**n**	40		47		

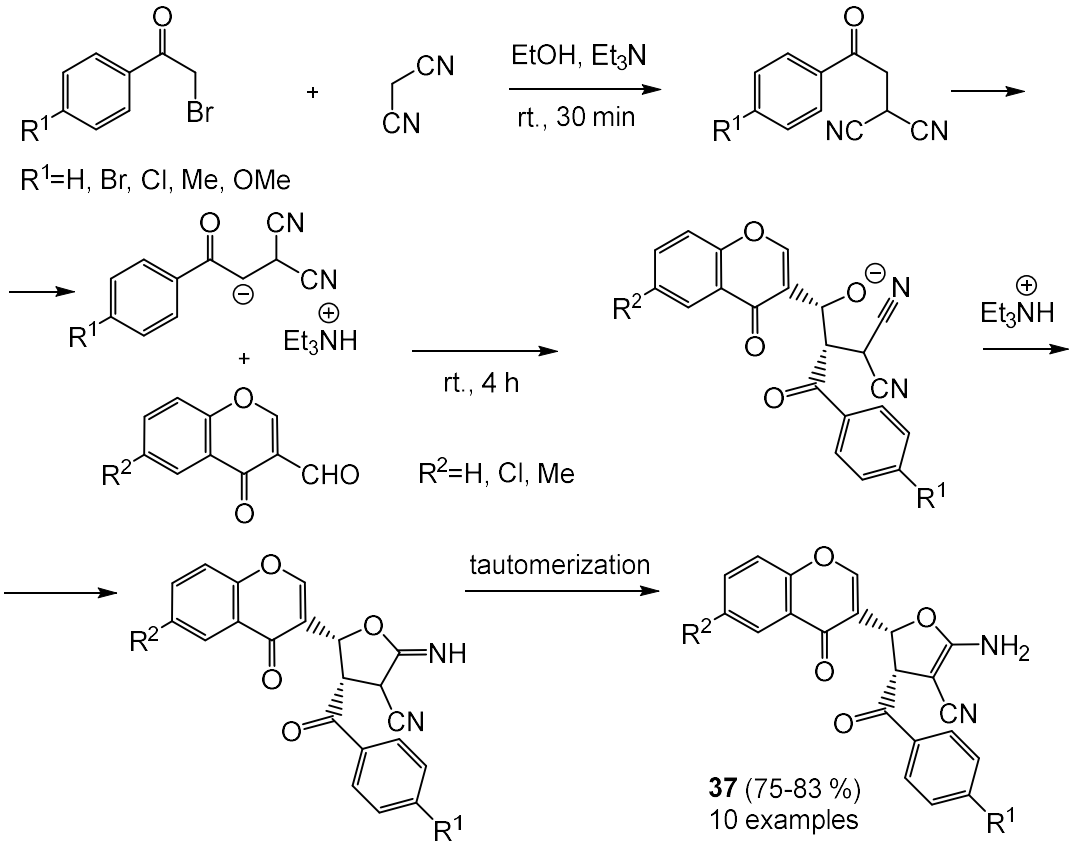
* in 5 ml of C_6H_6

The three-component reaction of 3-formylchromones **29**, dialkylacetylene-dicarboxylate **31**, and primary amines **35**, carried out in toluene at room temperature in the presence of phosphorus oxychloride, represents a highly efficient and practical approach for the synthesis of 3-amino-5-chromenylbutenolides **36** (**Scheme 12**) [15]. This transformation involves the initial reaction of primary amines with dialkylacetylenedicarboxylate to form the enaminone, which is then added to the activated form of 3-formylchromone by nucleophilic addition. Further cyclization of the intermediate, elimination of the alkoxy group and finally tautomerization lead to the desired alkyl 4-(allylamino)-2,5-dihydro-5-oxo-2-(4-oxo-4*H*-chromen-3-yl)furan-3-carboxylates **36**. The authors suggest that phosphorus oxychloride plays an essential role in the addition of the enaminone to 3-formylchromone by activating the lone pairs of carbonyl oxygen, facilitating the removal of the alkoxy group, as well as cyclization to obtain the lactone moiety, and the participation of the neighboring phosphorus group plays an effective role in this transformation.



Scheme 12. The three-component reaction of 3-formylchromones, dialkylacetylenedicarboxylates and primary amines

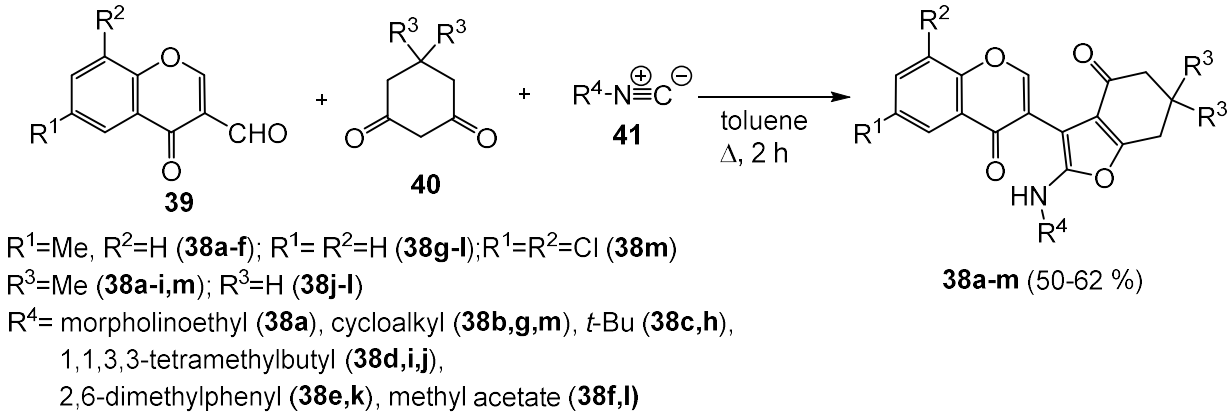
A number of highly functional 2-amino-4,5-dihydrofuran-3-carbonitrile derivatives **37** were synthesized using a rapid diastereoselective sequential three-component one-pot reaction of phenacyl bromide, malononitrile, and (un)substituted 3-formylchromone (**Scheme 13**).



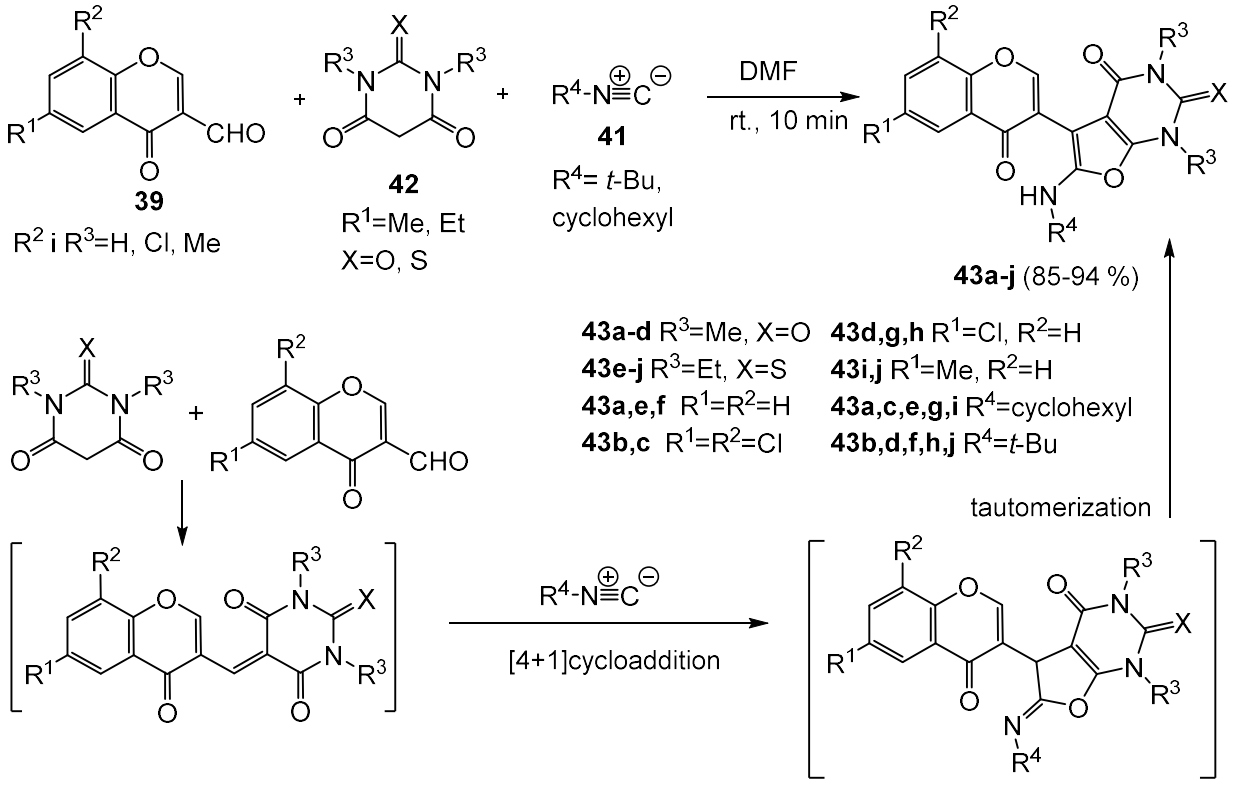
Scheme 13. The three-component reaction of phenacyl bromides, malononitrile and 3-formylchromones

Isocyanide-induced multicomponent reactions have become an important tool for the synthesis of complex molecules.

The novel tetrahydrobenzofuran-chromone conjugates **38a-m** were obtained by a one-pot three-component synthesis using 3-formylchromones **39** and 1,3-cyclohexanediones **40** in the presence of various alkyl or aryl isocyanides **41** (**Scheme 14**). The reaction sequence consists of an initial Knoevenagel condensation of 3-formylchromones with 1,3-cyclohexanedione derivatives, followed by a [4+1] cycloaddition with isocyanides and subsequent imino-enamine tautomerization [17].



Scheme 14. The three-component reaction of 3-formylchromones with 1,3-cyclohexanediones and isocyanides

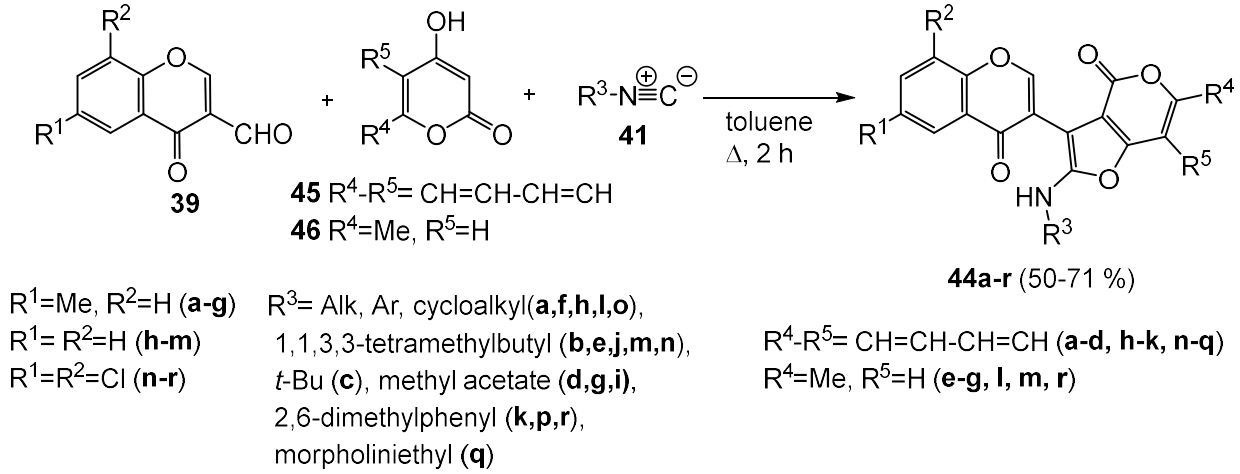


Scheme 15. The three-component reaction of 3-formylchromones with alkylisocyanides and barbituric acids

One-pot three-component reactions involving 3-formylchromones **39**, alkylisocyanides **41**, and 1,3-disubstituted barbituric acid derivatives **42** proceed smoothly at room temperature in DMF within 10 min to afford the corresponding chromone-containing furopyrimidine derivatives **43a–j** in good yields (**Scheme 15**). This three-component reaction represents a facile and efficient route to furo[2,3-*d*]pyrimidine derivatives, which have become synthetic targets for many organic and medicinal chemists. During the formation of the fused furopyrimidine ring, three bonds (C=C, C–C, and C–O bonds) are newly formed [18].

A series of furopyranone and furocoumarin-chromone conjugates **44a-r** were

successfully synthesized by one-pot three-component condensation reactions of 3-formylchromone derivatives **39**, CH-acids (4-hydroxycoumarin **45** or 4-hydroxy-6-methylpyrone **46**) and alkyl or aryl isocyanides **41** under reflux in toluene for 2 h (**Scheme 16**) [19].

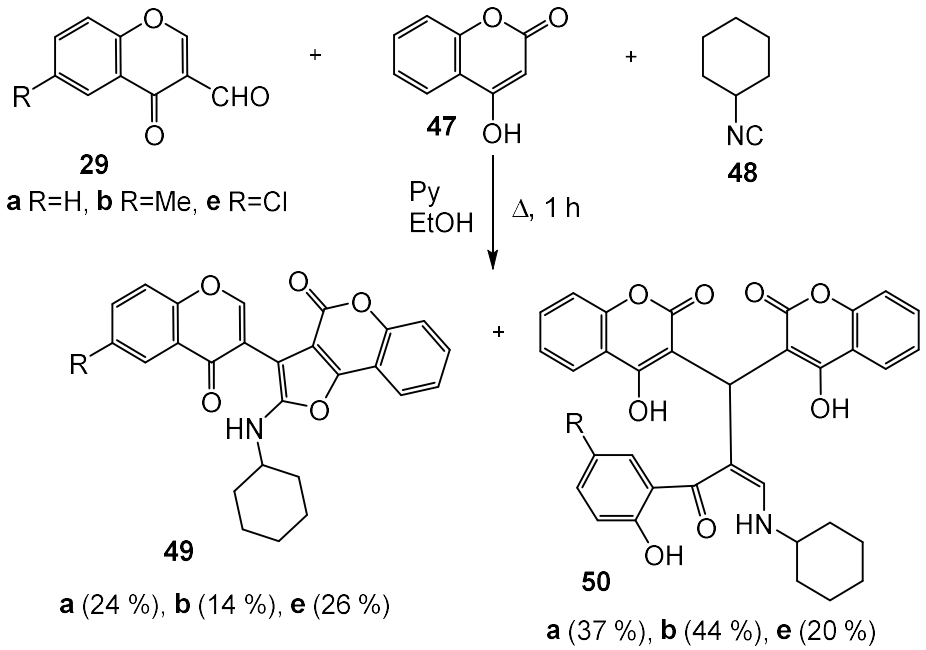


Scheme 16. The three-component reaction of 3-formylchromones with isocyanides and 4-hydroxy(benzo)pyran-2-ones

Molecular docking studies of cyclooxygenase enzymes (COX-1, COX-2) showed that most of the derivatives **44a-r** have higher or moderate binding affinity than 3-formylchromone, which was used as a reference compound. In general, all the new products form one to three hydrogen bonds with amino acid residues in the active site of both enzymes. In addition, the cytotoxic activity of some selected compounds was investigated against human foreskin fibroblast (BJ) cells and human breast cancer cells (MDA-MB-231) using the MTT assay. All the isolated compounds were found to be more active than 3-formylchromone against cancer cells and showed low toxicity towards normal cells. The activity of the compounds according to their IC_{50} is as follows: **44k**: 2.56 $\mu g.mL^{-1}$ > **44i**: 2.72 $\mu g.mL^{-1}$ > **44p:** 3.05 $\mu g.mL^{-1}$ > **44q**: 6.12 $\mu g.mL^{-1}$ > **44h**: 11.44 $\mu g.mL^{-1}$ > 3-formylchromone: 25.50 $\mu g.mL^{-1}$. Thus, compounds **44k** and **44i** with a slight difference ($p \geq 0.05$) were found to be the most active compounds against cancer cells. At a concentration of 30 $\mu g.mL^{-1}$, almost 90% of cancer cells were inhibited by the new derivatives. All selected compounds were found to be less harmful to normal cells (BJ, human foreskin fibroblast), and approximately 85% of BJ cells survived at the tested concentrations of all samples.

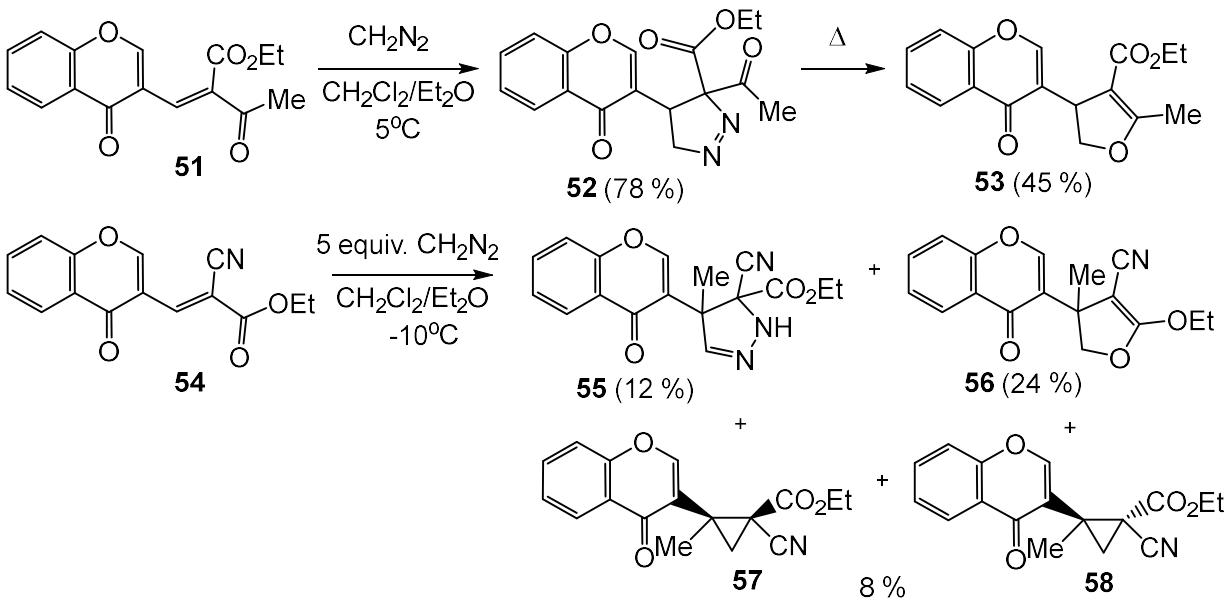
Three-component reactions involving chromone-3-carbaldehydes **29a,b,e**, 4-hydroxycoumarin **47** and cyclohexyl isocyanide **48**, which took place under heating in ethanol containing a catalytic amount of pyridine, within 1 h resulted in the formation of the expected

chromone-linked furocoumarins **49a,b,e** together with the unexpected products **50a,b,e**, which were biscoumarin derivatives (**Scheme 17**). In the formation of products **50**, cyclohexyl isocyanide acted as a disguised source of cyclohexylamine [20].



Scheme 17. Products of the three-component reaction of 3-formylchromones with 4-hydroxycoumarin and cyclohexyl isocyanide

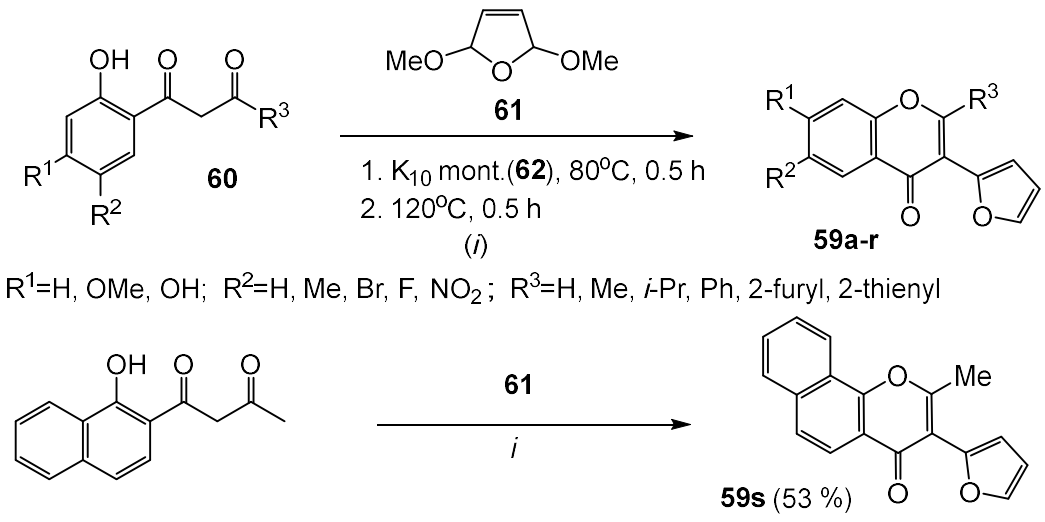
Addition of CH_2N_2 to the double bond of benzopyranyl acrylates **51** leads to 3-pyrazolinylchromone **52**, which upon heating gives 3-dihydrofuranylchromone **53**. Reaction of benzopyranyl acrylate **54** with diazomethane leads to 3-pyrazolinylchromone **55**, 3-dihydrofuranylchromone **56**, and a mixture of isomeric benzopyranylcyclopropane derivatives **57** and **58** (**Sheme 18**) [21, 22].



Scheme 18. Products of the reaction of benzopyranyl acrylates with diazomethane

2.1.2. Synthesis by cyclization into the chromone system

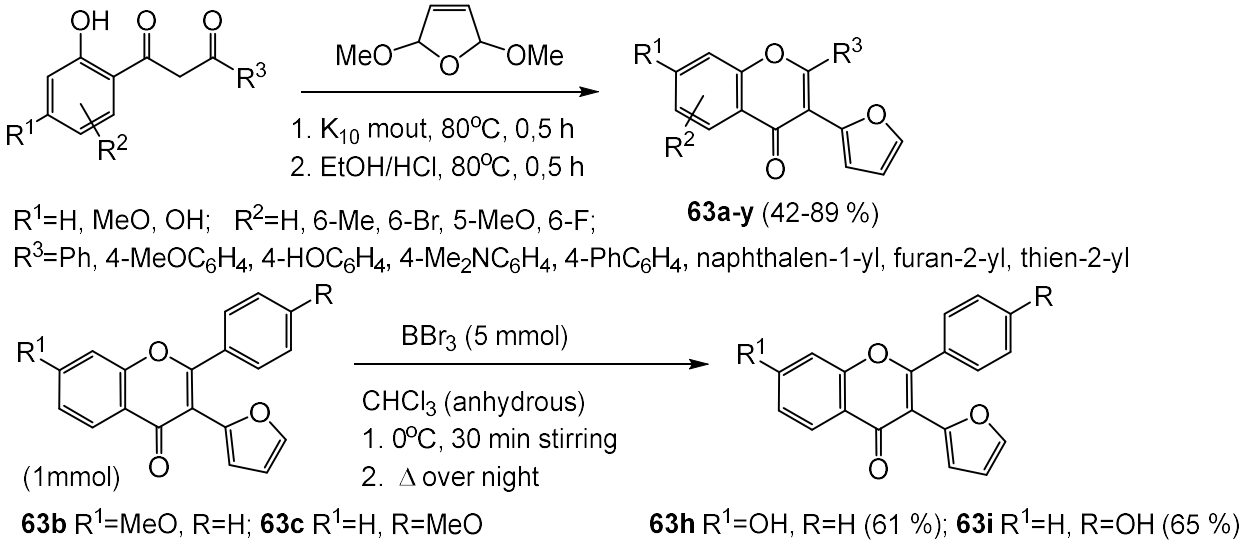
The method for the synthesis of 3-(furan-2-yl)chromones **59a-r** by the reaction of 1-(2-hydroxyphenyl)-3-R^3-propane-1,3-diones **60** and 2,5-dimethoxy-2,5-dihydrofuran (**61**) catalyzed by montmorillonite K10 (**62**) was patented [23] and described in [24]. According to the protocol [24], the reaction proceeds under the conditions indicated in **Scheme 19** without solvents, with a reactant ratio of **60**:**61**:**62** = 1:1.5:1. 3-(Furan-2-yl)-2-methyl-4*H*-benzo[*h*]chromen-4-one **59s** was also synthesized by this method in 53% yield.



Scheme 19. The synthesis of 3-(furan-2-yl)chromones by the reaction of 1-(2-hydroxyphenyl)butane-1,3-diones and 2,5-dimethoxy-2,5-dihydrofuran

It should be noted that the yield of the reaction significantly depends on the substituents in the 2-position of the chromone system. Thus, the yield of compounds **59a-f** with R^3= CH_3 and **59g-j** with R^3=*i*-Pr is 64-89%. Compounds **59n-q** with R^3=H (26-29%) and **59q,r** with R^2= NO_2 (26-27%) were synthesized with low yields. The authors explained this result using the example of the reaction of 3-(2-hydroxyphenyl)-3-oxopropanal (**60n**), in which, together with the desired 3-(furan-2-yl)chromone (**59n**), 4*H*-chromen-4-one (45%) was obtained as a by-product of the synthesis in a yield of 27%. The formation of this by-product occurred due to the property of 3-(2-hydroxyphenyl)-3-oxopropanal (**60n**) to easily isomerize to the hemiacetal tautomer, which, in the presence of montmorillonite K10 as a catalyst at 80°C, was transformed into a dehydration product. Compounds **59k-m** with R^3=Ph, 2-furyl and 2-thienyl were synthesized in low yields - 34%, 25% and 23%, respectively. However, for 2-phenyl/(2-furyl)/(2-thienyl)-3-(furan-2-yl)-chromones **59k-m** the yield can be significantly increased to 89%, 68% and 80%, respectively, if instead of heating at 120°C for 0.5 h, boiling in alcohol with concentrated hydrochloric acid (30 μL) is carried out.

The patented 3-(furan-2-yl)chromones **59a-r** are compounds with pesticidal activity against plant epiphytes, such as fungi causing apple rot, tomato gray mold, potato tuber dry rot, etc. The test results indicate that 2-methyl-3-(furan-2-yl)-7-hydroxychromone, 2-methyl-3-(furan-2-yl)-6-fluorochromone and 3-(furan-2-yl)chromone provide the effect of obvious resistance to plant epiphytes, with 2-methyl-3-(furan-2-yl)-6-fluorochromone showing the best activity [23].



Scheme 20. The synthesis of a new series of 2,3-di(hetero)arylchromen-4-ones **63a-y**

A new series of 2,3-di(hetero)arylchromen-4-ones **63a-y** was synthesized using a modified protocol according to **Scheme 20** [25]. Compounds **63h** and **63i** were obtained by demethylation of methoxy groups in compounds **63b** and **63c**.

Derivatives of α-hetaryl-2-hydroxyacetophenones can also serve as starting products for the synthesis of 3-furyl/benzofurylchromones. The methods for obtaining 3-hetarylchromones from α-hetaryl-2-hydroxyacetophenone derivatives using various formylating and acylating agents are based on the principle of C-formylation/acylation on the methylene group of α-hetaryl-2-hydroxyacetophenone derivatives followed by their cyclization. For functionalized furan and benzofuran nuclei in 3-furyl/benzofurylchromones, the following letter designations are adopted (**Figure 3**):

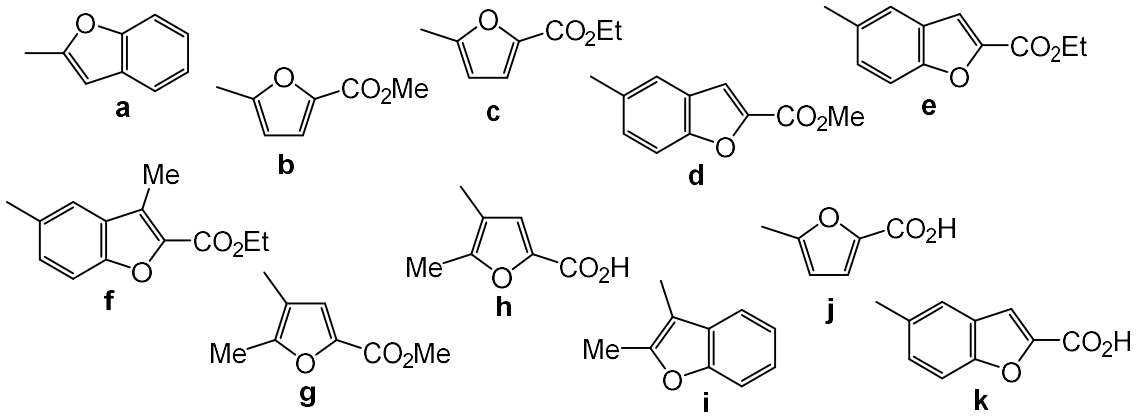


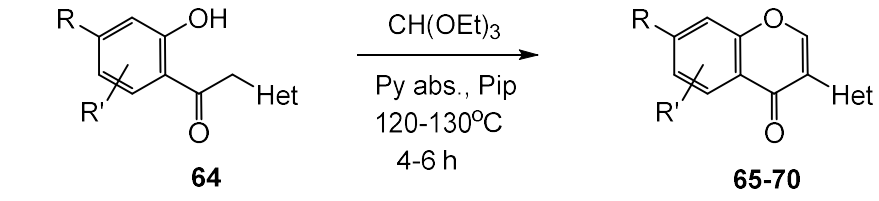
Figure 3. Letter designation, adopted for the functionalized furan and benzofuran nuclei in 3-(benzo)furylchromones

The Venkataraman method, often referred to as the ethyl orthoformate method (Method A, **Scheme 21**), is recognized as a general method for the synthesis of 3-furyl/benzofurylchromones lacking substituents in position 2 of the pyrone ring by cyclization of hetarylmethylketones **64**. According to this method, terminal 3-furyl/benzofurylchromones **65-70** are formed by heating α-hetaryl-2-hydroxyacetophenone derivatives **64** with ethyl orthoformate in pyridine in the presence of catalytic amounts of piperidine at 120-130°C for 4-6 hours [26-33]. The starting α-hetaryl-2-hydroxyacetophenones **64** were obtained by condensation of (poly)phenols with furylacetonitriles and benzofurylacetonitriles in a medium of dry benzene and ether in the presence of zinc chloride.

The preparation of 7-hydroxy-3-furylchromone **66h** took place during the acylation of 7-hydroxy-3-furylchromone **66g** followed by deacylation, which indicates the process of simultaneous hydrolysis of the 7-AcO group and the ester group of the heterocycle during the deacylation [30].

An attempt to obtain benzofuran and furan analogues of natural isoflavones by demethylation of 7-methoxy groups in 7-

methoxy-3-furyl/benzofurylchromones **69a,b,d** by boiling them with pyridine hydrochloride at 170-180°C for 8 hours was successful only for the conversion of **69a** into **66a** with a yield of 56% [27, 28].



64

R=H, OH, Me, OMe
R'=H, 5-Et, 6-OH, 6-Me

65-70

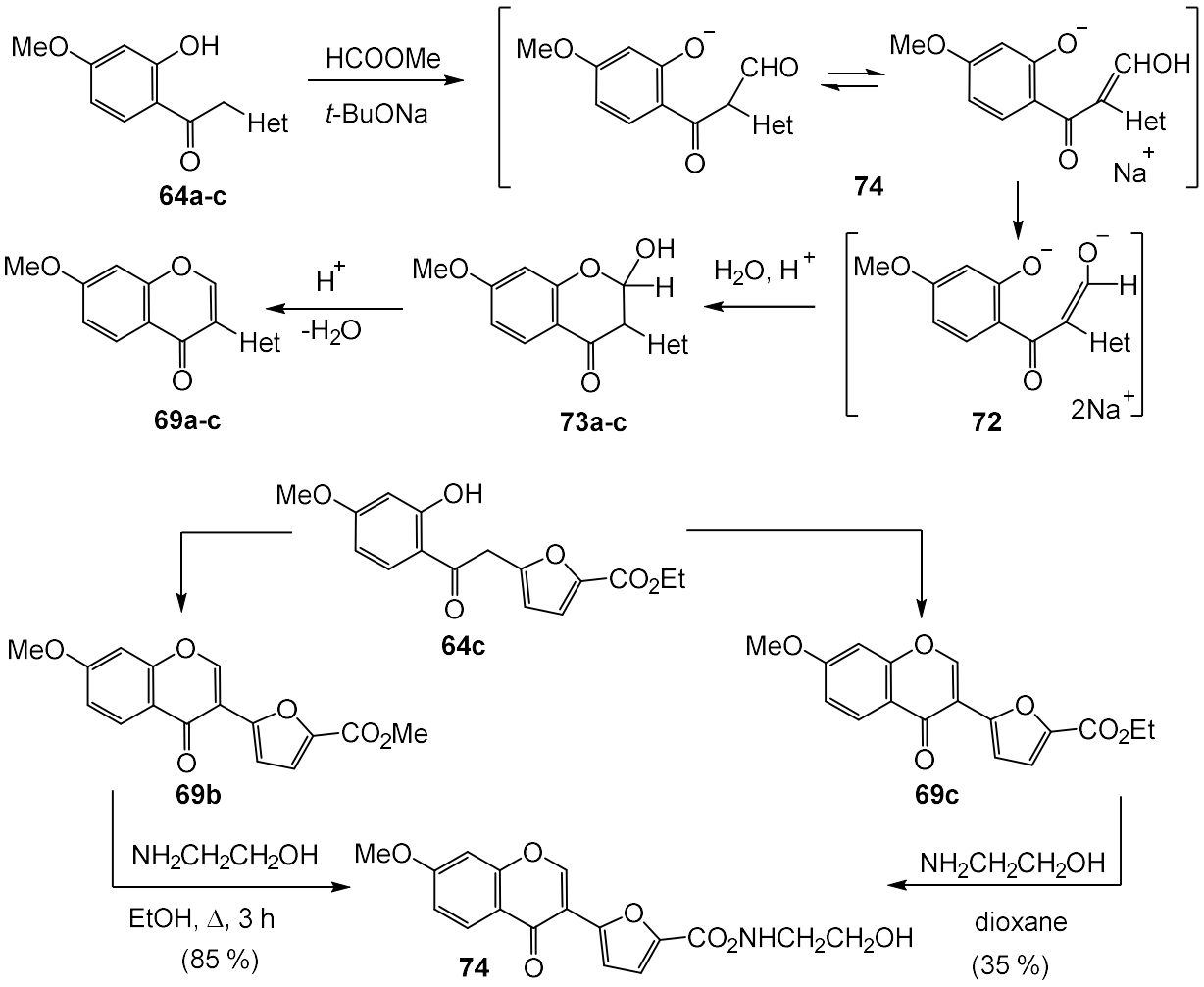
65a (R=R'=H) (52 %) [26]
66 (R=OH, R'=H) : **66a** (95 %), **66b** (92 %),**66c** (77 %), **66d** (86 %), **66e** (90 %) [27, 28], **66f** (98 %) [29],**66g** (74 %) [30] $\xrightarrow{Ac_2O}$ $\xrightarrow{H^+}$ **66h** (80 %) [30]
67 (R=OH, R'=6-Et) : **67a** (94 %) [31], **67c** (98 %) [32]
68c (R=OH, R'=5-Me) (70 %) [33], **68'c** (R=Me, R'=5-OH) (23 %) [33]
69 (R=OMe, R'=H) : **69a** (75 %), **69b** (58 %), **69d** (85 %) [27, 28], **69f** (97 %) [29]
70 (R=OMe, R'=6-Et) : **70a** (60 %) [30], **70c** (73 %) [32]

Scheme 21. The synthesis of 3-furyl/benzofurylchromones by the Venkataraman method

Another approach to obtaining furan and benzofuran analogues of isoflavones with a protected 7-OH group (**69a-e**) consists in the interaction of α-hetaryl-2-hydroxy-4-methoxyacetophenones **64a-e** (R=OMe, R^1=H) with excess methyl formate in the presence of sodium *tert*-butylate at 35-40°C by the Claisen condensation type (Method B, **Scheme 22**) [27, 28]. Moreover, the mixing of the reagents was carried out at 0-3°C, after which the temperature of the reaction mixture was gradually brought to 35-40°C and maintained there for 4-8 hours. The compounds **71**, **72** formed in the first stage were converted by treatment with an acidic buffer (pH 0.5-1) into 3-hetarylchromones **69** with impurities of 2-hydroxy-3-hetarylchromanones **73**. The latter were easily dehydrated into 3-hetarylchromones **69** upon heating the reaction mixture with alcoholic hydrochloric acid. In the case of the formation of 3-hetarylchromones **69a,b**, the impurities of 2-hydroxychromanones were insignificant. On the contrary, during the closure of ketone **64e**, the intermediate compound **73e** was present in larger quantities.

During the interaction of ketones **64c,e** (R=OMe, R^1=H) with methyl formate, transesterification of ester groups occurred parallel to the formation of the chromone system, as a result of which 3-hetarylchromones with melting points identical to the melting points of compounds **69b** and **69d** were isolated. Evidence of the observed transesterification was also provided by the fact that α-(5-ethoxycarbonyl-2-furyl)-2-hydroxy-4-methoxyacetophenone (**64c**) was transformed into chromone **69c** upon interaction with ethyl formate under similar conditions. The latter, like chromone **69b**, obtained from ketone **64c** and methyl formate,

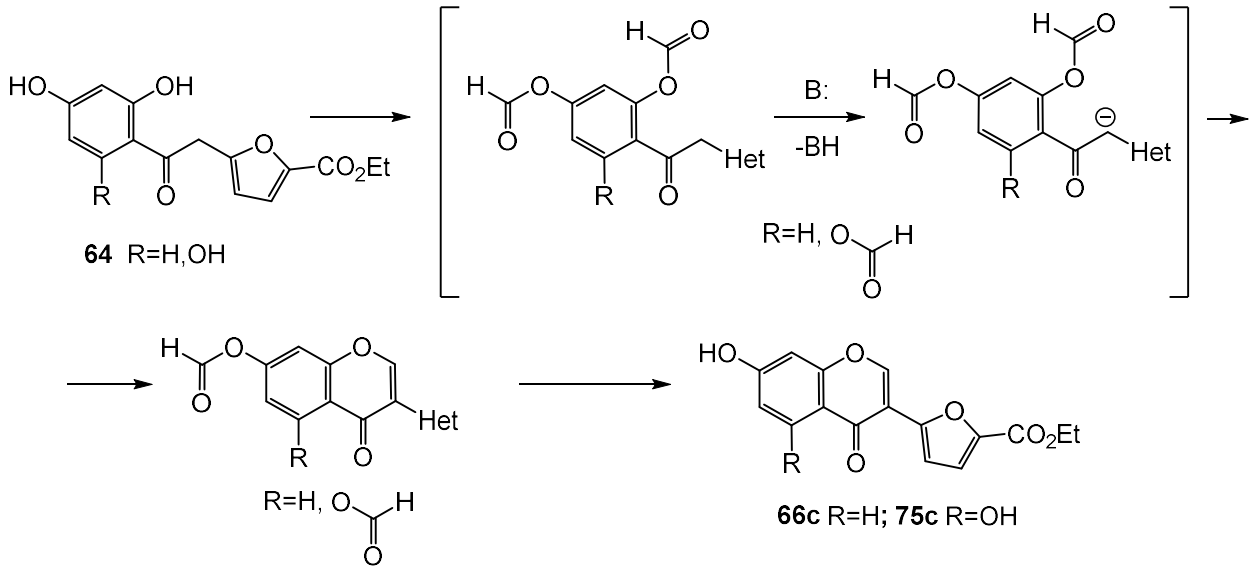
forms the same compound **74** with ethanolamine (**Scheme 22**) [27, 28]. α-Hetaryl-2,4-dihydroxyacetophenones **64a-e** (R=OH, R^1=H) also react with formic acid esters in the presence of sodium *tert*-butylate and after treatment of the reaction mixture with a 1% solution of hydrochloric acid form the corresponding 7-hydroxy-3-hetarylchromones **66a-e**, but the yields of products **66a-e** (56.5-88.5%) are slightly lower than those of 7-methoxy-3-hetarylchromones **66a-d** obtained when ketones with a protected 4-hydroxy group were used as starting compounds.



Scheme 22. The synthesis of 3-furylchromones by Claisen condensation

Acetoformic anhydride was found to be an effective reagent in the synthesis of 7-hydroxy- and 5,7-dihydroxy-3-(5-ethoxycarbonyl-2-furyl)chromones **66c**, **75c** by cyclization of α-hetaryl-2,4-dihydroxy- and α-hetaryl-2,4,6-trihydroxyacetophenones **64** in the presence of bases (Method C, **Scheme 23**). The initial stage of this cyclization is the exhaustive formylation of phenolic hydroxyls of the starting ketones. The formed formyloxyacetophenones under the influence of bases are further cyclized

into 7-formyloxy- and 5,7-diformyloxychromones, which are easily deformylated directly in the reaction mixture upon short-term heating [34-36].



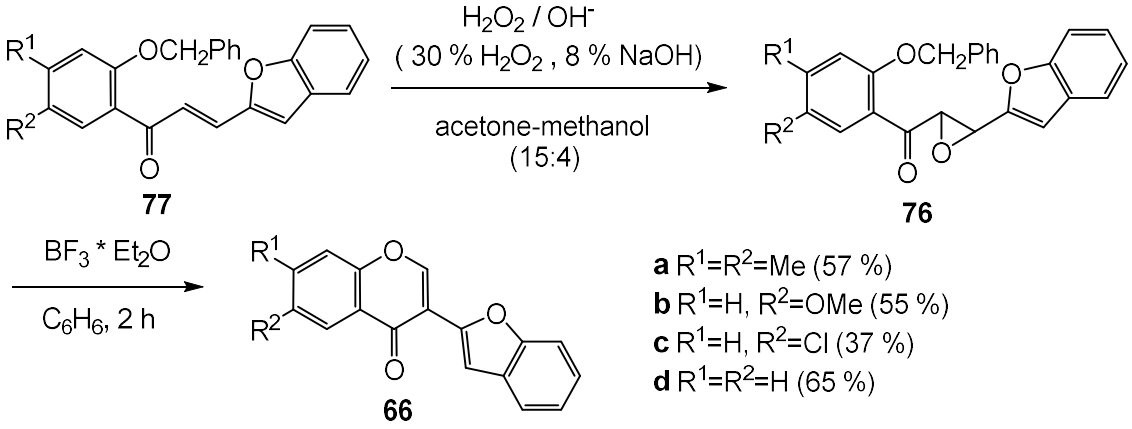
Scheme 23. The synthesis of 3-furylchromones using acetoformic anhydride

The conditions and results of the cyclization of α-(5-ethoxycarbonyl-2-furyl)-2,4-dihydroxy- and α-(5-ethoxycarbonyl-2-furyl)-2,4,6-trihydroxyacetophenones (**64**) with acetoformic anhydride to 7-hydroxy- and 5,7-dihydroxy-3-(5-ethoxycarbonyl-2-furyl)-chromones **66c**, **75c** are presented in **Table 2.**

Table 2. Conditions and results of the cyclization of α-(5-ethoxycarbonyl-2-furyl)-2,4-dihydroxy- and α-(5-ethoxycarbonyl-2-furyl)-2,4,6-trihydroxyacetophenones (**64**) with acetoformic anhydride

Compound	Starting compound	Reaction conditions					
66c	**64c** R=H	1 mL of anhydride, 6 mmol of HCO_2Na per 1 mmol of ketone		1 mL of anhydride, 7 mmol of Et_3N per 1 mmol of ketone			
		time (hours)	yield (%)	time (hours)		yield (%)	
		120	20 (according to TLC data)	10		92	
75c	**64c** R=OH	0.1 mol HCO_2Na per 1 mol ketone		6 mol HCO_2Na per 1 mol ketone		6 mol Et_3N per 1 mol ketone	
		time (hours)	yield (%)	time (h)	yield (%)	time (h)	yield (%)
		50	90 degree of conversion (80 yield after recrystallization)	10	100 (92)	1	100 (97)

Epoxides of benzofuran analogues of chalcones **76** were used as synthons in the synthesis of terminally substituted 3-(2-benzofuryl)chromones **66**. Chalcones **77** obtained by alkaline condensation of 2-formylbenzofuran and *o*-benzyloxy-acetophenones were oxidized with hydrogen peroxide in an alkaline medium to epoxychalcones **76**, which under the action of boron trifluoride etherate underwent intramolecular isomerization with subsequent cyclization to 3-(2-benzofuryl)chromones **66** (**Scheme 24**) [26, 37, 38]

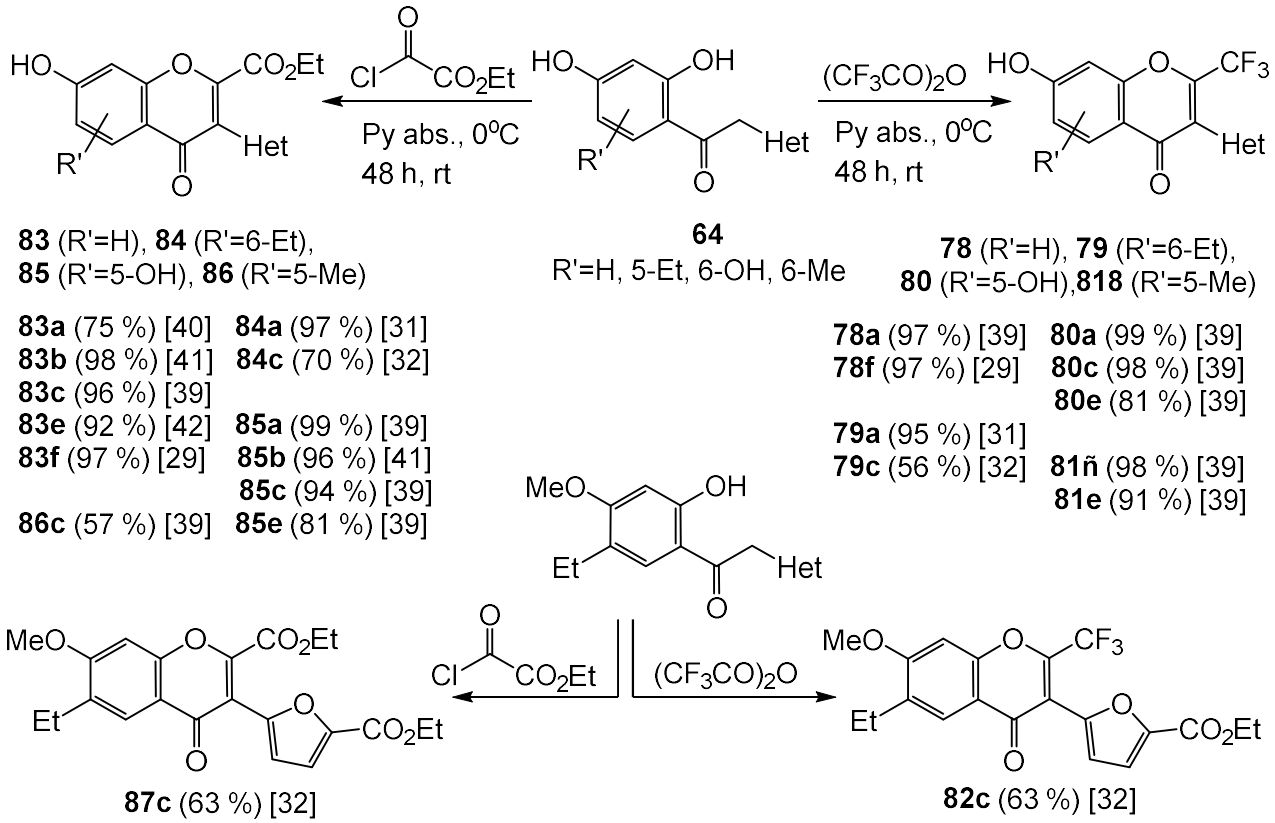


Scheme 24. The synthesis of 3-benzofurylchromones from epoxychalcones

Functionalized 3-furyl/benzofuryl-chromones with trifluoromethyl **78-82** or ethoxycarbonyl **83-87** groups in position 2 of the chromone nucleus were synthesized by the reaction of α-hetaryl-2-dihydroxyacetophenones **64** with trifluoroacetic anhydride or ethoxalyl chloride in the presence of pyridine under mild conditions (**Scheme 25**). The cleavage of acyl groups occurs immediately when the reaction mixture is poured into water [29, 31, 32, 39-42].

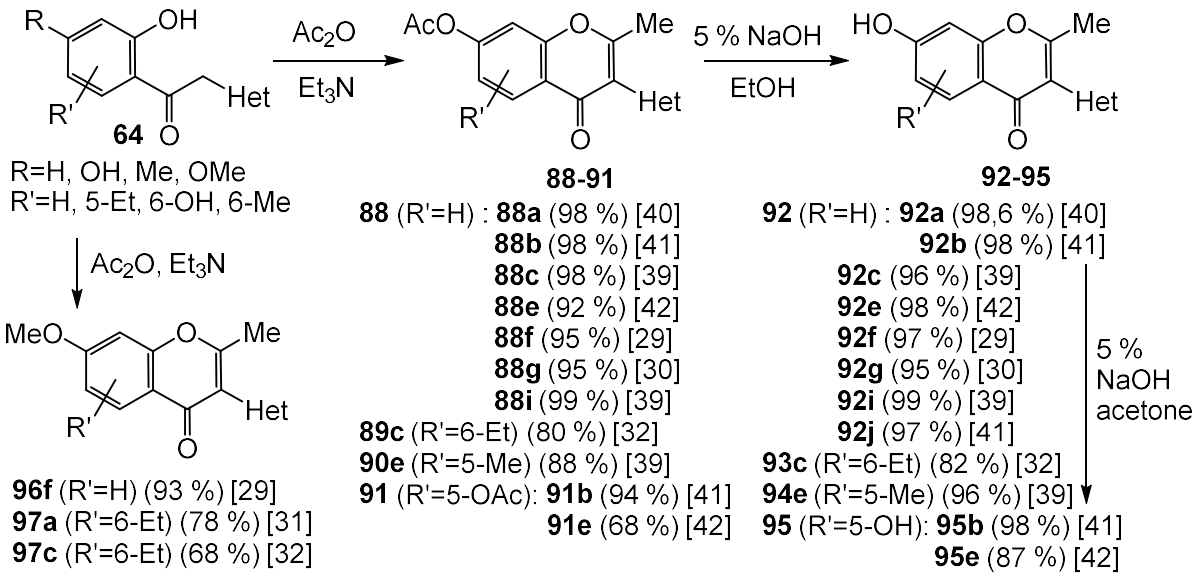
An attempt to obtain furan and benzofuran analogues of natural isoflavones by removing the 2-ethoxycarbonyl group from the obtained 2-ethoxycarbonyl-3-furyl/benzofuryl-chromones **85a,b,e** by treating them with pyridine hydrochloride was successful only for the conversion of **85a** to **66a** in 60% yield [27, 28].

A virtual screening for plant-based EBβ-selective ligands as potential preventive therapies against age-related neurodegenerative diseases showed that the 2-trifluoromethyl-7-hydroxy-3-(benzofuran-2-yl)chromone molecule (**78a**) did not bind to the receptor, or that the binding affinity was very low, with an IC_{50} greater than 1 μM, while the baseline 2,4-dihydroxy-α-(benzofuran-2-yl)acetophenone showed binding selectivity to ERa over ERR. (IC_{50} ERα 85.7 μM, ERβ 43.0 μM, ERα/ERβ selectivity 1.99) [43, 44].



Scheme 25. The synthesis of 2-trifluoromethyl- and 2-ethoxycarbonyl-3-furyl/benzofurylchromones

Functionalized 3-furyl/benzofuryl-chromones with methyl groups in position 2 of the chromone nucleus were synthesized by the interaction of α-hetaryl-2-dihydroxy-acetophenones **64** with acetic anhydride in the presence of triethylamine at a temperature of 120-130°C or 145-150°C for Het= **a**,**e**,**i** for 2-7 hours (**Scheme 26**) [29-32, 39-42]. First, acetyl derivatives of 2-methyl-7-hydroxychromones **88-90**, or diacetyl derivative of 5,7-dihydroxychromone **91** are formed, from which, under the action of dilute alkali (5% NaOH) and brief heating, free 7-hydroxy-3-furyl/benzofurylchromones **92-94** and 5,7-dihydroxy-3-furyl/benzofurylchromone **95** are formed. The preparation of 7-hydroxy-3-furylchromone **92j** occurred as a result of hydrolysis of the ester group of the heterocycle of 7-hydroxy-3-furylchromone **92b** by adding 5% NaOH solution to a warm solution of chromone **92b** in acetone and brief heating. When α-hetaryl-2-hydroxy-4-methoxyaceto-phenones **64** were used as starting compounds, 2-methyl-7-methoxy-3-furyl/benzofuryl-chromones **96**, **97** were obtained.

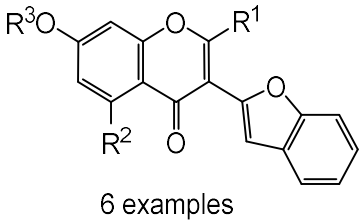
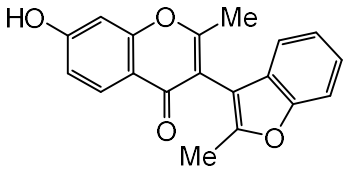
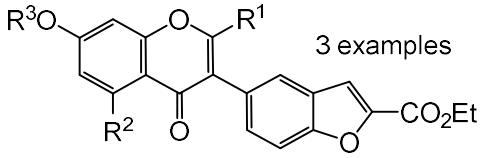
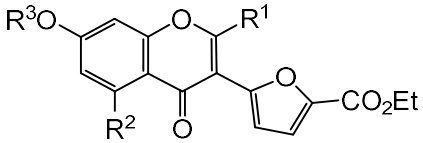


Scheme 26. The synthesis of 7-acetoxy- and 7-hydroxy-2-methyl-3-furyl/benzofurylchromones

The antitumor activity of 3-furyl/benzofurylchromones (13 samples) was tested in *in vitro* experiments by the method of serial dilutions and diffusion in agar. The initial test culture was *Staph. aureus* UV_3. The activity of the compounds was calculated by the diameter of the zone of no growth of *Staph. aureus* UV_3. For quantitative assessment of activity, 10 μg/mL of individual substance was taken as a unit of activity. Below are data on the activity of the studied compounds. from which it follows that the nature of the heterocycle and the substituent at C-2 of the chromone are the main factors affecting the activity (**Table 3**). The greatest activity was shown by 3-(2-benzofuryl)chromones [39].

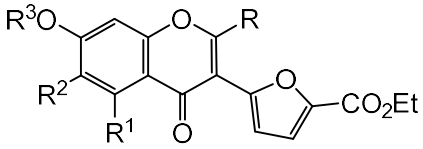
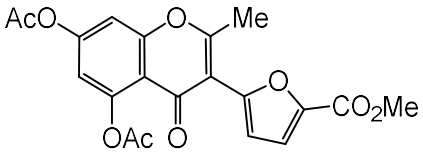
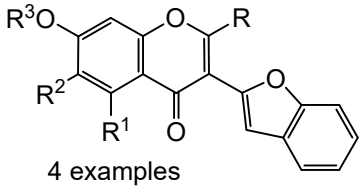
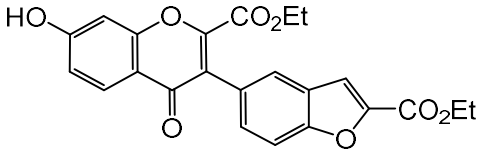
The study of the hypolipidemic activity of 3-furyl/benzofurylchromones (19 samples) was carried out at doses of 200 mg/kg of animal weight by intraperitoneal administration to white Wistar rats using the hyperlipidemia method, which was induced by intraperitoneal administration of triton WR 1339 at a dose of 225 mg/kg. The standard for comparison was the drugs cetamifen and polysponin. The blood serum of rats was examined for the content of cholesterol (CHOL) and triglycerides (TG). According to the results of the studies of 3-furyl/benzofurylchromones of various structures, all compounds inhibit the development of hyperlipidemia, and for compounds with the most pronounced effect on cholesterol and triglyceride indicators, the levels of cholesterol and TG reduction are given (**Table 4**).

Table 3. Antiblastic (antitumor) activity of 3-furyl/benzofurylchromones

Compound	R^1	R^2	R^3	D zone, mm
 6 examples	H	H	H	65
	Me	H	H	60
	CF_3	H	H	10
	CF_3	OH	H	60
	Me	H	Ac	55
	Me	H	Me	50
				20
 3 examples	Me	H	H	50
	Me	H	Me	35
	Me	OH	H	20
 6 examples	CO_2Et	H	H	30
	CO_2Et	Me	H	20
	CO_2Et	OH	H	10
	CF_3	Me	H	30
	Me	Me	H	35
	CF_3	OH	H	50

The most significant contribution to the hypolipidemic activity of the studied compounds is made by the chromone nucleus, electron-withdrawing substituents at position 7. The introduction of groups such as -OCOMe into the chromone nucleus leads to an increase in activity both in terms of cholesterol and triglyceride indicators. A somewhat smaller effect is observed in the presence of electron-donating groups OH and OMe at position 7. Substituents CF_3, Me, COOEt, compared with the free position C-2, slightly increase the hypolipidemic activity, mainly in terms of triglyceride indicator. The introduction of electron-donating alkyl substituents at position 6 into the structure of 3-hetarylchromone contributed to an increase in overall activity and to a somewhat greater extent in terms of cholesterol indicator. The influence and contribution to the overall activity of 3-hetarylchromones of the heterocyclic substituent is more complex.

Table 4. Hypolipidemic activity of 3-furyl/benzofurylchromones

Compounds	R	R^1	R^2	R^3	% decrease	
					CHOL	TG
 13 examples R=H, Me, CO_2Et, CF_3 R^1=H, Me, OH R^2=H, Et, Pr R^3=H, Me, Ac	Me	H	Pr	Me	40,1	33,8
	H	H	Pr	Me	41,3	30,5
	Me	H	Pr	Ac	42,1	35,2
					37,1	46,1
 4 examples R=H, Me, CO_2Et R^1=H, R^2=H, Pr R^3=H, Me	Me	H	H	H	32,3	41,6
	Me	H	Pr	Me	38,3	40,1
					21,8	46,9

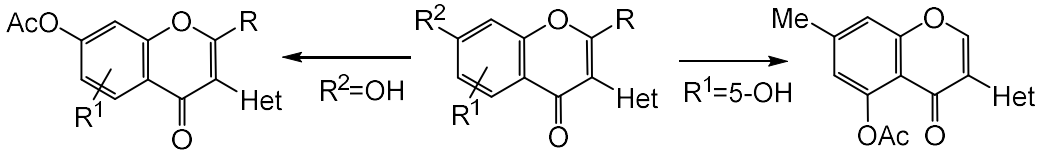
2.2. Chemical properties of 3-furyl/benzofurylchromones

Due to their polyfunctional nature, chromones can enter into various reactions: reactions at phenolic hydroxyl, electrophilic substitution reactions, thionation, reactions with nucleophilic reagents, reduction, condensation, intramolecular cyclization, etc. The directed modifications of 3-hetarylchromones or their transformation into new heterocyclic systems carried out as a result of these reactions open up broad horizons for obtaining new substances, the spectrum of biological activity of which is significantly expanded and modified.

2.2.1. Reactions at phenolic hydroxyls (acetylation, alkylation)

Furan and benzofuran analogues of isoflavones are easily acetylated at the phenolic hydroxyl. The action of acetic anhydride on

pyridine solutions of **66a-g**, **67a,c, 68c, 79a,c, 84a,c** at room temperature leads to the corresponding acetyl derivatives **98a-g, 99a,c, 100c, 100'c, 101a,c, 102a,c**, which under the influence of 5% sodium hydroxide solution are quantitatively converted into free hydroxychromones (**Scheme 27**) [27-33]. The ease of obtaining acetyl derivatives at the hydroxyl group of 7-hydroxy-3-hetarylchromones allows this reaction to be widely used for the identification and purification of most 3-hetarylchromones.



98-102 **66a-g, 67a,c, 68c, 79a,c, 84a,c** **100'c** (75 %) [33]

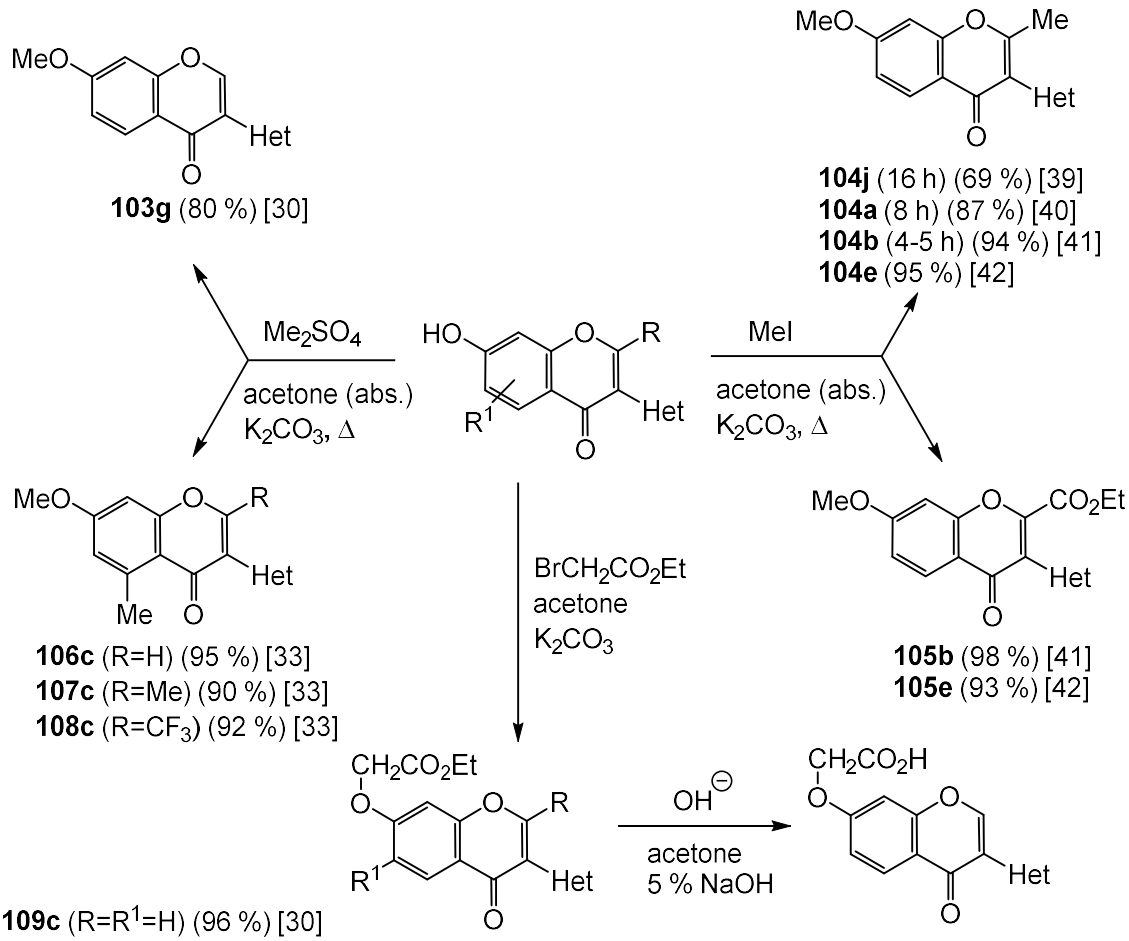
98 (R=R^1=H) : **98a-e** (77-95 %) [27, 28], **98f** (98 %) [29], **98g** (95 %) [30]
99 (R=H, R^1=6-Et) : **99a** (75 %) [31], **99c** (61 %) [32]
100c (R=H, R^1=5-Me) (95 %) [33]
101 (R=CF_3, R^1=6-Et) : **101a** (70 %) [31], **101c** (71 %) [32]
102 (R=CO_2Et, R^1=6-Et) : **102a** (71 %) [31], **102c** (63 %) [32]

Scheme 27. Acetylation of (benzo)furan analogues of isoflavones at the phenolic hydroxyl

At the same time, more stringent conditions are required for the acylation of 5-hydroxy-3-hetarylchromones. This can be explained by the fact that the rupture of an intramolecular hydrogen bond is necessary for the reaction to proceed. For example, 5-acetoxychromone **100'c** was formed only when boiling 3-(5-ethoxycarbonyl-2-furyl)-5-hydroxy-7-methylchromone (**68'c**) in acetic anhydride for 3 hours [33].

Methylation of 3-furyl/benzofuryl-chromones at the 7-OH group of the chromone ring proceeds smoothly when 7-hydroxychromone derivatives are treated with methylating agents in acetone solution in the presence of K_2CO_3 [30, 33, 39-42]. Examples of methylation of 3-furyl/benzofurylchromones to form 7-methoxy derivatives **103-108** are given in **Scheme 28**.

Alkylation of 3-furyl/benzofuryl-chromones at the 7-OH group of the chromone ring was also carried out with ethyl bromoacetic acid [30, 39-42] in acetone solution in the presence of K_2CO_3. The resulting 7-ethoxycarbonylmethoxychromones **109-111** can be converted into water-soluble acids. This transformation for 3-hetarylchromones with an ester group in the heterocycle can be carried out with its saponification, as in the example of the transformation of 3-(5-ethoxycarbonyl-2-furyl)-7-ethoxycarbonylmethoxychromone (**109c**) to 3-(5-carboxy-2-furyl)-7-carboxymethoxy-chromone (**112j**) given in **Scheme 28**.

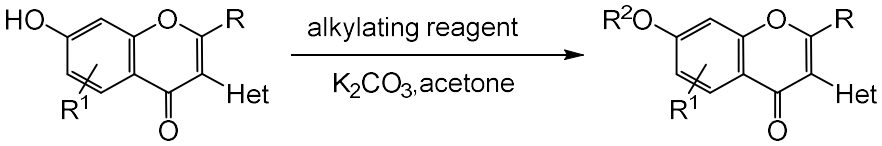


Scheme 28. Alkylation of (benzo)furan analogues of isoflavones at the phenolic hydroxyl

The effect of 3-(5-carboxy-2-furyl)-7-carboxymethoxychromone (**112j**) on cardiac muscle activity was studied by hemodynamics in rabbits [30]. Hetarylchromone was administered at a dose of 1-100 mg/kg intravenously. The effect of the furan analogue of the isoflavone on hemodynamic parameters (stroke volume, cardiac index, systolic index, total peripheral resistance, left ventricular work index) was somewhat weaker than that of the sodium salt of 3-(2-pyridyl)-7-carboxymethoxychromone (decrease in cardiac index 5 minutes after administration at a dose of 10 mg/kg and 1 minute after administration at a dose of 100 mg/kg, decrease in systolic index 1 minute after administration at a dose of 100 mg/kg).

The results of the alkylation of 3-furyl/benzofurylchromones at the 7-OH group of the chromone ring with halogen derivatives of the aliphatic series [39-42], benzyl bromide [39, 41] and some chloromethyl derivatives of heterocycles [40-42, 45], carried out under similar conditions, are presented in general form in **Table 5**.

Table 5. 7-Alkoxy-3-furyl/benzofurylchromones **113**



113

Het	R	R^1	R^2	Yield %	Reference
a	CF_3	5-OH	Et	68	[39]
		H	Et	56	
	CO_2Et	5-OEt	Et	79	
	Me	H	Et	65-73	[40]
			Pr		
			Bu		
			CH_2CN		
			A*	50	
			B*	72	
			C*	45	
b	CO_2Et	H	Et	98	[41]
			Pr	98	
			Bu	50	
	Me	H	Et	98	
			Pr	82	
			CH_2Ph	19	
	CO_2Et	H	A*	83	[45]
			D*	86	
			E*	77	
	Me	H	A*	53	
			D*	12	
			E*	65	
			F*	68	
	Me	5-OH	F*	31	
j	Me	H	CH_2Ph	40	[41]
			D*	29	[45]
i	Me	H	Et	51	[39]

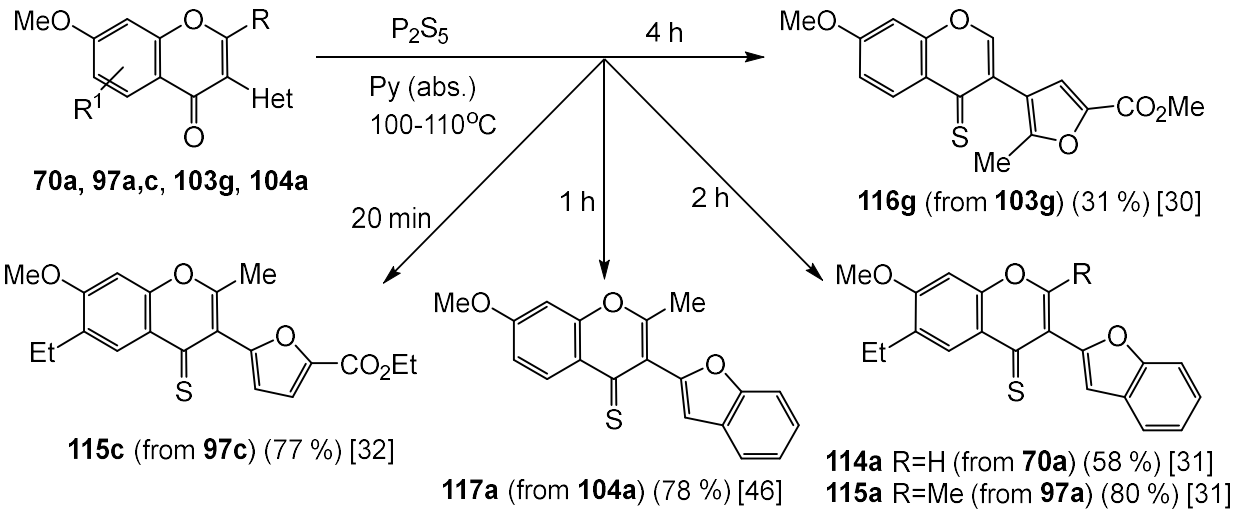
			Pr	86	
			Bu	86	
			CH_2Ph	77	
			$4\text{-}NO_2C_6H_4CH_2$	91	
c	CO_2Et	5-OH	Et	94	[39]
		5-Me	CH_2Ph	98	
e	Me	H	Et	95	[42]
			Pr	45	
			Bu	70	
			CH_2CN	65	
			B*	50	
			C*	76	
	CO_2Et	H	Et	70	
	CF_3	5-OEt	Et	74	
		5-Me	Et	74	
		$5\text{-}OCH_2Ph$	CH_2Ph	81	

A* - benzothiazolyl-2-methylene, B - 5-carbomethoxyfuryl-2-methylene,
C – 2-carboethoxybenzofuryl-5-methylene, D – 2-methylthiazol-4-ylmethylene,
E – 5-methoxycarbonyl-2-furylmethylene, F – thienyl-2-methylene

When alkylating 5,7-dihydroxy-3-furyl/benzofurylchromones, the formation of both 7-alkoxy and 5,7-dialkoxy derivatives is possible, the degree of alkylation is easily determined by NMR spectroscopy [39, 45]. In most cases, alkylation reactions with chloromethyl derivatives of thiazole and benzothiazole are much more difficult than alkylation with similar derivatives of furan and thiophene. When alkylating 2-methyl-3-(2-furyl-5-methoxycarbonyl)-7-hydroxychromone with 2-methyl-4-chloromethylthiazole, two compounds are formed: one of them is a compound with an ester group in the heterocycle (12%), and the second is with a carboxyl group (29%). The introduction of an ethoxycarbonyl group in position 2 of the compounds undergoing alkylation significantly accelerates the reaction [45].

2.2.2. Thionation reactions

When 7-methoxy-3-furyl/benzofuryl-chromones **70a, 97a,c, 103g, 104a** are heated with an excess of P_2S_5 in dry pyridine at 100-110°C, 3-furyl/benzofuryl-4-thioxo-7-methoxy-chromone derivatives **114-117** are formed (**Scheme 29**) [30-32, 46].

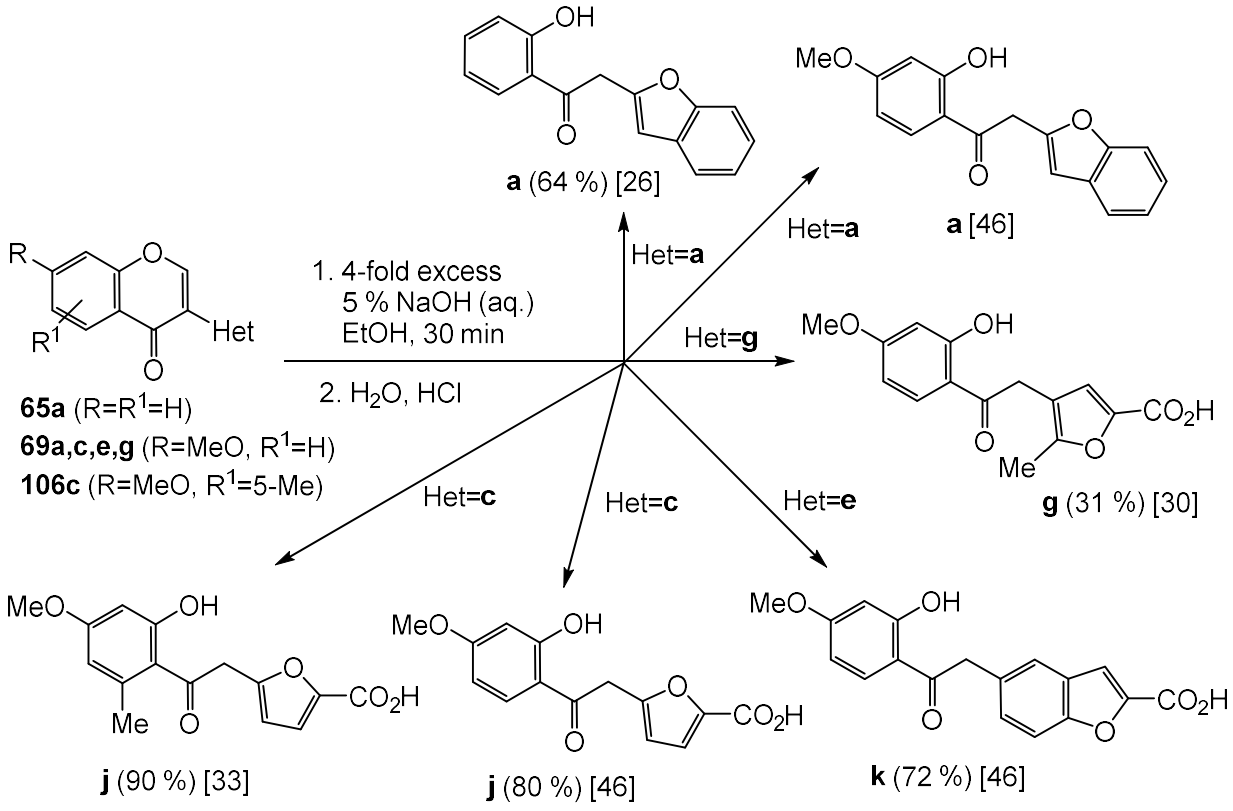


Scheme 29. Thionation of 3-furyl/benzofurylchromones

2.2.3. Reactions with nucleophilic reagents

a) with alkalis

The effect of alkalis on some furan and benzofuran analogues of isoflavones was investigated in [26, 30, 33, 46] (**Scheme 30**).



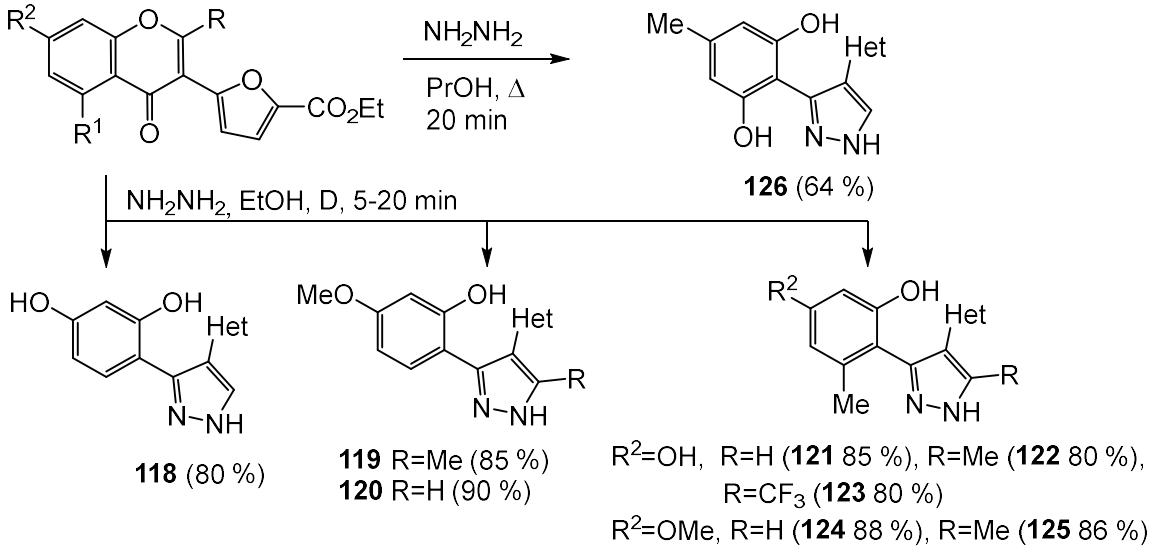
Scheme 30. The effect of alkalis on 3-furyl/benzofurylchromones

It was found that when 3-furyl/benzofurylchromones **65a, 69a,c,e,g, 106c** are heated with a fourfold excess of 5% sodium hydroxide solution in aqueous alcohol, the

pyrone ring is opened, and in the case of 7-methoxychromones **69a,c,e,g, 106c**, along with the opening of the pyrone ring, the ester groups are saponified and derivatives of α-hetaryl-2-hydroxyacetophenone **64** are formed: α-(2-benzofuryl)-2-hydroxyacetophenone [26], α-(2-benzofuryl)-2-hydroxy-4-methoxyacetophenone [46], α-(5-carboxy-2-furyl)-2-hydroxy-4-methoxyacetophenone [46], α-(5-carboxy-2-furyl)-2-hydroxy-4-methoxy-6-methylaceto-phenone [33], α-(2-methyl-5-carboxy-3-furyl)-2-hydroxy-4-methoxyacetophenone [30], α-(2-carboxy-5-benzofuryl)-2-hydroxy-4-methoxyacetophenone [46] (**Scheme 30**).

b) with hydrazine hydrate

As a result of the action of hydrazine hydrate on alcohol solutions of 3-(5-ethoxycarbonyl-2-furyl)chromones **66c, 104c, 103c, 68c, 95c, 81c, 106c, 107c, 68′c** (**Scheme 31**), 3-furylchromones **16a,c, 17c,** 3-benzofurylchromones **65a, 70a, 97a, 69a, 92a, 104a** (**Scheme 32**) *o*-hydroxyphenylpyrazole derivatives **118-135** are formed.

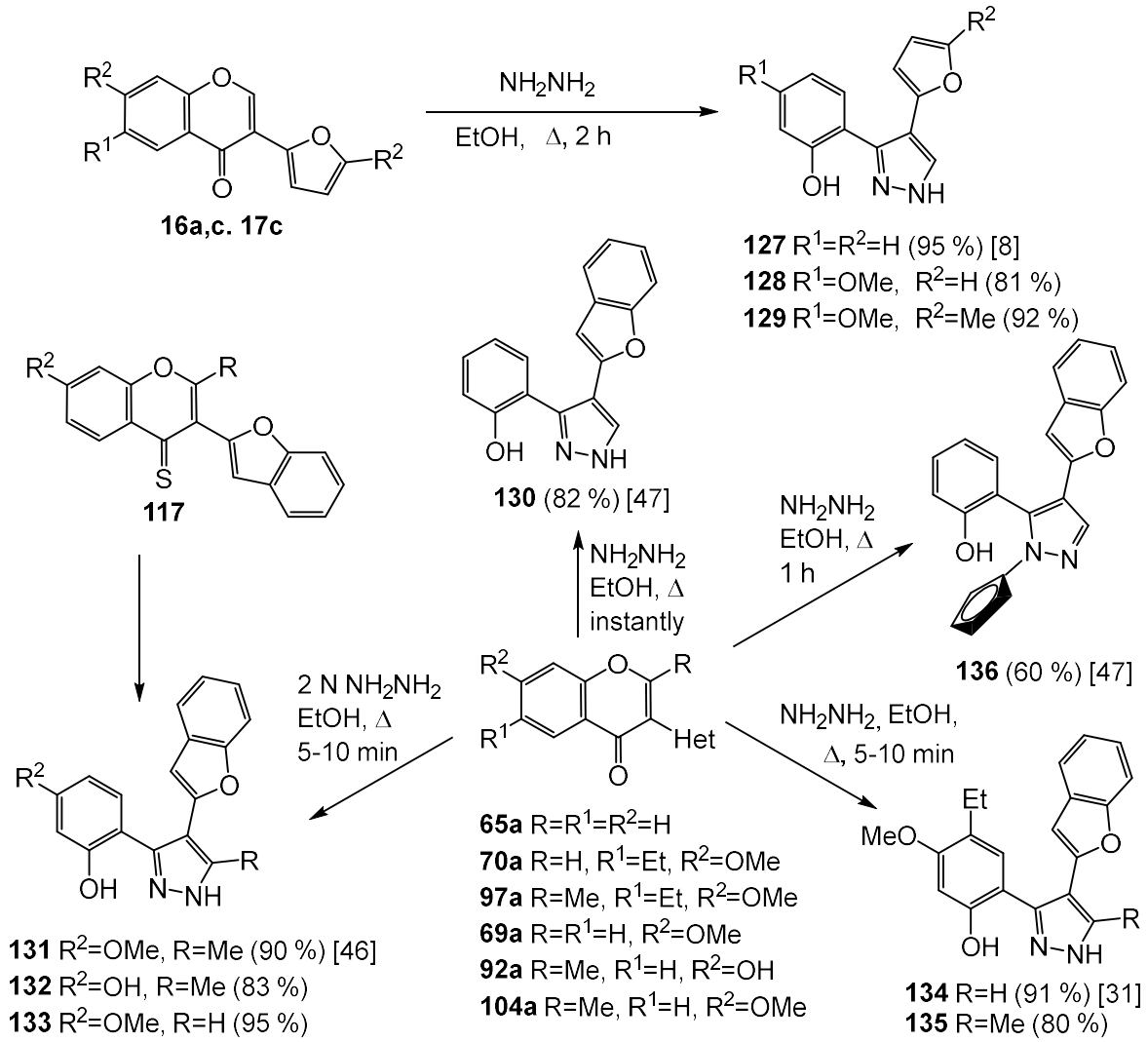


Scheme 31. The effect of hydrazine hydrate on 3-(5-ethoxycarbonyl-2-furyl)chromones

The formation of pyrazoles **118-135** occurs as a result of nucleophilic attack of hydrazine molecules on the C2 carbon atoms of chromones, after which the γ-pyrone ring opens and the intermediate compound is converted into an *o*-hydroxyphenylpyrazole derivative. In [8], the molar ratio of 3-furylchromone : hydrazine hydrate was 1:3, and for 3-benzofurylchromones and 3-(5-ethoxycarbonyl-2-furyl)chromones the molar ratio of 3-hetarylchromone : hydrazine hydrate was 1:12 [31, 33, 46, 47]. The reaction rate depends to a large extent on the structure of the starting 3-hetarylchromone.

1-Phenyl-5-(2-hydroxyphenyl)-4-(2-benzofuryl)pyrazole **136** was obtained by a similar reaction of 3-benzofurylchromone **65a** with phenylhydrazine (molar ratio 1:3) [47]. The reaction of hydrazine hydrate with 2-methyl-7-

methoxy-3-(2-benzofuryl)chromone (**104a**) as well as with its thioxo analogue **117a** proceeds with the formation of 3(5)-methyl-4-(2-benzofuryl)-5(3)-(2-oxyphenyl)pyrazole (**131**) [46].



Scheme 32. The effect of hydrazine hydrate on 3-furyl/benzofurylchromones

The obtained pyrazoles **118-136** are easily soluble in 2N aqueous alkali, which indicates the presence of free phenolic hydroxyl. Pyrazoles **121-125**, formed from chromones obtained on the basis of orcine, do not give a color reaction with a solution of ferric chloride due to the impossibility of chelate formation due to steric hindrance from the 6-CH_3-group of the phenolic part of the molecule. Pyrazole **136** does not give a color reaction with a solution of ferric chloride due to the impossibility of chelate formation due to steric hindrance from the phenyl substituent on the nitrogen atom of the pyrazole ring. The remaining pyrazoles form blue-green complexes with an alcoholic solution of ferric chloride due to the presence of a hydroxyl group in the *o*-position to the nitrogen atom in the heterocyclic residue.

Pyrazoles **127-129** [8] were tested for antifungal activity at a concentration of 100 μg/ml *in vitro* against *Cytospora sp., Colletotrichum gloeosporioides, Botrytis cinerea, Alternaria solani* and *Fusarium solani*. None of the tested compounds was active against *Fusarium solani*. The most effective antifungal activity against *Colletotrichum gloeosporioides*, which was significantly higher than the activity of the drug hymexazole (IC_{50} >100 μg/ml), was demonstrated by pyrazole **129** with IC_{50} 29.52 μg/ml. The activity of compound **129** (IC_{50} 49.05 μg/ml) against *Alternaria solani* was lower than that of the drug hymexazole (IC_{50} 18.41 μg/ml).

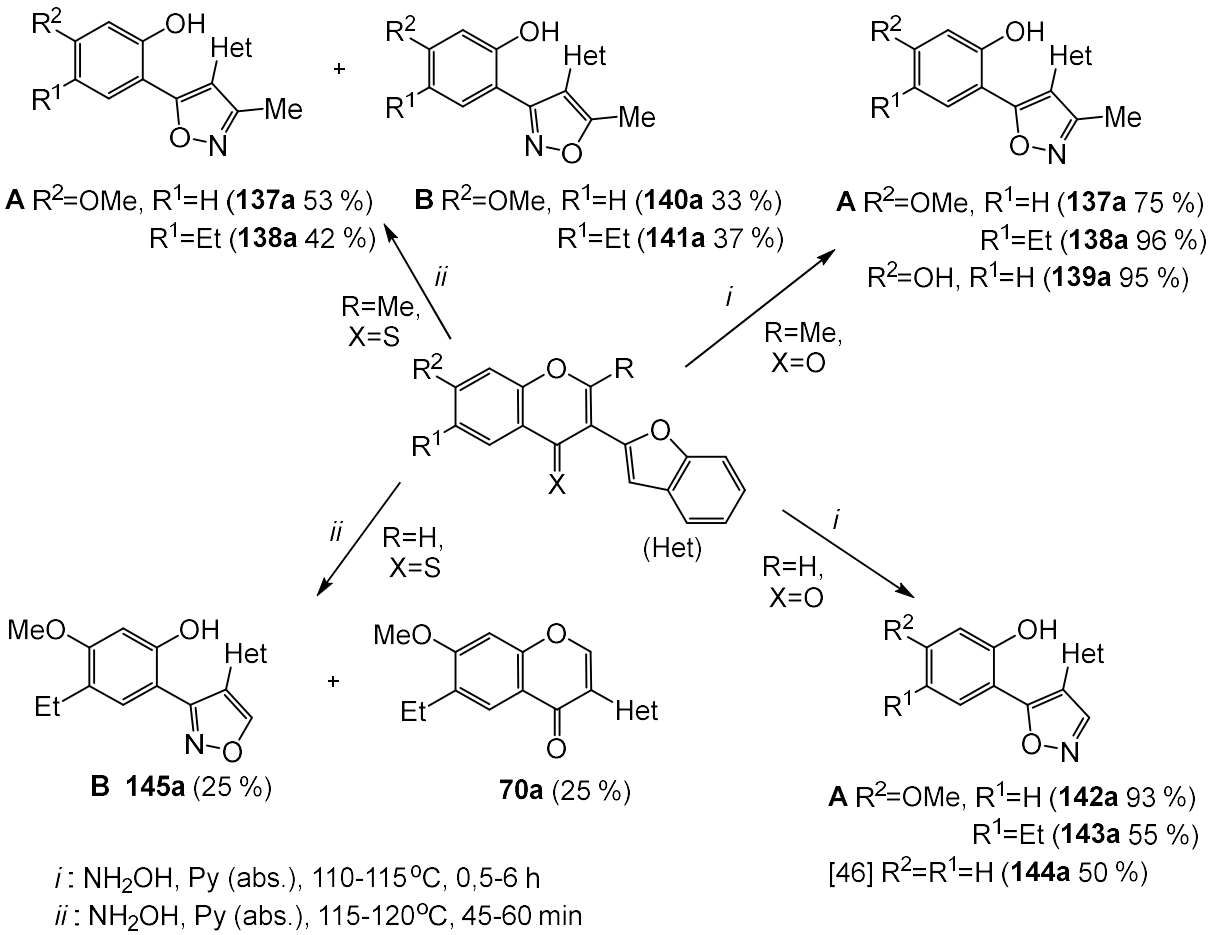
Antiviral activity among 3-furylchromones and their recyclization products was found in 7-acetoxy-6-propyl-3-(5-ethoxycarbonyl-2-furyl)chromone and obtained as a result of its recyclization under the action of hydrazine hydrate 3-(2,4-dihydroxy-5-propylphenyl)-4-(5-ethoxycarbonyl-2-furyl)pyrazole.

c) with hydroxylamine

The variability of products that can be formed during the interaction of 3-hetarylchromones with hydroxylamine hydrochloride in pyridine and the establishment of their structure based on physicochemical characteristics and differences in chemical properties are discussed in detail in the review [48].

The course of the reaction and the products obtained directly depend on both the substituents in the benzopyrone fragment and the nature of 3-hetaryl (**Scheme 33**).

In the case of (un)substituted 2-methyl-7-methoxy-3-(2-benzofuryl)chromones **97a, 104a** or 2-methyl-7-hydroxy-3-(2-benzofuryl)-chromones **92a**, in the reaction with hydroxylamine hydrochloride in pyridine, 5-(2-hydroxyphenyl)isoxazole derivatives **137a, 138a** or **139a** (type A) were formed. These compounds are soluble in 2N sodium hydroxide solution and do not give a color reaction with an alcoholic solution of ferric chloride. Their formation can be represented as the result of nucleophilic attack of the hydroxylamine molecule on the C(2) atom of the chromone. In similar reactions with thioxochromones **117a** and **115a**, 2 products were formed. Some of them were identical to compounds **137a, 138a** (type A), and the others – **140a, 141a** are derivatives of 3-(2-hydroxyphenyl)isoxazole (type B), which give a positive reaction with a solution of ferric chloride and dissolve in 2N sodium hydroxide solution. The formation of isoxazoles of type B can be considered as the result of nucleophilic attack of hydroxylamine molecules on atoms C(2) and C(4), which leads to the opening of the γ-pyrone ring with subsequent cyclization of intermediate products into *o*-hydroxyphenylisoxazoles [31].

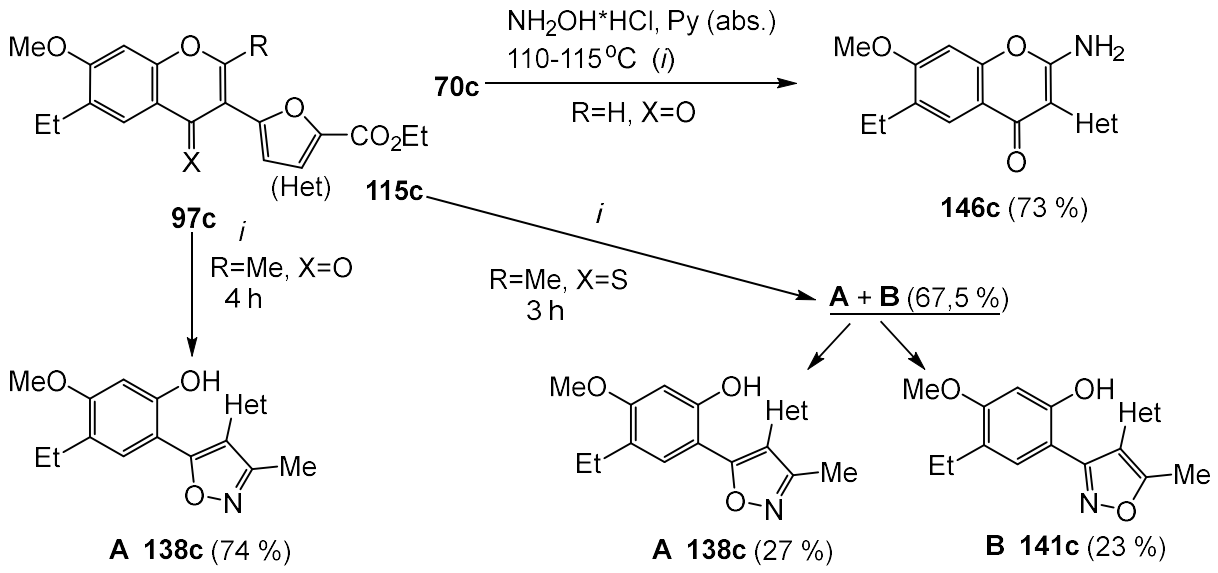


Scheme 33. The effect of hydroxylamine on 3-benzofuryl(thio)chromones

Isoxazoles of type A **142a, 143a** [31] and **144a** [47] were also isolated in the reactions with hydroxylamine of terminal (un)substituted 7-methoxy-3-(2-benzofuryl)chromones **69a, 70a** and 3-(2-benzofuryl)chromone **65a**. However, if thioxochromone **114a**, obtained from 7-methoxy-6-ethyl-3-(2-benzofuryl)chromone **70a**, was introduced into the reaction, isoxazole of type B **145a** (25%) was isolated, which gives a positive reaction with an alcoholic solution of ferric chloride and chromone **70a** (25%).

In the reaction with hydroxylamine, 2-methyl-6-ethyl-7-methoxy-3-(5-ethoxy-carbonyl-2-furyl)chromone (**97c**) is recycled exclusively into the isoxazole derivative **138c** (type A), and 2-methyl-6-ethyl-7-methoxy-4-thioxochromone **115c** forms a mixture of isomeric isoxazoles, which were separated by TLC into individual compounds - **138c** (27%) type A and **141c** (23%) type B (**Scheme 34**) [49].

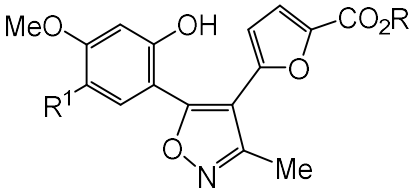
The reaction of terminal 7-methoxy-6-ethyl-3-(5-ethoxycarbonyl-2-furyl)chromone (**70c**) with hydroxylamine upon heating in dry pyridine occurs extremely selectively with the formation of 2-amino-6-ethyl-7-methoxy-3-(5-ethoxycarbonyl-2-furyl)chromone (**146c**), the formation of which can be represented as the result of successive recyclings and isomerizations [48].



Scheme 34. The effect of hydroxylamine on 3-furyl(thio)chromones

Pharmacological studies on the study of hypoglycemic activity among the recycling products of oxygen-containing analogues of isoflavones were carried out using the example of 3,4,5-trisubstituted isoxazoles. The dynamics of blood sugar lowering under the influence of compounds **147** and **148** compared to the official hypoglycemic agent butamide is presented in **Table 6**.

Table 6. Dynamics of blood sugar lowering under the influence of 3,4,5-trisubstituted isoxazoles



147 R=Pr, R^1=H
148 R=Et, R^1=Pr

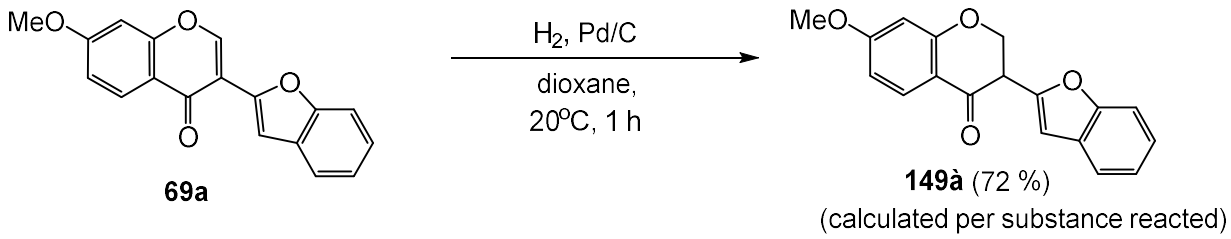
Compound	Percentage of reduction in blood sugar levels relative to baseline						Average % reduction per day
	2	4	6	8	10	24	
147	1,85	9,26	23,15	26,86	20,38	13,89	18,33
148	10,00	10,80	12,60	20,70	14,40	13,50	13,66
Butamide	21,60	25,60	30,20	23,60	23,40	4,90	21,30

As can be seen from **Table 6**, isoxazoles **147**, **148** exhibit a hypoglycemic effect, more pronounced for compound **147**, but lower than the effect of butamide. The maximum reduction in blood sugar levels under the influence of compounds **147** and **148** is achieved in 8 hours

and gradually decreases over the next 14 hours, showing a percentage reduction in sugar levels of 13.50-13.89% in 24 hours versus 4.90% in butamide. The acute toxicity of isoxazoles was more than 2000 mg/kg. Low toxicity and the detected hypoglycemic effect showed the prospect of searching for potential hypoglycemic agents among isoxazole derivatives.

2.2.4. Reduction reactions

Catalytic hydrogenation of the C2-C3 double bond of 3-(2-benzofuryl)-7-methoxychromone (**69a**) afforded 3-(2-benzofuryl)-7-methoxychromanone (**149a**) (**Scheme 35**).

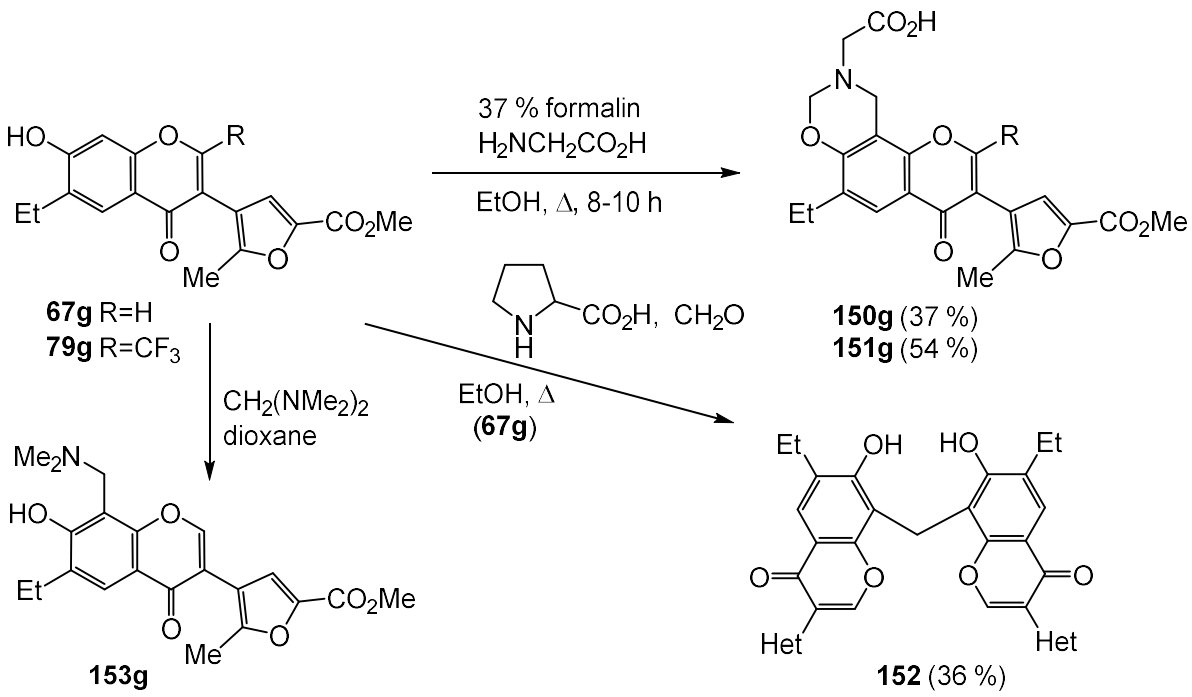


Scheme 35. Catalytic hydrogenation of 3-(2-benzofuryl)-7-methoxychromone

2.2.5. Aminomethylation reactions with amino acids and bisdimethylaminomethane

To clarify the possibilities of aminomethylation of 3-hetarylchromones with amino acids, the interaction of 2-R-6-ethyl-3-(2-methyl-5-methoxycarbonylfuran-3-yl)-7-hydroxychromones (**67g** R=H and **79g** R=CF_3) with amino acids (glycine, proline) and formaldehyde was studied at a molar ratio of reagents of 1:1:2, respectively (**Scheme 36**) [50]. The reaction was carried out at boiling in a water-alcohol medium for 8-10 hours. In the case of glycine, 2-[(6-ethyl-3-hetaryl-4-oxo)-9,10-dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-9-yl]acetic acids (**150g**, **151g**) were isolated after the reaction. The nature of the R substituent does not affect the yields of the products. In the Mannich reaction involving the secondary amino acid proline with formaldehyde and chromone **67g**, the expected aminomethylation product was not obtained, and the isolated product had the structure of substituted *bis*(chromone-8-yl)methane **152**.

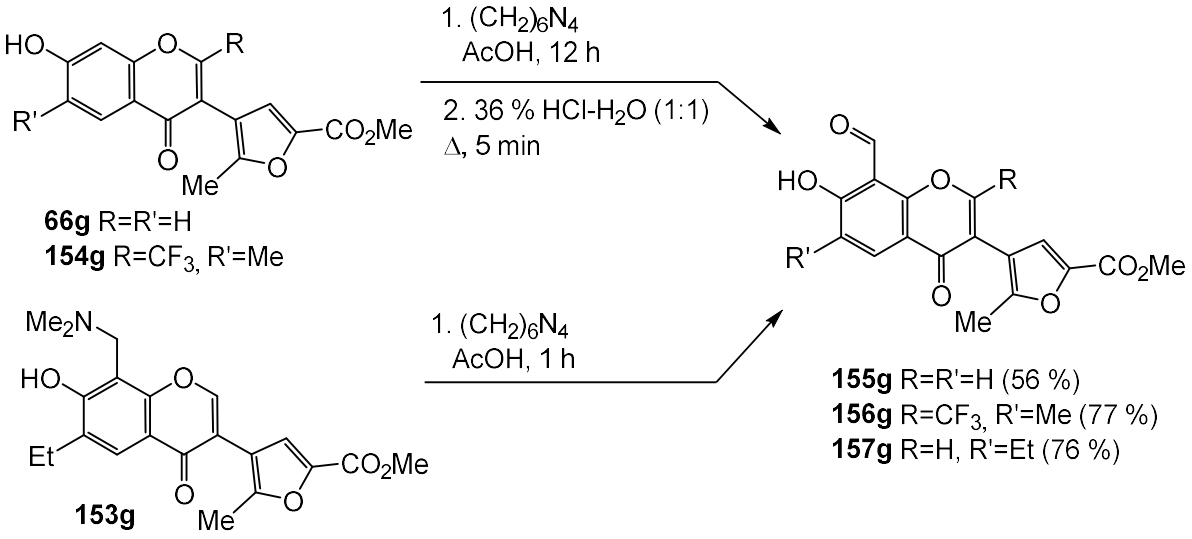
Aminomethylation using aminals is a convenient method for introducing an aminomethyl moiety into 3-hetarylchromones. By this method, 8-aminomethyl-7-hydroxychromone **153g** was obtained by the reaction of chromone **67g** with *bis*dimethylaminomethane while boiling in dioxane. The aminomethylation occurs at the 8-position, which is the most active position for electrophilic attack in 7-hydroxychromones.



Scheme 36. Aminomethylation of 3-furylchromones

2.2.6. Formylation of chromones

The main method for the formylation of 7-hydroxychromones is the Duff reaction. According to this method, (un)substituted 7-hydroxy-3-(2-methyl-5-methoxycarbonylfuran-3-yl)chromones **66g**, **154g** were formylated with hexamethylenetetramine (molar ratio 1:10) in acetic acid by boiling in a water bath for 12 hours and subsequent acid hydrolysis, forming 8-formyl derivatives **155g**, **156g** (**Scheme 37**) [51].



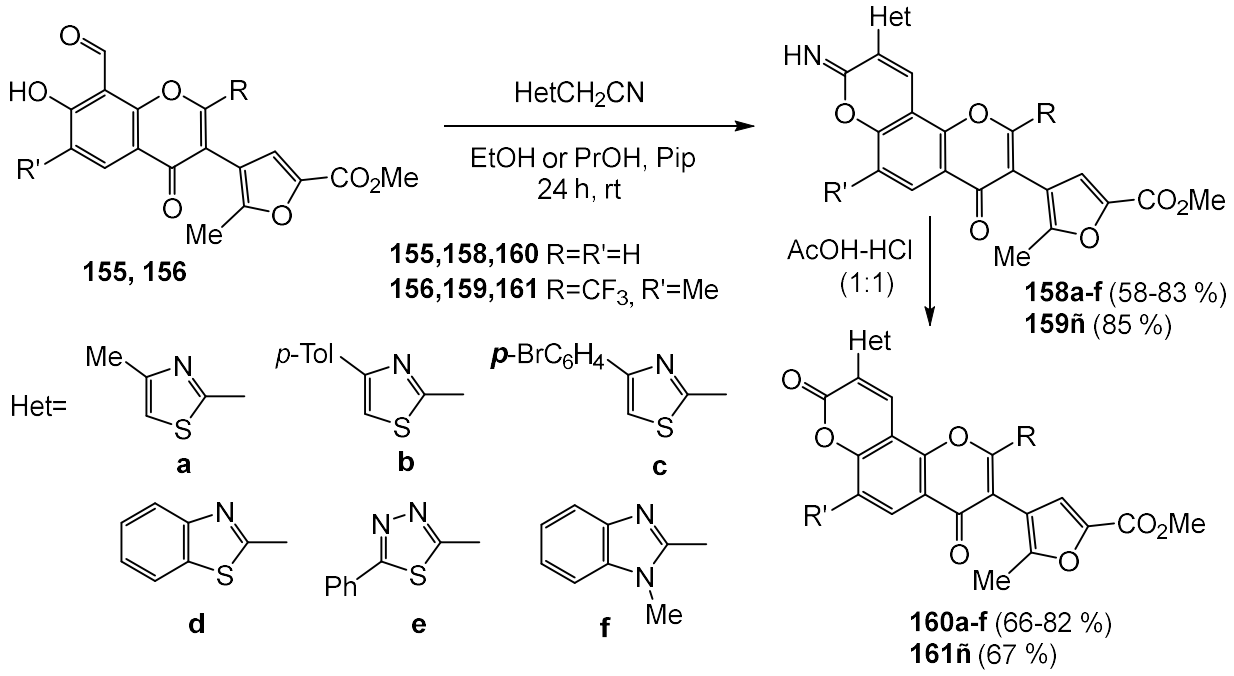
Scheme 37. Formylation of 3-furylchromones

A convenient method for the synthesis of 3-hetaryl-7-hydroxy-8-formylchromones, starting from Mannich bases under Duff reaction conditions, was used to obtain 7-hydroxy-3-(2-

methyl-5-methoxycarbonylfuran-3-yl)-8-formyl-6-ethylchromone (**157g**) [52]. The reaction was carried out by boiling for 1 hour the 8-dimethylaminomethyl derivative of 7-hydroxychromone **153g** with a 1.75-fold excess of hexamethylenetetramine in acetic acid and subsequent acid hydrolysis with a yield of 76%.

2.2.7. Furyl analogues of α-pyrono[2,3-f]isoflavones

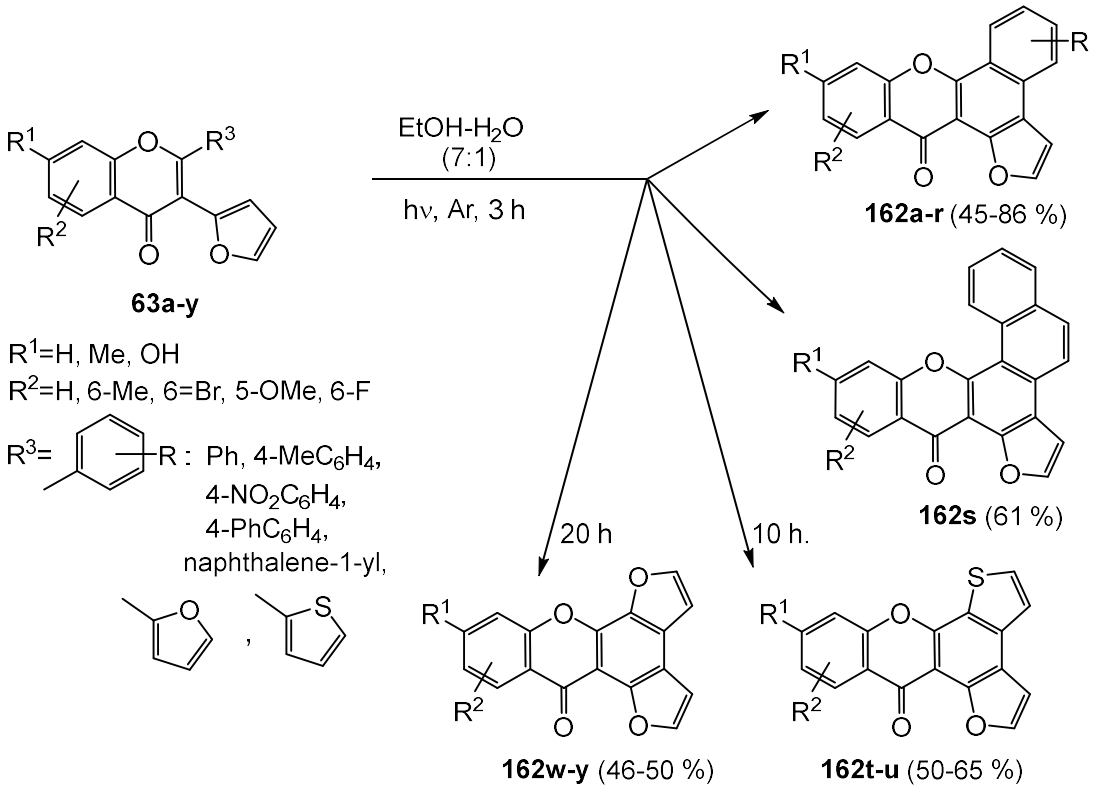
The condensation of 7-hydroxy-3-(2-methyl-5-methoxycarbonylfuran-3-yl)-8-formylhomones **155**, **156** with 2-azahetarylacetonitriles was carried out in alcohol in the presence of a catalytic amount of piperidine, which allowed the isolation of intermediate 9-azolyl-8-imino-3-(2-methyl-5-methoxycarbonylfuran-3-yl)-4*H*,8*H*-pyrano[2,3-*f*]chromen-4-ones **158**, **159**, the acid hydrolysis of which leads to furyl analogues of 9-azolyl-α-pyrono[2,3-*f*]isoflavones **160**, **161** (**Scheme 38**). The optimal conditions for hydrolysis are boiling in a mixture of acetic and 36% hydrochloric acids for 5-10 minutes [51].



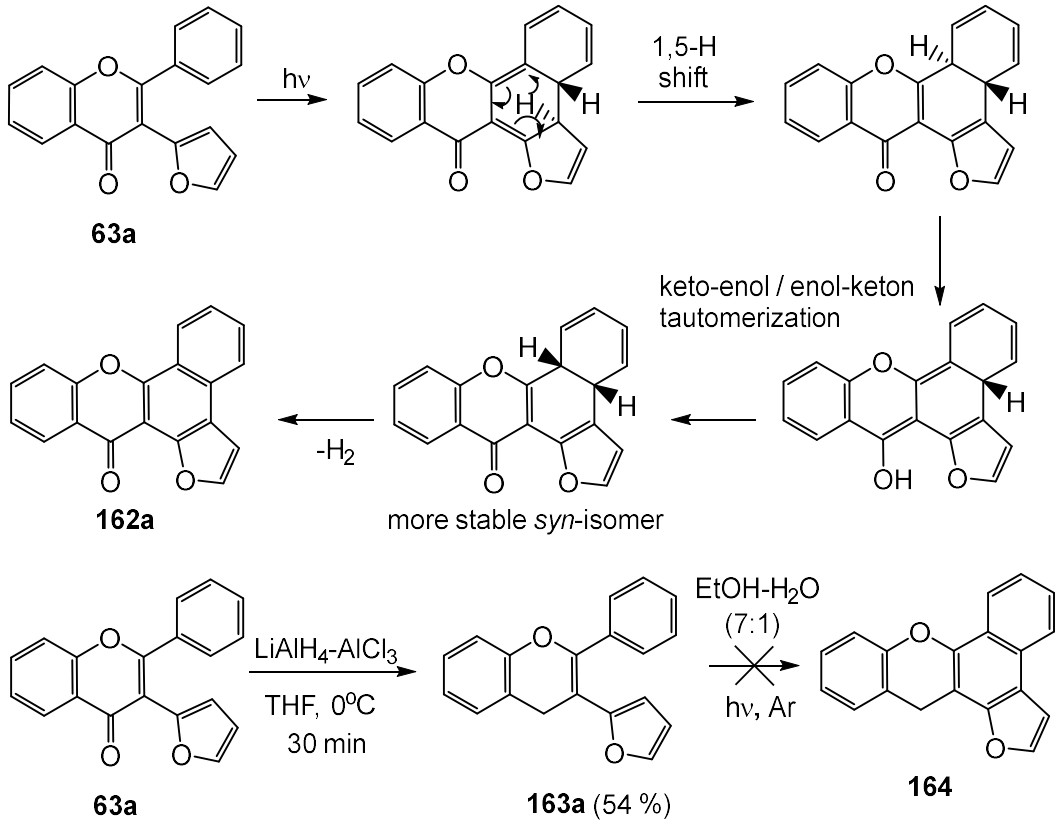
Scheme 38. The synthesis of furyl analogues of α-pyrono[2,3-*f*]isoflavones

2.2.8. Cyclization into complex condensed heteroaromatic systems

As a result of photoinduced intramolecular cyclization of 2,3-di(het)arylchromones **63a-y** in EtOH−H2O (7:1, v/v) at room temperature, complex condensed heteroaromatic systems **162a-y** - derivatives of 13*H*-benzo[*c*]furo[2,3-*a*]xanthen-13-one, 10*H*-furo[2,3-*a*]naphtho[2,1-*c*]xanthen-10-on, 12*H*-furo[2,3-*a*]thieno[3,2-*c*]xanthen-12-one and 12*H*-difuro[2,3-*a*:3',2'-*c*]xanthen-12-one were synthesized (**Scheme 39**).



Scheme 39. Photoinduced intramolecular cyclization of 2,3-di(het)arylchromones



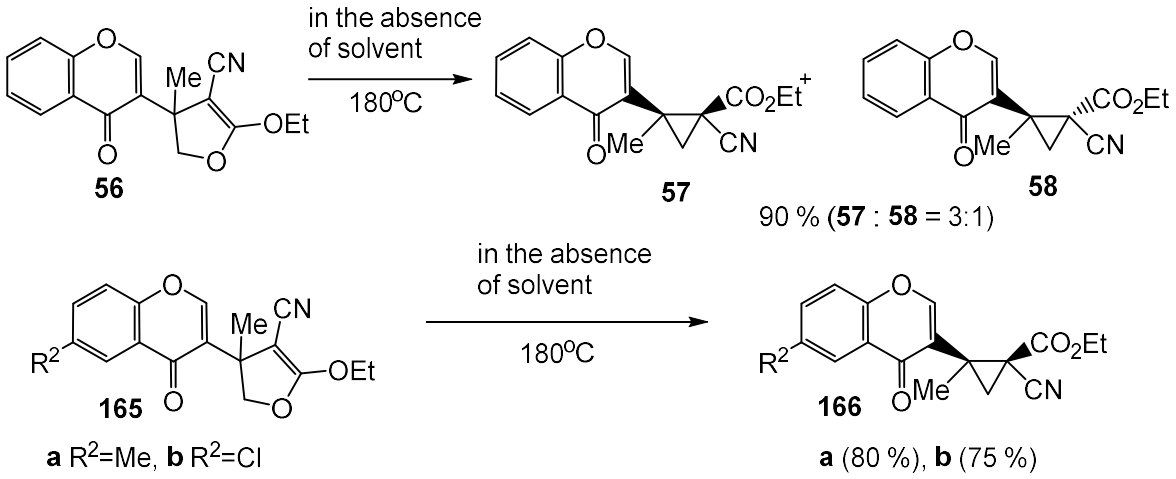
Scheme 40. The mechanism of photoinduced intramolecular cyclization of 2,3-di(het)arylchromones

The reaction proceeds smoothly, without the use of transition metal catalysts or any additives, and the annulated products were generally isolated in good yields [25].

The mechanism of this cyclization proposed by the authors is presented in example of compound **63a** in **Scheme 40**. To confirm the rationality of the proposed cyclization mechanism, in particular, the reduction of compound **63a** with $LiAlH_4$ $AlCl_3$ in THF at 0°C for 30 min was carried out to obtain product **163a** in 53% yield (hv, rt, $EtOH/H_2O$ 7:1 (v/v)), as shown in **Scheme 40.** The product of dehydrogenative annulation **164** was not detected, and the starting substrate was removed. The failure of the annulation of **163a** further proves the rationality of the proposed mechanism and the importance of keto-enol tautomerization in the described mechanism.

2.2.9. Thermal rearrangement

Heating dihydrofuran **56** gives a 3:1 mixture of *cis*- **57** and *trans*-**58** isomers. A similar reaction of substituted dihydrofurans **165** leads to *cis*-**166** isomers (**Scheme 41**). This thermal rearrangement represents the first example of the reverse transformation of alkoxycarbonylcyclopropane → 5-alkoxy-2,3-dihydrofuran [21, 22].



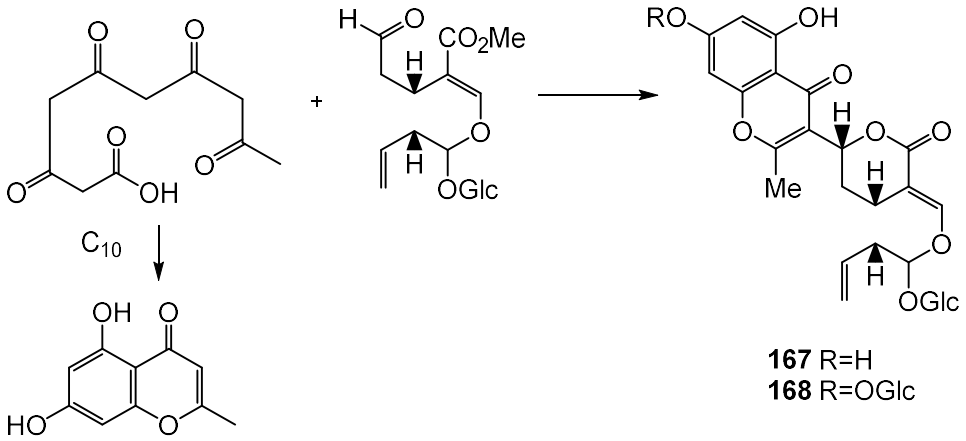
Scheme 41. Thermal rearrangement of 3-dihydrofuranylchromones

3. Pyranofunctionalized isoflavone analogs

This subsection presents natural and synthetic pyranofunctionalized and pyranoannulated isoflavone analogs.

Chromone secoiridoid glycosides, sessilifoside **167** and 7"-*O*-β-*D*-glucopyranosylsessilifoside **168**, were isolated from the dried roots of *Neonauclea sessilifolia*, representing the first chromone-linked secoiridoid glucosides (**Scheme 42**). The compounds can be biosynthesized via the aldol

condensation of secologanin with a C10 unit via the acetate-malonate pathway [53].



Scheme 42. Biosynthesis of chromone secoiridoid glycosides

A new isoflavone neocorylin (**169**) was isolated from the seed extract of *Psoralea corylifolia* L. (Fabaceae), an annual plant of the legume family widely distributed in Southeast Asian countries, together with eight known constituents such as bakuchiol, psoralen, bavachromene, isobavachromene, bavachalcone, isobavachalcone, 7,8-dihydro-8-(4-hydroxyphenyl)-2,2-dimethyl-2*H*,6*H*-[1,2-*b*:5,4-*b*′]dipyran-6-one and bavachinin [54]. The structure of the new isoflavone **169** was recognized as 7-hydroxy-3-[2-methyl-2-(4-methylpenten-3-yl)-2*H*-chromen-6-yl]-4*H*-chromen-4-one by spectral analysis methods, which correlated well with the data for corylin **169a** (**Figure 4**) [55].

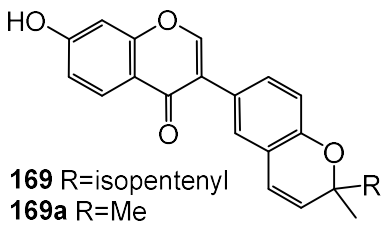


Figure 4. Structures of neocorylin and corillin

During the investigation of the inhibitory effect of various plant extracts on BACE-1 (Beta-secretase 1) *in vitro*, it was revealed that the seed extract of *P. corylifolia* L. (Fabaceae) exhibits a significant inhibitory effect on BACE-1 in dose-dependent order. Inhibition of BACE-1 (β-secretase) is considered a key target for therapeutic treatment in Alzheimer's disease. During the purification process of the dichloromethane-soluble fraction of the extract, which demonstrated potent inhibitory activity for the enzymes, a novel isoflavone neocorylin (**169**) (**Figure 4**) was isolated in small amounts (0.001 %). Neocorylin exhibited a pronounced inhibitory activity against baculovirus-expressed BACE-1 *in vitro*, with an IC_{50} value of 0.7 μM, significantly greater than that of the standard reference peptide (IC_{50} = 0.07 μM) or some synthetic BACE-1 inhibitors (IC_{50} = 0.022 μM). Although the novel isoflavone **169** appears to be a potent inhibitor of BACE-1, further studies on

the inhibition of other aspartyl proteases, such as cathepsin D or BACE-2, would be necessary to clarify the selectivity of the enzyme [54].

Among the flavonoids that were isolated as the main secondary metabolites from the roots of plants of the genus *Eriosema* (Fabaceae) and first systematized in a review [56], are isoflavone and pyranoisoflavone derivatives with a 2,2'-dimethyl-7-hydroxy-2*H*-1-benzopyran substituent (**Figure 5**).

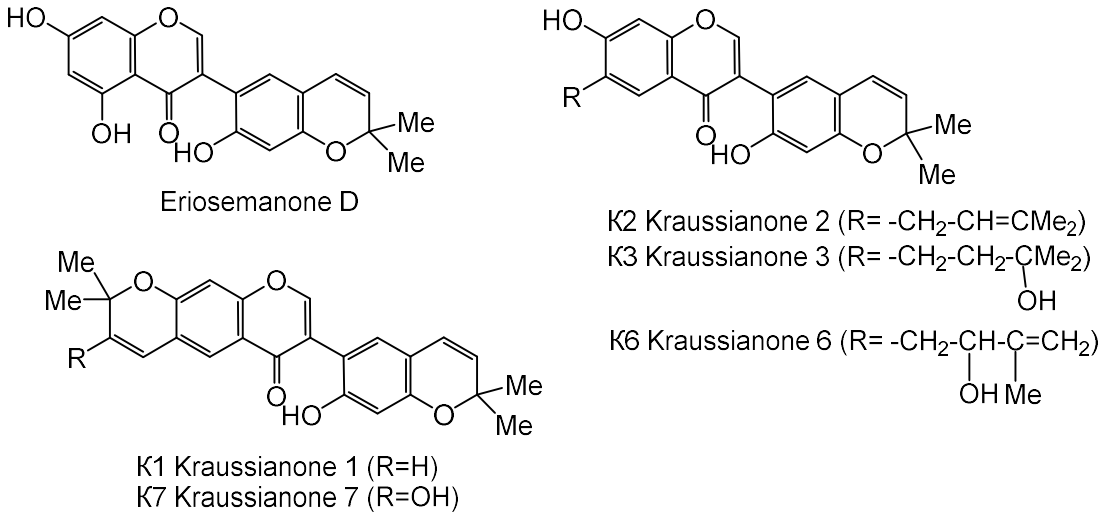
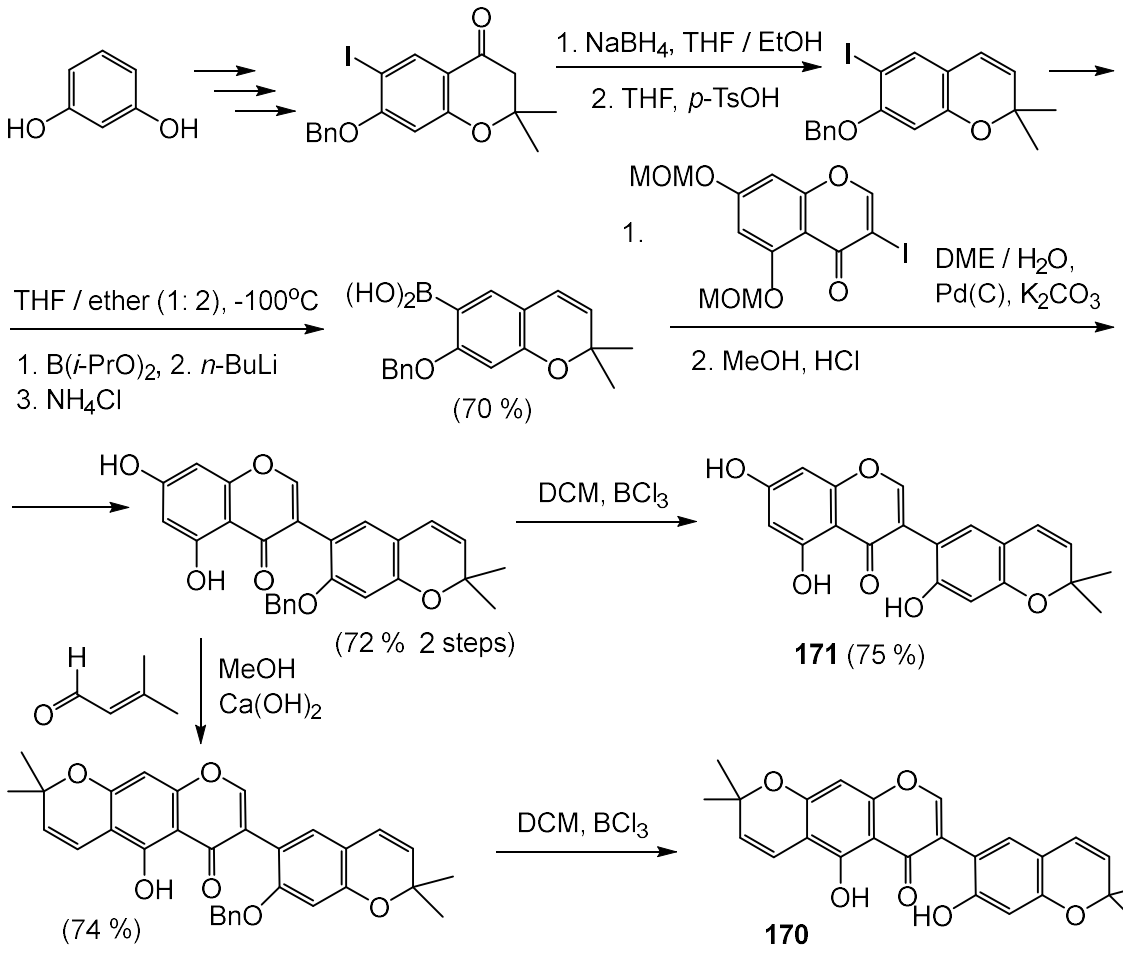


Figure 5. Structures of eriosemaone D and kraussianones K1-K3, K6, K7

The first such isoflavone, isolated from a dichloromethane extract of *E. tuberosum* roots, was named eriosemaone D and showed antifungal activity against *Cladosporium cucumerinum* and *Candida albicans* by TLC bioautography [57]. Five compounds, named Kraussianones K1, K2, K3, K6, K7, were isolated from the roots of *Eriosema kraussianum* N. T. Br. [58, 59]. The plant *Eriosema kraussianum* is traditionally used to treat male impotence and urinary problems in South Africa. In a drug evaluation assay for erectile dysfunction, all compounds K1-K3, K6, K7 were active. K1 and K2 were found to be the most potent metabolites for cavernosal smooth muscle relaxation, demonstrating 85% and 65% activity, respectively, compared to sildenafil (Viagra) at 78 ng/mL. Compounds K1 and K2 also demonstrated significant hypoglycemic and vasorelaxant effects in experimental rat models [60]. Administration of K2 improved various fetal and physiological parameters in pregnant Sprague–Dawley rats treated with L-NAME [61].

3.1. Synthesis of Pyran-Functionalized Isoflavone Analogues

The first general regioselective synthesis of two biologically active compounds, kraussianone 1 (**170**) and eriosemaone D (**171**), using the Suzuki-Miyaura reaction at key stages is shown in **Scheme 43** [62].



Scheme 43. The first general regioselective synthesis kraussianone 1 (**170**) and eriosemaone D (**171**)

Xanthones, whether natural or synthetic, have been the subject of much research due to their broad spectrum of biological activities [63, 64]. The xanthone skeleton has been shown to play a vital role in the development of anticancer drugs, as many of its derivatives have shown anticancer activity in various cell lines. In addition, targeting xanthone derivatives to epigenetic markers of cancer has shown promising results. Biologically active natural compounds with the axially chiral 3-(chromon-3-yl)xanthone skeleton are represented by compounds such as vinaxanthone, (α*R*)-2′-methoxyvinaxanthone, and chaetocyclinone C produced by *Penicillium vinaceum*, which have diverse bioactivities (**Figure 6**).

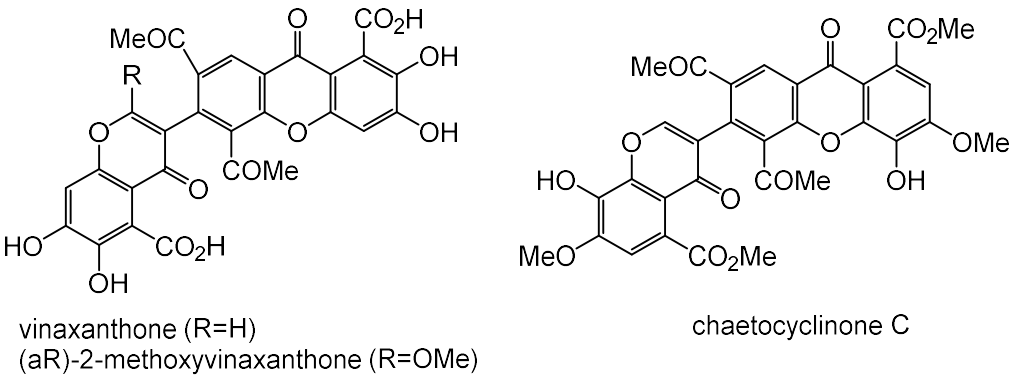
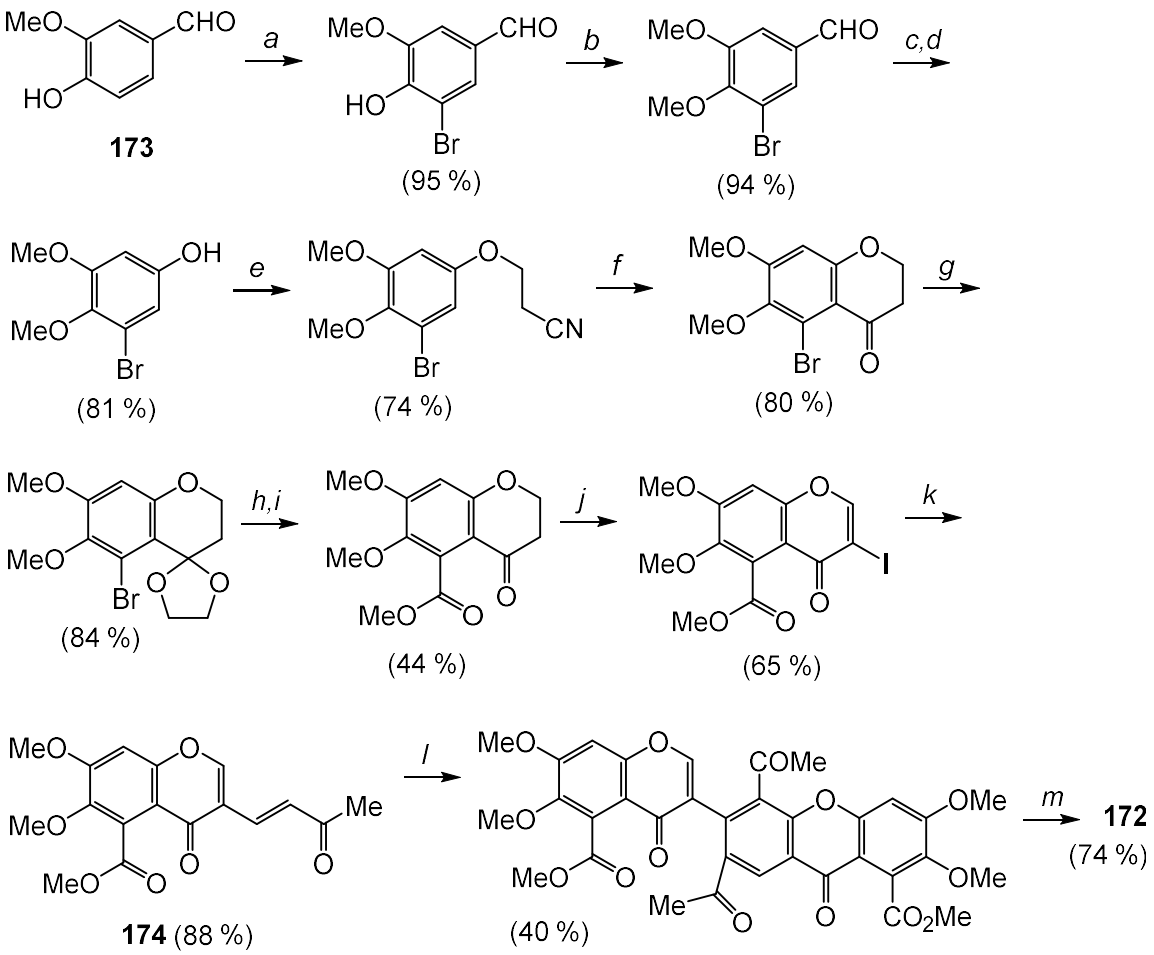


Figure 6. Structures of vinaxanthone, (αR)-2-methoxyvinaxanthone and chaetocyclinone C

Vinaxanthone, first isolated in 1991 from the culture broth of the fungus *Penicillium vinaceum*, exhibited selective inhibitory activity against rat brain phospholipase C, mouse colon 26 adenocarcinoma, and mouse NIH3T3 fibroblasts with IC_{50} of 5.4, 9.3, and 44 μM, respectively [65], is a selective and potent inhibitor of the bacterial enzyme enoyl-AKB reductase of *Staphylococcus aureus* (FabI), and exhibits antibacterial activity against gram-positive multidrug-resistant bacteria, such as methicillin-resistant *S. aureus* (MRSA) and quinolone-resistant *S. aureus* [66].

In addition, vinaxanthone demonstrated significant semaphorin inhibitory activity with an IC_{50} value of 0.1 μg/ml in a semaphorin 3A-induced growth cone collapse assay using cultured chick dorsal root ganglion neurons [67], and exhibits potent inhibitory activity on CD4-anti-Leu3a binding (IC_{50} 2 μM), CD4-MHC class II binding (IC_{50} 1 μM), and antigen-induced proliferation of CD4-dependent T cells (IC_{50} 1–10 μM [68, 69]. Chaetocyclin C, also isolated from the culture broth of the marine fungus *Chaetomium sp*., is active against selected phytopathogenic fungi but is not cytotoxic [70, 71]. The compound (α*R*)-2′-methoxyvinaxantone showed significant inhibition of crown gall tumor growth on potato discs (*Agrobacterium tumefaciens*), indicating antitumor activity *in vivo* and positive results in an antiproliferative, antimitotic, and cytotoxicity assay using eggs and sperm from the gonads of a sea urchin (*Paracentrotus lividus*) [72].

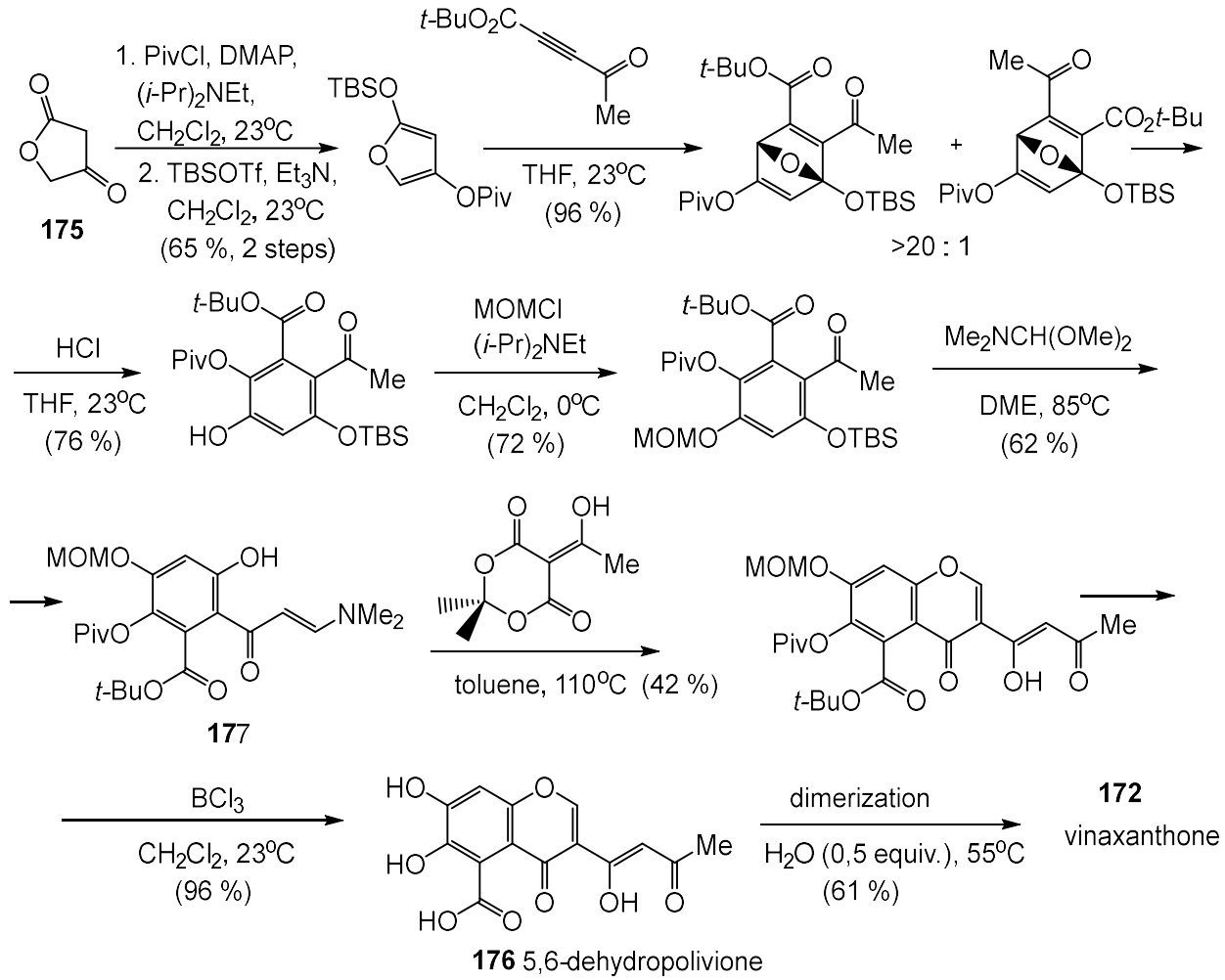
Vinaxanthone (**172**) was biomimetically synthesized from vanillin (**173**) by an intermolecular Diels–Alder cycloaddition between two molecules of precursor **174** (**Scheme 44**) [73].



(*a*) Br_2/AcOH, rt, 6 h; (*b*) Me_2SO_4, K_2CO_3 / acetone. 50°C, 9.5 h;
(*c*) *m*CPBA / CH_2Cl_2, Δ, 11 h; (*d*) 0.1 M Et_3N-MeOH, rt, 3 h;
(*e*) acrylonitrile, DBU, 75°C, 72 h; (*f*) $AlCl_3$ /aq. $MeNO_2$, 60°C, 0.5 h;
(*g*) ethylene glycol, TsOH, $CH(OMe)_3$ / PhMe, 80°C, 11 h;
(*h*) *n*-BuLi, $ClCO_2Me$, THF, -78°C, 1 h; (*i*) 5 % HCl-MeOH,rt, 2 h;
(*j*) I_2 / DMSO, 110°C, 5 h; (*k*) methyl ethyl ketone, $Pd(OAc)_2$, Et_3N / MeCN, 50°C, 7.5 h;
(*l*) DTBMP (2,6-di-tert-butyl-4-methylpyridine) / PhMe, air. 200°C (sealed tube), 24 h;
(*m*) $AlCl_3$ / PhMe, 110°C, 2 h

Scheme 44. The synthesis of vinaxanthone (**172**) from vanillin

The synthesis of vinaxanthone (**172**) from tetronic acid (**175**) by dimerization of the key precursor 5,6-dehydropolivione (**176**) upon heating in deionized water to 55°C (**Scheme 45**) was proposed in [74]. The procedure described above allowed the synthesis of vinaxanthone in nine steps, whereas the previous synthesis [73] required 14 steps to obtain this natural product.

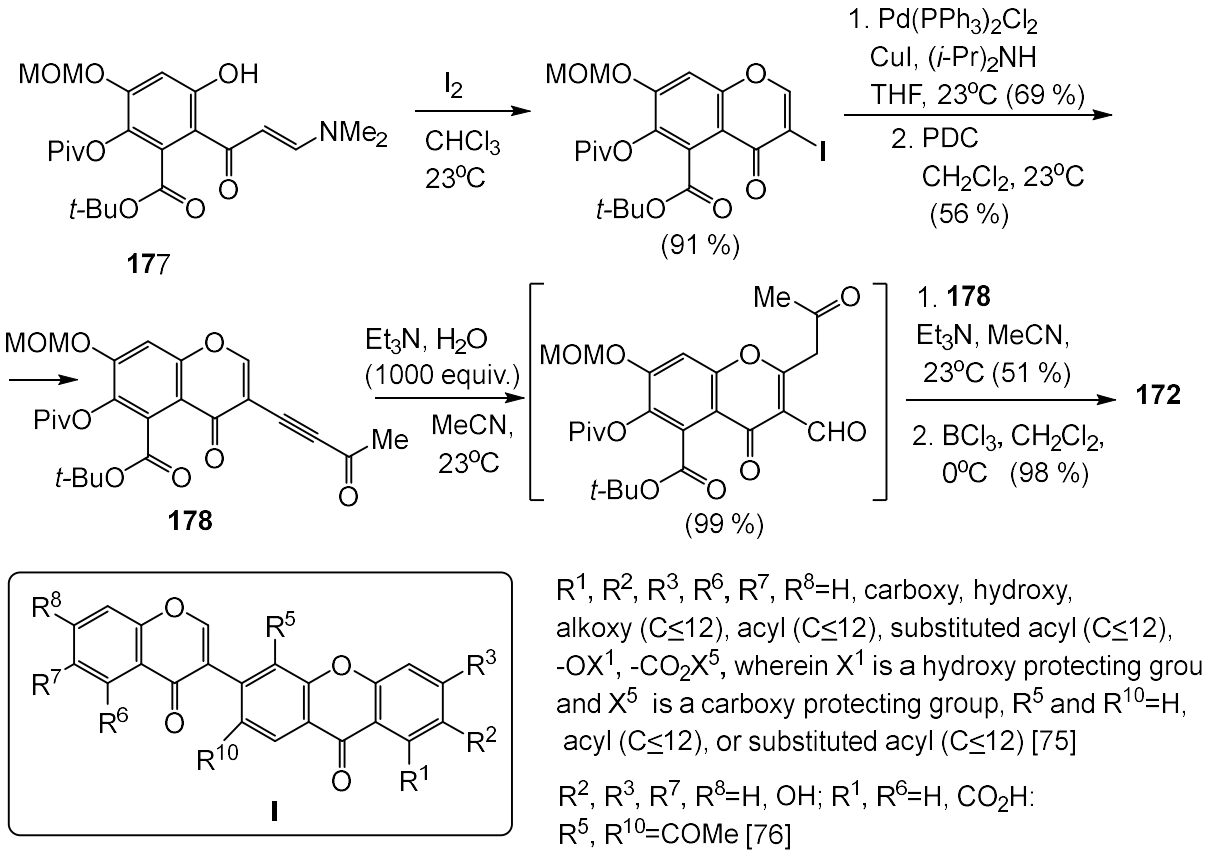


Scheme 45. The synthesis of vinaxanthone (**172**) from tetronic acid

Vinaxanthone was found to enhance neuronal growth in an *in vivo* neurite outgrowth assay. This assay uses green fluorescent protein (GFP)-labeled cholinergic neurons in *C. elegans* to visualize increased branching following treatment with neurotrophic compounds. Similar to other known neurotrophic compounds, vinaxanthone was found to increase the rate of branching in *C. elegans* with 31% of treated animals exhibiting 2 mm of outgrowth. This activity is comparable to dibutyryl cAMP, which promotes branching in 36% of animals at 2 mm [74].

Natural products that promote spinal cord regeneration have significant potential for the accelerated development of new therapeutics and provide a unique and promising platform for therapeutic treatment.

Thanks to the development of a new synthetic strategy based on the coupling reaction of the inone precursor **178**, presented in **Scheme 46**, rapid access to vinaxanthone and its optimized analogs of Formula **I** became possible, with *n* inones generating the formation of n^2 analogs of vinaxanthone [75, 76].



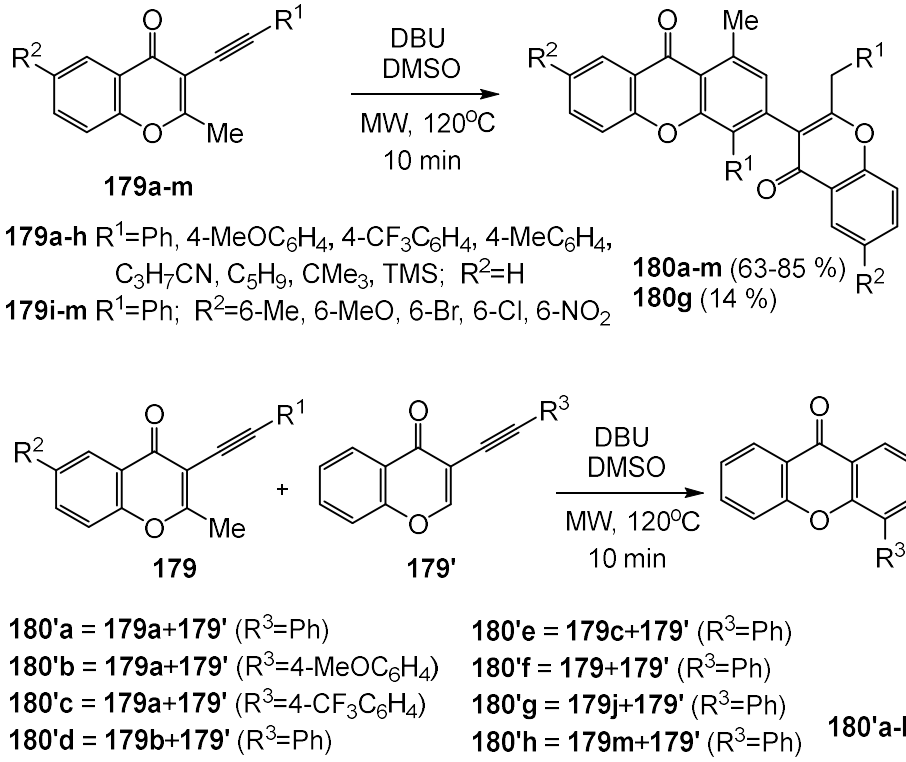
Scheme 46. The synthesis of vinaxanthone (**172**) based on the coupling reaction of the inone precursor **178**

The natural product vinaxantone has demonstrated a remarkable ability to promote neuronal regrowth after injury or transplantation. In rats after complete spinal cord transection, vinaxanthone enhances axonal regeneration, remyelination, and angiogenesis at the site of injury, resulting in improved recovery of motor function [75].

The patented compositions of vinaxanthone (**172**) and its analogs of general Formula **I** promote modulation of G-coupled protein receptor activity, dendritic cell activation, axonal regeneration, neuronal regeneration, cell survival, and are useful for the treatment of a disease or disorder associated with G-coupled protein receptor dysregulation, inflammation, or vascular proliferation, wherein the disease or disorder is various types of cancer, diabetic retinopathy, infection, neurological disease or disorder (e.g., Alzheimer's disease, Parkinson's disease, spinal cord injury) [76].

The synthesis of compounds with a 3-(chromon-3-yl)xanthone skeleton with axial chirality similar to natural compounds was carried out by a cascade dimer reaction of 2-methyl-3-(1-alkynyl)chromones **179** under basic conditions (**Scheme 47**) [77]. Under the selected optimal conditions (**179a-m** (0.4 mmol), DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) (1 equiv.), solvent –DMSO, MW, 120°C) the reaction proceeds in 10 minutes with yields of the target products **180a-m** of 63-85%. And as a result of

the reaction of **179g** (0.6 mmol) at 140°C, a mixture of 4-(*tert*-butyl)-1-methyl-3-(2-neopentyl-4-oxo-4*H*-chromen-3-yl)-9*H*-xanthen-9-one (**180g**) (14%) and 1-neopentyl-3-(2-neopentyl-4-oxo-4*H*-chromen-3-yl)-9*H*-xanthen-9-one (**180'g**) was obtained with a yield of 57%.

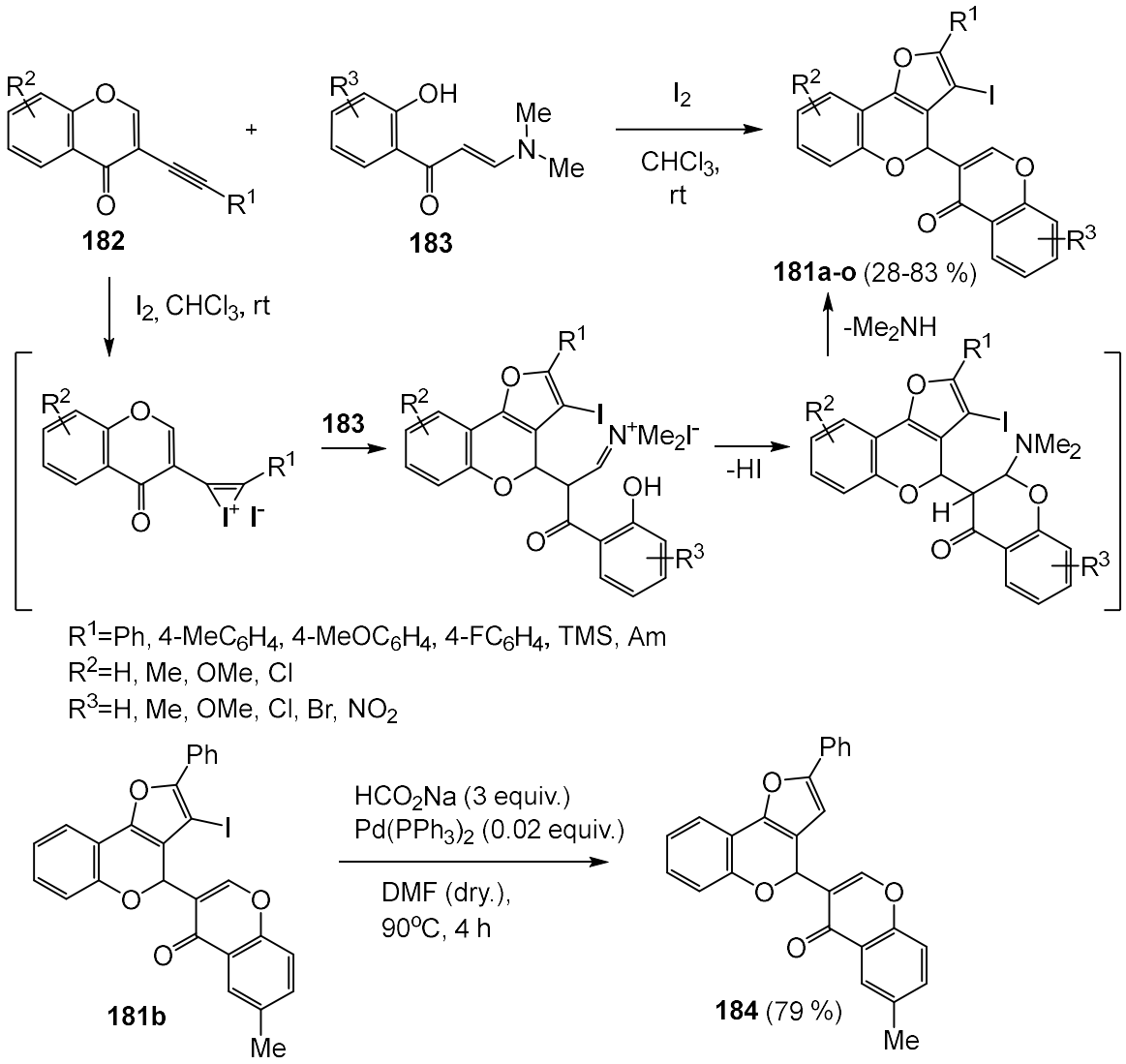


Scheme 47. The synthesis of 3-(4-oxo-4*H*-chromen-3-yl)-9*H*-xanthen-9-ones **180** and **180'**

Investigating the limits of the application of this reaction under selected optimal conditions, cross-dimerization reactions of 2-methyl-3-(1-alkynyl)chromones **179** and 3-(1-alkynyl)chromones **179'** were carried out with the formation of products of the structure **180'**, sometimes together with self-dimeric side products from **179** and **179'.** The reaction of **179** with **179'** (R=Ph) was carried out at 130°C with the formation of 5-(4-oxo-3-(9-oxo-4-phenyl-4*H*-xanthen-3-yl)-4*H*-chromen-2-yl)pentane nitrile (**180'**) in 76% yield.

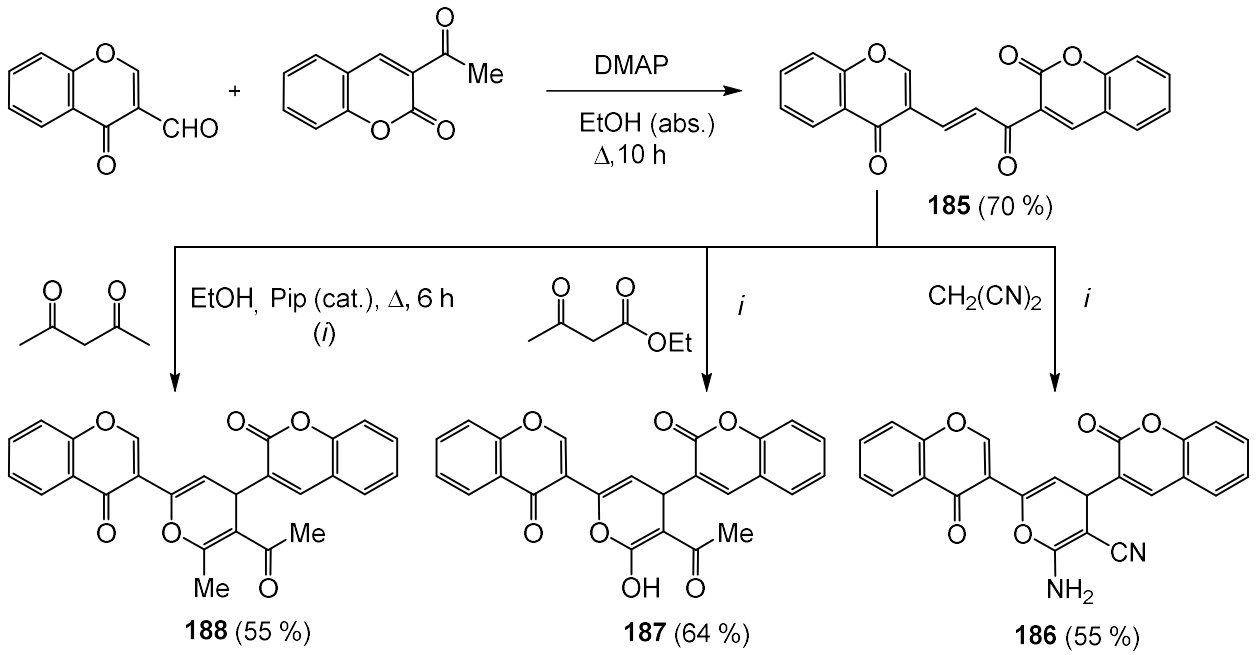
An interesting example of the construction of hybrid structures consisting of furochromene and chromone fragments is 4-(3-chromonyl)furo[3,2-*c*]chromenes **181a-o**, which were reported in [78]. Compounds **181a-o** were obtained by the iodine-catalyzed cascade reaction of 3-(1-alkynyl)chromones **182** with 1-(2-hydroxyaryl)-3-dimethylaminoprop-2-en-1-ones **183**, which serve as nucleophiles. The mechanism of this reaction is illustrated in **Scheme 48** and includes the steps of electrophilic and nucleophilic addition, double cyclization to furan and chroman, and elimination of

dimethylamine. Two new C–O, one C–C, and one C–I bonds are formed in this one-pot cascade reaction, which proceeds under mild conditions without the use of a transition metal, an inert atmosphere, and a dry solvent. The possibility of deiodination of products **181** was investigated using compound **181b** as an example by reductive cleavage of the C–I bond to form 4-(3-chromonyl)furo[3,2-*c*]chromene **184** in 79% yield.



Scheme 48. The synthesis of 4-(3-chromonyl)furo[3,2-*c*]chromenes **181a-o** by the iodine-catalyzed cascade reaction and deiodination of **181b**

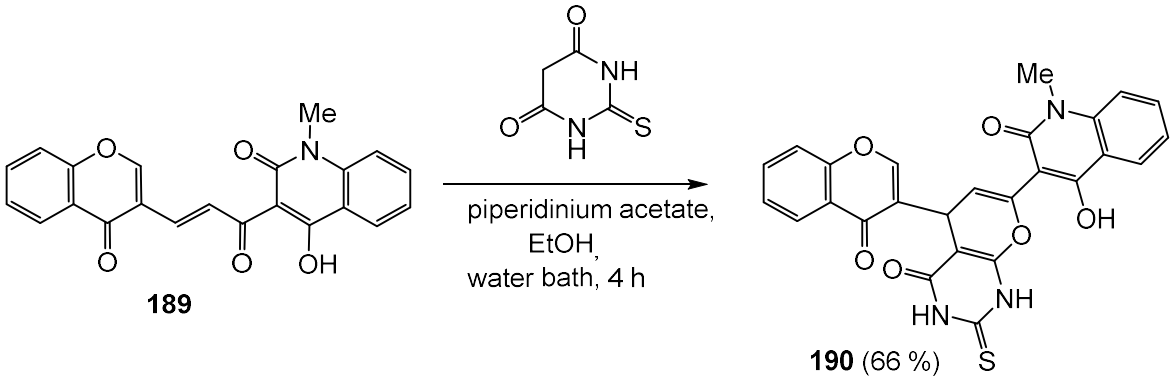
Condensation of the target chromonyl chalcone 3-(3-(4-oxo-4*H*-chromen-3-yl)-acryloyl)-2*H*-chromen-2-one (**185**), synthesized by the reaction of 3-acetylcoumarin with 3-formylchromone using DMAP ($(CH_3)_2NC_5H_4N$) as a catalyst, with active methylene reagents such as malononitrile, ethyl acetoacetate, acetylacetone in alcohol in the presence of a catalytic amount of piperidine leads to the formation of new heterocyclic compounds **186-188** with a combination of chromone, coumarin, and pyran nuclei in one molecule (**Scheme 49**) [79].



Scheme 49. The synthesis of chromone, coumarin and pyran hybrids **186-188**

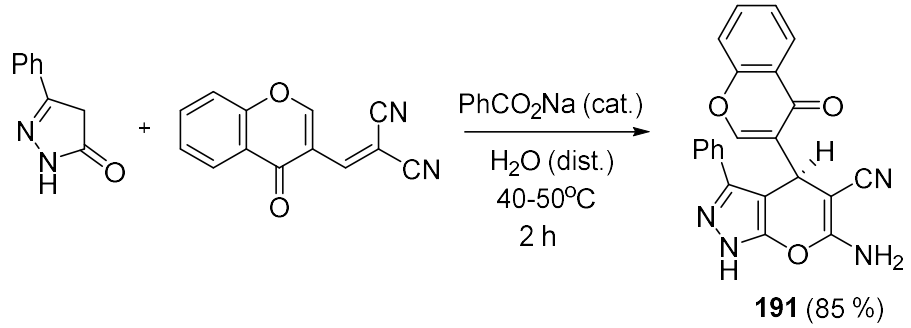
The resulting compounds were tested *in vitro* for their antimicrobial activity: antibacterial activity against two gram-positive (*Staphylococcus aureus* RCMB010010, *Bacillus subtilis* 015(1) NRRL B-543) and two gram-negative bacteria (*Escherichia coli* (RCMB 010052) ATCC 25955, *Proteus vulgaris* RCMB 004(1) ACC 13315) and antifungal activity against yeast strains (*Aspergillus flavus* (RCMB 002002, *Candida albicans* RCMB 005003(1) ATCC 10231). Ketoconazole and gentamicin were used as antifungal and antibacterial standards, respectively, and the test was performed using diffusion agar (6 mm diameter). None of the compounds showed antifungal activity against *C. albicans* and only compound **186** showed activity against *A. flavus* with a mean zone of inhibition of 10 mm versus 16 mm for ketoconazole. Compound **186** showed more potent antibacterial activity than gentamicin. Compound **188** showed moderate activity only against *S. aureus*.

Treatment of another chromonyl chalcone, 4-hydroxy-1-methyl-3-[*E*-3-(4-oxo-4*H*-chromen-3-yl)acryloyl]quinolin-2(1*H*)-one (**189**) (obtained from 3-acetyl-4-hydroxyquinolin-2(1*H*)-one and 3-formylchromone) with 2-thiobarbituric acid in a molar ratio (1:1) in the presence of piperidinium acetate gave a triheterocyclic system containing quinolinone, pyrano[2,3-*d*]pyrimidinone and chromone moieties - 7-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-5-(4-oxo-4*H*-chromen-2-yl)-2-thioxo-1,2,3,5-tetrahydropyrano[2,3-*d*]pyrimidin-4-one (**190**) in 66% yield (**Scheme 50**) [80].



Scheme 50. The synthesis of 7-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-5-(4-oxo-4*H*-chromen-2-yl)-2-thioxo-1,2,3,5-tetrahydropyrano[2,3-*d*]pyrimidin-4-one (**190**)

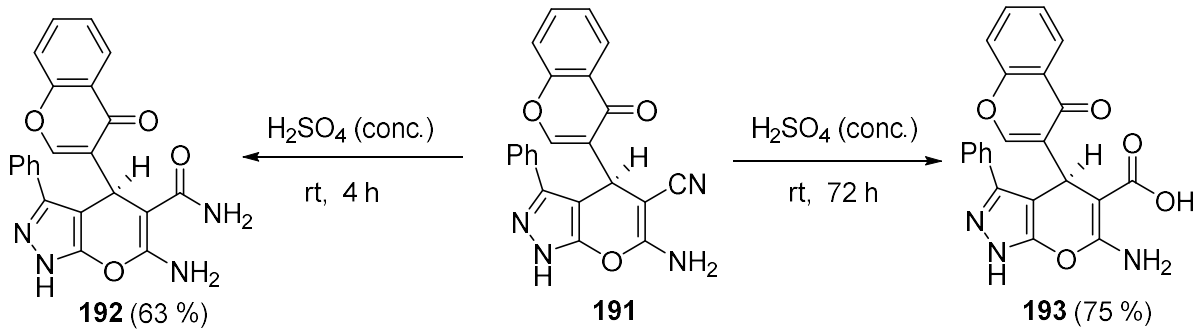
A series of chromone-containing functionalized pyrano[2,3-*c*]pyrazoles, pyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidines, and pyrazolo[4',3':5,6]pyrano[2,3-*d*]oxazines were synthesized from 6-amino-4-(4-oxo-4*H*-chromen-3-yl)-3-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**191**) [81]. The parent compound **191** was obtained by stirring 5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one with 2-[3-(4-oxo-4*H*-chromen-3-yl)methylene]malononitrile in distilled water in the presence of sodium benzoate as a catalyst for 2 h at 40–50°C (**Scheme 51**).



Scheme 51. The synthesis of 6-amino-4-(4-oxo-4*H*-chromen-3-yl)-3-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**191**)

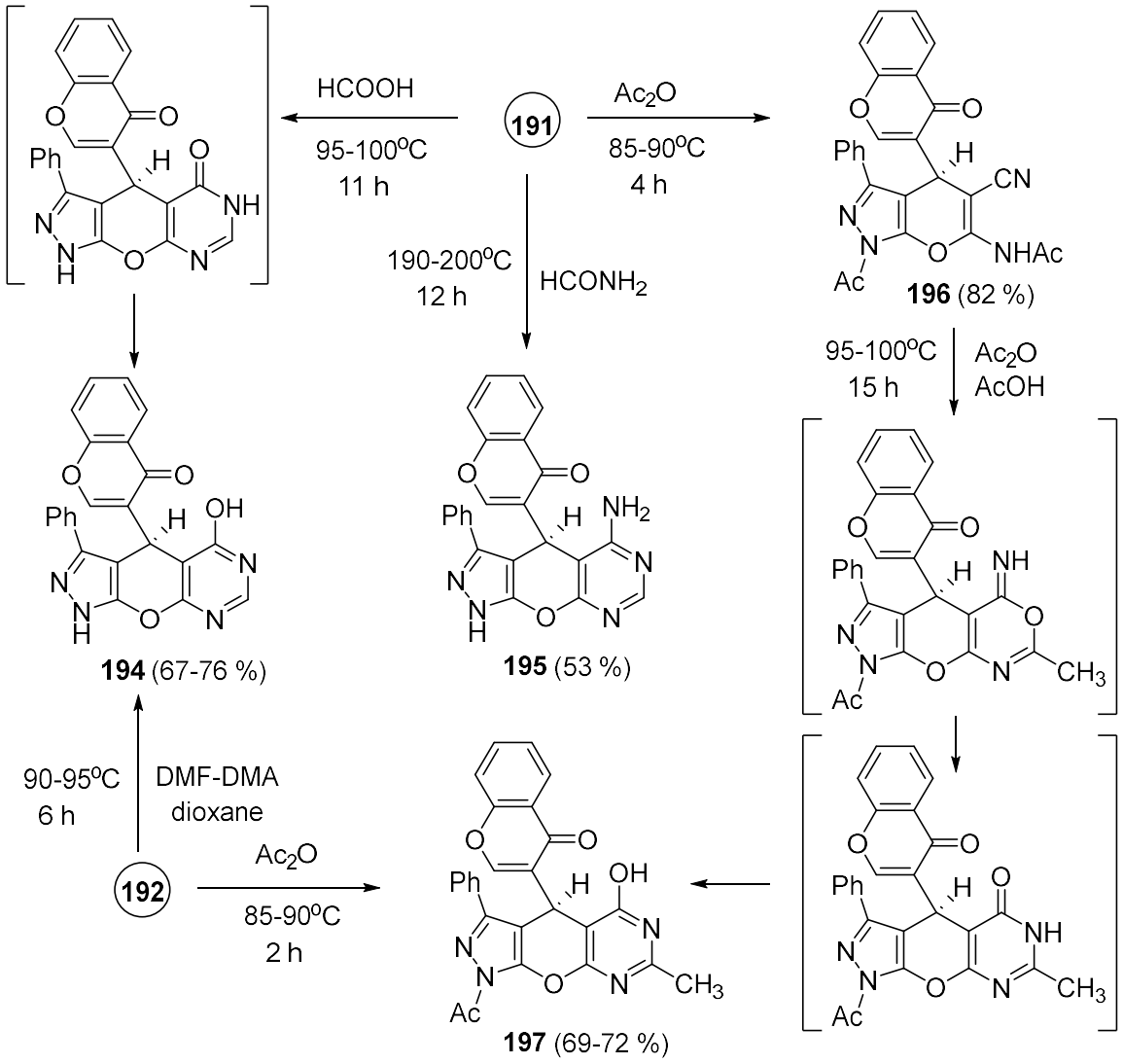
The synthetic possibilities of the base compound **191** are realized through modifications and heterocyclizations carried out on the pyrano[2,3-c]pyrazole fragment.

Modifications of the functional groups of the pyrano[2,3-*c*]pyrazole fragment of the base compound **191** through hydrolysis of the nitrile group under acidic conditions with the formation of 6-amino-4-(4-oxo-4*H*-chromen-3-yl)-3-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxamide (**192**) and 6-amino-4-(4-oxo-4*H*-chromen-3-yl)-3-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylic acid (**193**) are presented in **Scheme 52**.



Scheme 52. The products of hydrolysis of the nitrile group in **191**

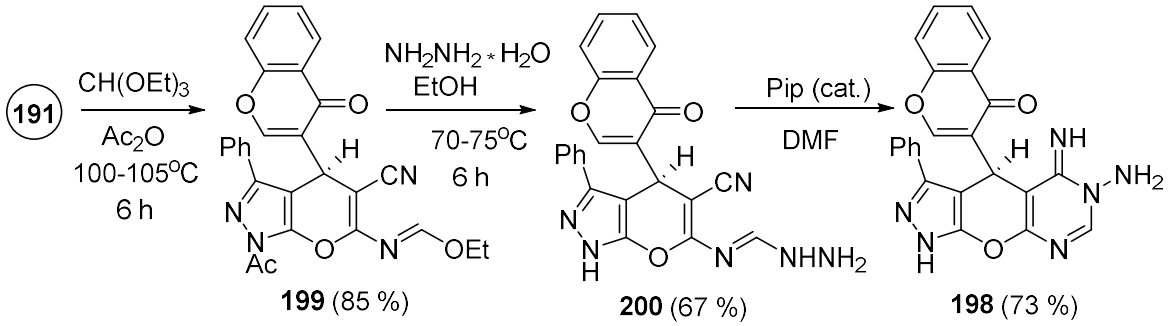
Heterocyclizations at the pyrano[2,3-*c*]pyrazole moiety of compound **191** to form functionalized pyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidines **194**, **195** were carried out by reactions of the parent compound **191** with formic acid and formamide (**Scheme 53**).



Scheme 53. Heterocyclizations at the pyrano[2,3-*c*]pyrazole moieties of **191 and 192** to form functionalized 3-(pyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidin-4-yl)chromones **194**, **195** and **197**

Modifications of the functional groups of the pyrano[2,3-*c*]pyrazole fragment of the parent compound **191** through acylation of the amino group and NH-pyrazole led to the formation of the diacetyl derivative **196**, which upon further heating in a mixture of acetic anhydride and acetic acid forms the functionalized pyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine **197**. Heterocyclization products **194** and **197** were also obtained by the reaction of the aminoamide derivative **192** with dimethylformamide - dimethyl acetal and acetic anhydride. The conditions and yields of the products of the above transformations are presented in **Scheme 53**.

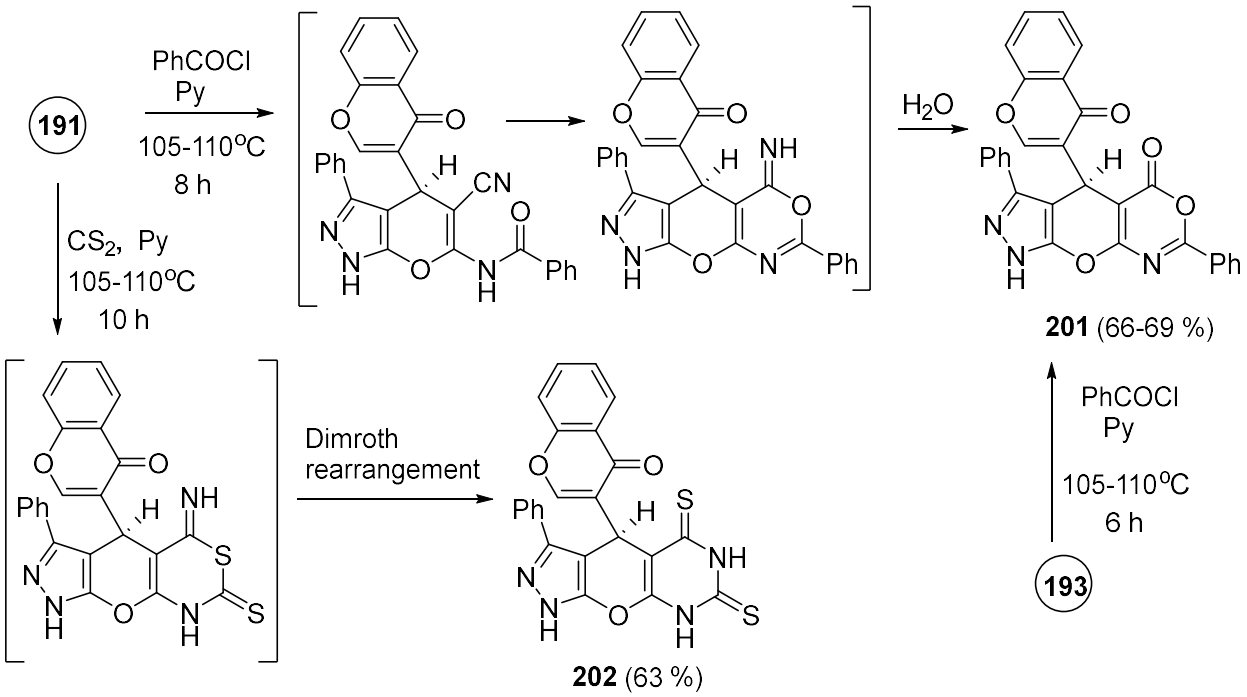
Another variant of heterocyclization at the pyrano[2,3-*c*]pyrazole fragment of compound **191**, which led to the formation of functionalized pyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine **198**, is presented in **Scheme 54**.



Scheme 54. The synthesis of 3-(6-amino-3-phenyl-1,4,5,6-tetrahydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimimidin-4-yl)-4*H*-chromen 4-one **198**

By reacting the base compound **191** with triethyl orthoformate in the presence of acetic anhydride, the formamidate derivative **199 -** the product of modification at the amino group and possible acetylation of the pyrazole nitrogen was obtained. When treating compound **199** with a quantity of hydrazine hydrate in ethanol, the corresponding formimidohydrazide derivative **200** is formed, which was cyclized by boiling in DMF containing a few drops of piperidine to the heterocyclization product **198**.

Heterocyclizations at the pyrano[2,3-*c*]pyrazole fragment, presented in **Scheme 55**, were carried out by reacting both the base compound **191** and its derivative with the carboxyl group **193** with benzoyl chloride to form the functionalized pyrazolopyranooxazine derivative **201** and the reaction of compound **191** with carbon disulfide with formation of a new 5,7-dithioxo-pyrazolopyranopyrimidine derivative **202**.

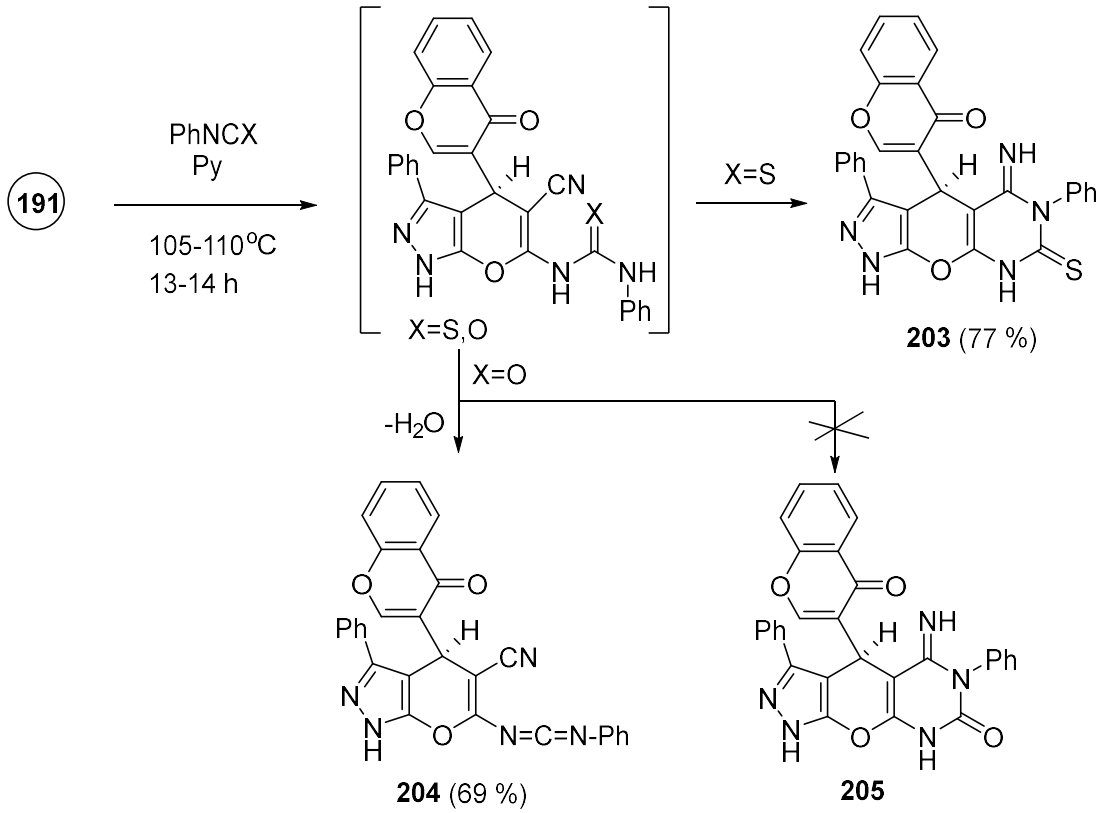


Scheme 55. The synthesis of pyrazolopyranooxazine **201** and 5,7-dithioxo-pyrazolopyranopyrimidine **202**.

The study of the reactivity of the parent compound **191** towards phenylisothiocyanate and phenylisocyanate showed that the reaction with phenylisothiocyanate in dry pyridine via a thiourea intermediate produces the heterocyclization product 3,6-diphenyl-5-imino-4-(4-oxo-4*H*-chromen-3-yl)-7-thioxo-1,4,5,6,7,8-hexahydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine (**203**). In contrast, the use of phenylisocyanate gave the unexpected 4-(4-oxo-4*H*-chromen-3-yl)-3-phenyl-6-{[(phenylimino)methylene]amino}-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**204**) rather than the heterocyclization product **205** (**Scheme 56**).

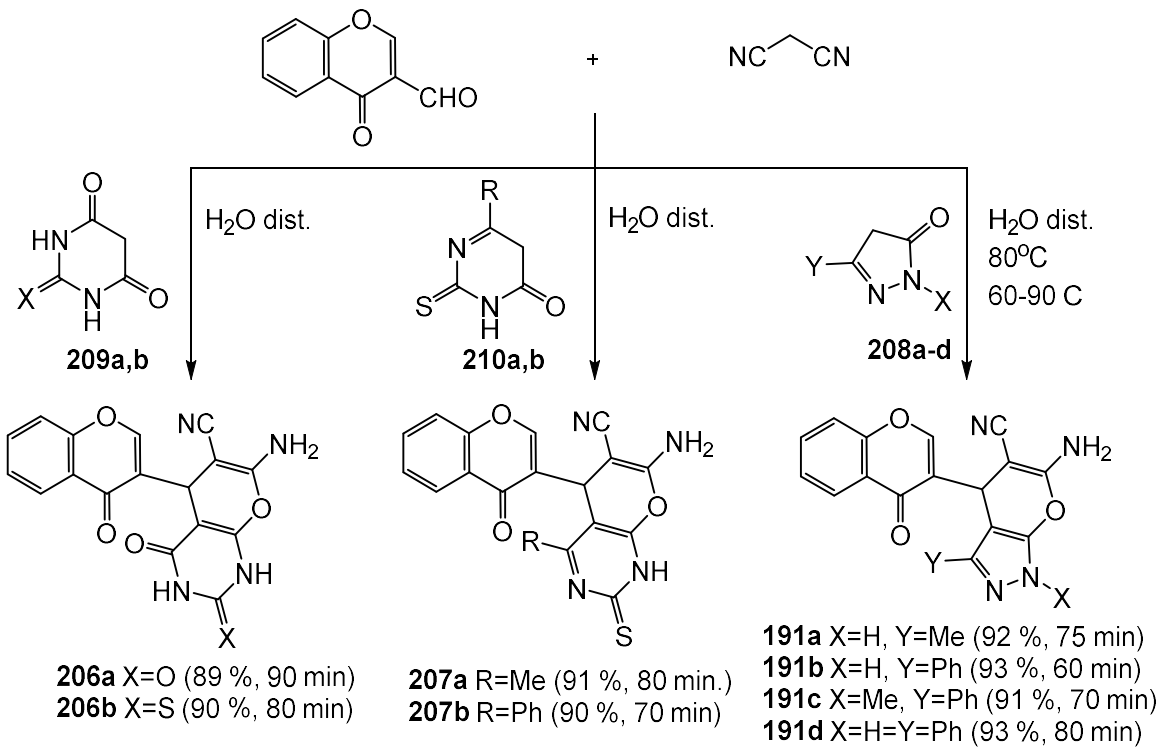
The synthesized compounds were tested for their antioxidant activity *in vitro* using DPPH radical scavenging methods. All samples were evaluated at different concentrations (25, 50, 75, 100 mg/mL) using ascorbic acid as a standard. A preliminary structure–activity relationship study showed that the combination of the pyranopyrazole skeleton with the pyrimidine moiety along with NH and OH groups enhances the overall antioxidant properties. All compounds were able to scavenge DPPH in a concentration-dependent manner. Weak antioxidant activity was found in compounds **196**, **197**, **199**, **204**. Compounds **191** and **200** showed mild, while chromones **192**–**195**, **198**, **202** and **203** showed promising 1,1-diphenyl-2-picrylhydrazyl scavenging activity at all concentrations evaluated with the reference compound. Their high antioxidant activity is explained by the fact that the electronegative heteroatom groups present in them make their NH and OH bonds weak due to their electron-

withdrawing effect. Consequently, the NH and OH bonds are easily homolytically cleaved to form the corresponding free radicals. This study demonstrates that the synthesized derivatives can scavenge radicals, and interesting antioxidant properties are observed after coupling the chromonylpyranopyrazole system with a functionalized pyrimidine moiety.



Scheme 56. The effect of phenylisothiocyanate and phenylisocyanate on **191**

A series of functionalized 4-(chromonyl)pyrano[2,3-*c*]pyrazoles **191** and 5-chromonylpyrano[2,3-*d*]pyrimidines **206**, **207** were synthesized by a one pot three-component reactions of 3-formylchromone, malononitrile and cyclic active methylene compounds, namely pyrazolones **208** and barbituric acids **209a,b** and **210a,b**, respectively, carried out in water as a solvent at 80°C without a catalyst (**Scheme 57**) [82]. It should be noted that this method was more efficient (no catalyst required, higher yield, shorter reaction time) for the synthesis of 4-(chromonyl)pyrano[2,3-*c*]pyrazole **191b** compared to the method described for this compound in [81].



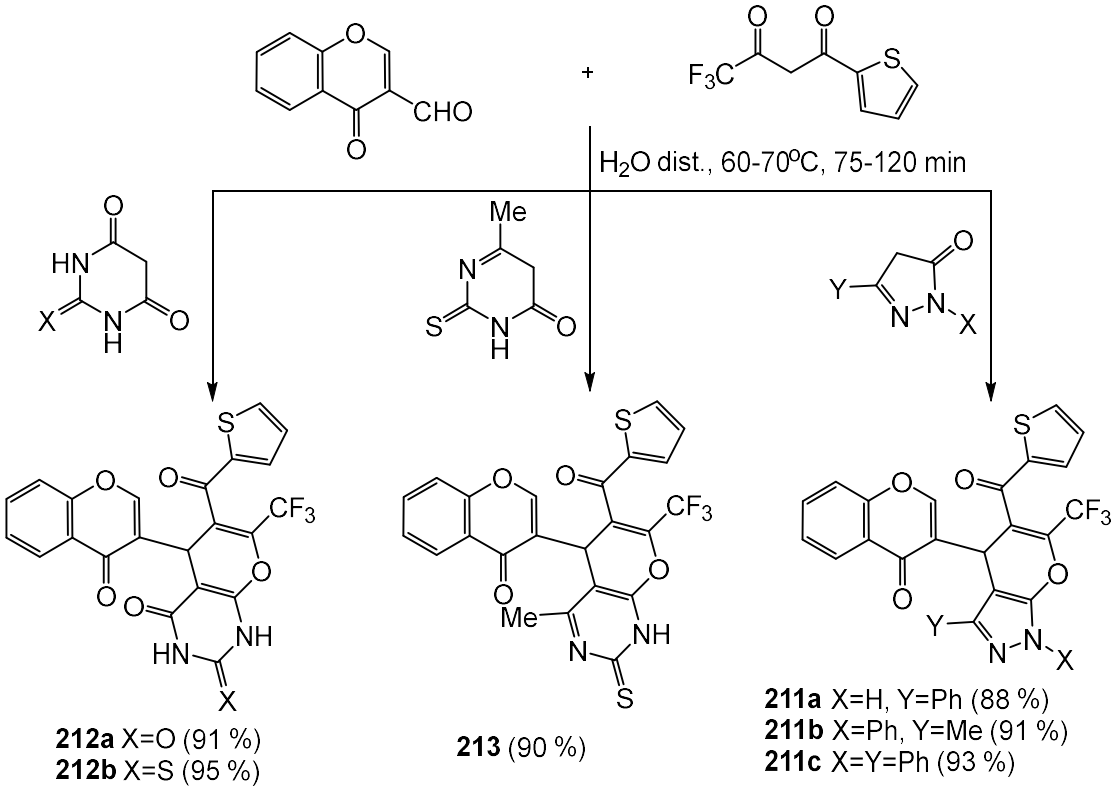
Scheme 57. The synthesis of functionalized 4-(chromonyl)pyrano[2,3-*c*]pyrazoles **191** and 5-chromonylpyrano[2,3-*d*]pyrimidines **206**, **207**

The antiproliferative activity of compounds **191a-d**, **206a,b** and **207a,b** was evaluated *in vitro* against three human cancer cell lines PC-3 (prostate cancer), SKOV3 (ovarian cancer) and HeLa (cervical cancer) in comparison with doxorubicin as a reference drug using the standard sulforhodamine B (SRB) assay. The compounds were tested at different concentrations and the results were expressed as half-maximal inhibitory concentration (IC_{50}) values, i.e. the concentration required to inhibit cell growth by 50% after 72 hours of incubation compared to untreated control cells.

Compounds **191a**, **191c**, **206a** and **207b** showed promising toxic effects in prostate cancer cells (PC-3) with IC_{50} values of 9.7, 13.2, 8.9 and 18.9 μg/mL, respectively, while compounds **191b**, **206b** and **207a** were weakly toxic with IC_{50} values of 34.2, 73.4 and 42.1 μg/mL, respectively. Compounds **191c**, **206a**, **206b** and **207b** showed potent cytotoxicity against human ovarian cancer cells (SKOV3) and cervical cancer cells (HeLa) with IC_{50} values ranging from 4.7 to 16.5 μg/ml. Furthermore, compounds **207a**, **191a** and **191b** have moderate cytotoxicity with IC_{50} values ranging from 32.8 to 55.4 μg/mL. Compound **191d** showed week-long cytotoxic effects against all human cancer cell lines tested. In general, functionalized 5-(4-oxo-4*H*-chromen-3-yl)pyrano[2,3-*d*]pyrimidines **206**, **207** were more active than 4-(4-oxo-4*H*-chromen-3-yl)pyrano[2,3-*c*]pyrazoles **191**. The 3-methyl-1-phenylpyrazole moiety in compound **191c** contributed to improved activity compared

to other pyrazole moieties. Similarly, the barbituric acid moiety fused to the pyran ring contributed to higher activity than the thiobarbituric acid moiety. In addition, the 6-phenylthiouracil moiety induced a better effect than the 6-methylthiouracil moiety.

An efficient method for the synthesis of a series of new 5-(thiophene-2-carbonyl)-6-(trifluoromethyl)pyrano[2,3-*c*]pyrazoles **211a-c** and 6-(thiophene-2-carbonyl)-7-(trifluoromethyl)pyrano[2,3-*d*]pyrimidines **212a,b**, **213** containing a chromone ring is based on a one pot three-component reaction of readily available starting materials 3-formylchromone, 2-thenoyltrifluoroacetone and cyclic active methylene compounds and corresponds to the concept of "green" chemistry. The reaction proceeds without a catalyst in distilled water at a temperature of 60-70°C for 75-120 minutes with yields of 88-95% [83] **(Scheme 58)**.

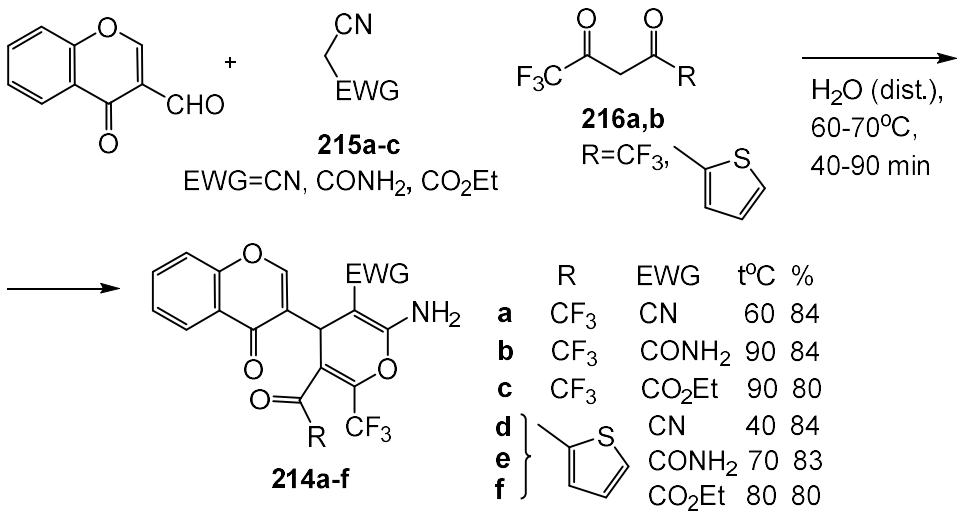


Scheme 58. The synthesis of functionalized 3-(thiophene-2-carbonyl-dihydropyrano[2,3-*d*]pyrimidinyl)- (**212, 213**) and [2,3-*c*]pyrazolyl)chromones **211**

The target compounds were evaluated for their *in vitro* anticancer activity against human breast cancer (MCF-7), liver cancer (HepG-2) and colon cancer (HCT-116) cell lines using the sulforhodamine B (SRB) assay, while doxorubicin was used as a standard comparator. Compounds **211a**, **211c** and **212b** showed excellent antitumor activity against all cancer cell lines with IC_{50} values ranging from 1.7 to 9.9 μg/mL.

The synthesis of 2-amino-4-(4-oxo-4*H*-chromen-3-yl)-5-(2,2,2-trifluoroacetyl)-6-

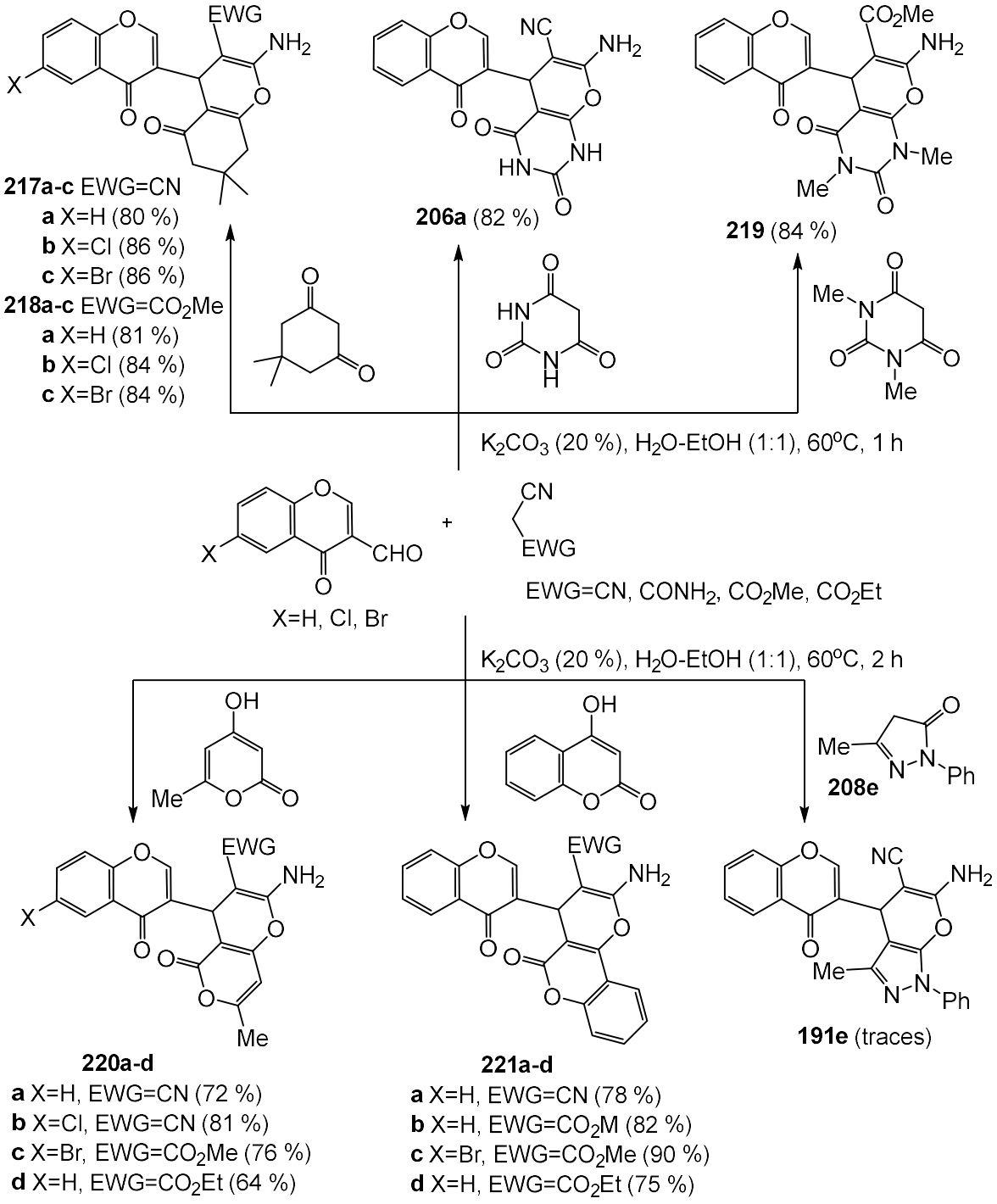
(trifluoromethyl)-4*H*-pyran derivatives **214a-c** and 2-amino-4-(4-oxo-4*H*-chromen-3-yl)-5-(thiophene-2-carbonyl)-6-(trifluoromethyl)-4*H*-pyran **214d-f** was carried out by a one pot three-component reaction of 3-formylchromone, malononitrile, cyanacetamide or alkyl cyanoacetates **215a-c** and 1,1,1,5,5,5-hexafluoropentane-2,4-dione (**216a**) or 1,1,1-trifluoro-5-(thiophene-2-yl)pentane-2,4-dione **216b** in distilled water at 60–70°C without catalyst [84] (**Scheme 59**).



Scheme 59. The synthesis of 2-amino-4-(4-oxo-4*H*-chromen-3-yl)-5-(2,2,2-trifluoroacetyl)-6-(trifluoromethyl)-4*H*-pyran derivatives **214a-c** and 2-amino-4-(4-oxo-4*H*-chromen-3-yl)-5-(thiophene-2-carbonyl)-6-(trifluoromethyl)-4*H*-pyran **214d-f**

The synthesized compounds **214a-f** were evaluated for their anticancer activity *in vitro* at concentrations ranging from 0.01 to 1000 μg/mL against human breast cancer (MCF-7), liver cancer (HepG-2) and colon cancer (HCT-116) cell lines using standard sulforhodamine B colorimetric assay results for cytotoxicity screening and compared with the results obtained for doxorubicin as a reference. Compounds **214d** and **214e** did not show any significant cytotoxicity on all cancer cells tested. Compounds **214b** and **214c** showed moderate cytotoxicity against human breast cancer (MCF-7) cell lines with IC_{50} values of 14.5 and 12.9 μg/mL, respectively. Promising activity against MCF-7 cell lines was observed for compounds **214a** and **214f** (IC_{50} of 1.3 and 1.6 μg/mL, respectively, versus 1.4 μg/mL for doxorubicin). Moderate cytotoxic effects with IC_{50} values of 23.2 and 16.7 μg/mL were observed for compound **214f** against HepG-2 and HCT-116 cancer cell lines, respectively. Compounds **214a-c** demonstrated excellent antitumor activity against HepG-2 and HCT-116 cancer cell lines with IC_{50} values ranging from 0.7 to 7.3 μg/mL. The presence of the trifluoroacetyl group in compounds **214a-c** contributes to the cytotoxic effect to a greater extent than the thienyl group in

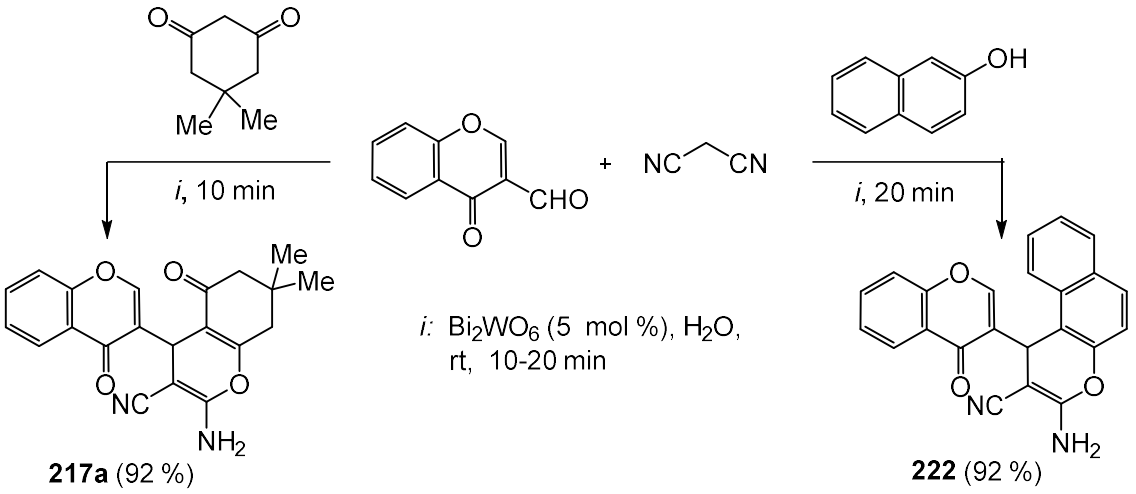
compounds **214d-f**. Nitrile **214a** was shown to be a more effective antitumor agent than amide **214b** or ester **214c**. The presence of the COOEt group in compound **214f** contributes to enhanced cytotoxic activity compared to nitrile **214d** and amide **214e**. 2-Amino-4-(4-oxo-4*H*-chromen-3-yl)-5-(2,2,2-trifluoroacetyl)-6-(trifluoromethyl)-4*H*-pyran-3-carbonitrile (**214a**) demonstrated excellent antitumor activity against all tested cancer cell lines with IC_{50} values ranging from 0.7 to 1.4 μg/mL [84].



Scheme 60. The synthesis of 3-hetarylchromones with various functionalized pyran-annelated heterocycles

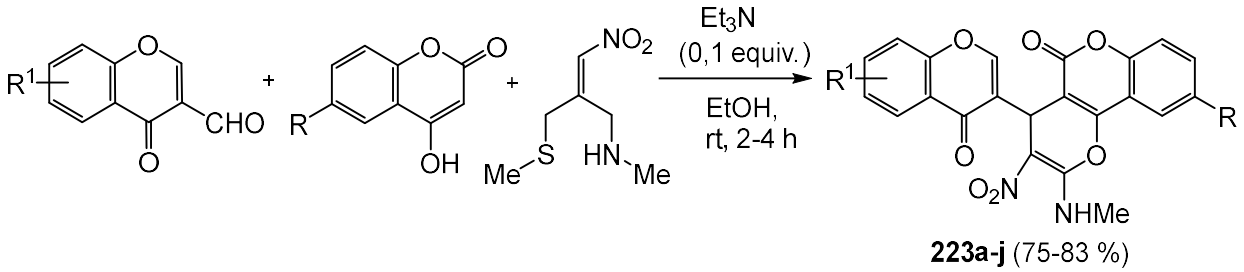
A series of 2'-amino-7',7'-dimethyl-4,5'-dioxo-5',6',7',8'-tetrahydro-4*H*,4′*H*-[3,4′-bichromene]-3′-carbonitrile/carboxylate derivatives **217**/**218**, 7-amino-2,4-dioxo-5-(4-oxo-4*H*-chromen-3-yl)-2,3,4,5-tetrahydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile/carboxylate derivatives **206a**/**219** and a series of chromenylpyrano[*b*]pyran and chromenylpyrano[*c*]coumarin derivatives **220** and **221** were prepared by a K_2CO_3 (20%) catalyzed a one pot three-component reaction of (un)substituted 3-formylchromone, malononitrile or alkylcyanoacetates and cyclic 1,3-diones, such as dimedone or barbiturates, and 4-hydroxy-6-methyl-2-pyrone or 4-hydroxycoumarin in aqueous media. It should be noted that in the three-component reaction of 3-formylchromone, malononitrile and 5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (**208e**) under the above conditions, the expected product chromenyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole **191e** was formed only in trace amounts [85] (**Scheme 60**).

Using the methodology of a one pot multicomponent reactions mediated by Bi_2WO_6 nanoparticles as a heterogeneous catalyst (at room temperature, in an aqueous medium) with the participation of 3-formylchromone, malononitrile and dimedone or β-naphthol, the synthesis of 2-amino-7,7-dimethyl-4,5-dioxo-5,6,7,8-tetrahydro-4*H*,4'*H*-(3,4'-bichromene)-3-carbonitrile (**217a**) and 3-amino-1-(4-oxo-4*H*-chromen-3-yl)-1*H*-benzo[*b*]chromene-2-carbonitrile (**222**) was carried out. Bi_2WO_6 nanoparticles showed excellent reactivity for generating a library of compounds with different frameworks (DHP (dihydropyran), polyhydroquinolines, 4*H*-chromenes and 2-amino-4*H*-benzo[*b*]pyrans), while the catalyst can be regenerated and reused up to 5 times without loss of catalytic activity [86] (**Scheme 61**).



Scheme 61. The synthesis of 3-hetarylchromones with functionalized pyran-annelated heterocycles **217** and-**222** via a one pot multicomponent reactions mediated by Bi_2WO_6

The efficient synthesis of a series of 2-(methylamino)-3-nitro-4-(4-oxo-4*H*-chromen-3-yl)pyrano[3,2-*c*]chromen-5(4*H*)-one (**CCN**) derivatives **223a-j** was carried out using domino reactions of Knoevenagel condensation/Michael addition/intramolecular *O*-cyclization of 4-hydroxycoumarin and 3-formylchromone with N-methyl-1-(methylthio)-2-nitroethylene-1-amine (NMSM) under the developed optimal conditions shown in **Scheme 62** [87].

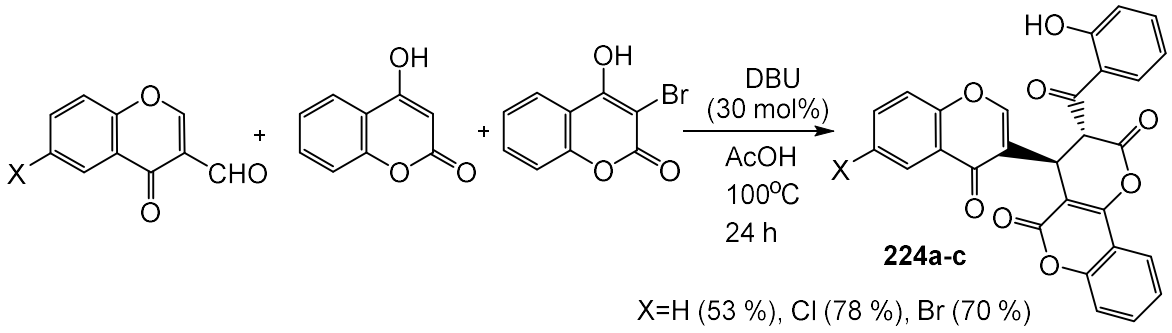


Scheme 62. The synthesis of 2-(methylamino)-3-nitro-4-(4-oxo-4*H*-chromen-3-yl)pyrano[3,2-*c*]chromen-5(4H)-one derivatives **223**

The results of the evaluation of compounds **223a-j** for antimicrobial activity against Gram-positive bacteria, Gram-negative bacteria and yeast showed that all compounds were inactive against yeast, and the best activity against Gram-positive and Gram-negative bacteria among all compounds was shown by compound **223a** (R=R^1=H) (**CCN**). When evaluated for cytotoxicity against MCF-7, Hep-2 and Vero cancer cell lines, compound **CCN** showed IC_{50} values of 5.4 μg/mL, 5.3 μg/mL and 68.4 μg/mL, respectively. The compound **CCN** impregnated into a collagen scaffold has the potential to mimic the function of the extracellular matrix as a biomaterial in the field of tissue engineering. The nature of the collagen scaffold impregnated with **CCN** molecule did not show any structural changes after impregnation with **CCN** molecule. It demonstrated good thermal, mechanical and swelling properties. The antimicrobial activity of collagen (COL) scaffold impregnated with **CCN** was evaluated selectively against two bacterial strains, *Staphylococcus aureus* and *Escherichia coli*. The COL scaffold with a **CCN** molecule concentration of 0.2 mg/20 x 10 mm^2 showed gradual diffusion of **CCN** from the COL scaffold to form a clear zone, indicating that the **CCN** compound exhibited excellent bactericidal activity. The COL-**CCN** scaffold material was found to be a promising biomaterial that would prevent infection around the wound area, and the NIH 3T3 fibroblast demonstrated excellent biocompatibility *in vitro*. The COL-**CCN** scaffold demonstrated enhanced cell attachment and proliferation of NIH 3T3 fibroblast cells.

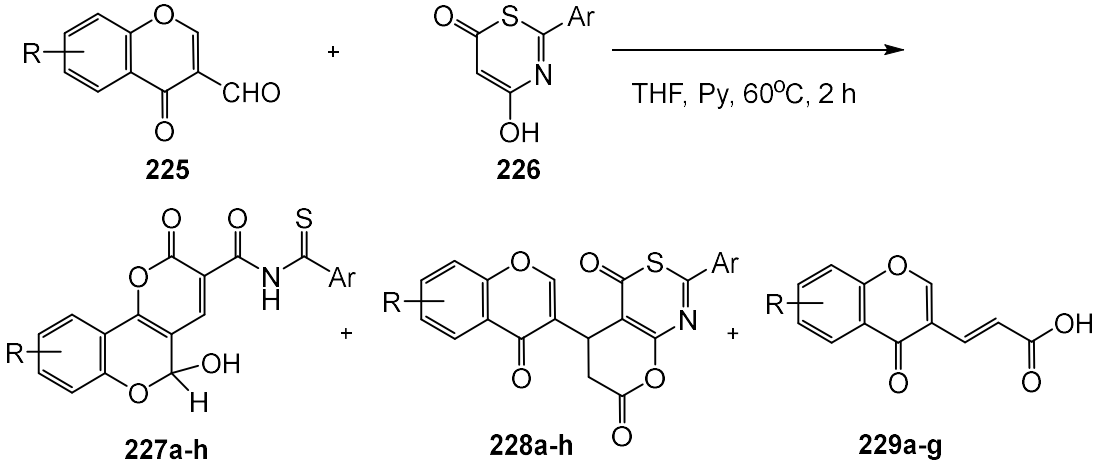
The diastereoselective synthesis of pyranofused coumarins functionalized with a

chromone moiety - derivatives of 3-(2-hydroxybenzoyl)-4-(4-oxo-4*H*-chromen-3-yl)-3,4-dihydropyrano[3,2-*c*]chromene-2,5-dione **224a-c** was achieved by a three-component tandem reaction of 3-bromo-4-hydroxycoumarin, (un)substituted 3-formylchromones and 4-hydroxycoumarin using the DBU/HOAc system organocatalyst in good yields [88] (**Scheme 63**). This synthesis serves as a good complement to group purification (GAP) chemistry because it does not require purification of the reaction products by chromatography and/or recrystallization, and pure products were obtained simply by washing the crude products with methanol.



Scheme 63. The synthesis of 3-(2-hydroxybenzoyl)-4-(4-oxo-4*H*-chromen-3-yl)-3,4-dihydropyrano[3,2-*c*]chromene-2,5-diones **224**

The reaction of 3-formylchromones **225** with 2-aryl-4-hydroxy-6*H*-1,3-thiazin-6-ones **226** in tetrahydrofuran in the presence of pyridine leads to the formation of a mixture of N-thioaroyl-5-hydroxy-2*H*,5*H*-pyrano[3,2-*c*]chromen-2-one-3-carboxamides **227a-h** and 2-aryl-5-(4'-oxochromen-3'-yl)-6,7-dihydro-4*H*,5*H*-pyrano[2,3-*d*][1,3]thiazin-4,7-diones **228a-h**. The common by-products are (2*E*)-3-(4-oxo-4*H*-chromen-3-yl)prop-2-enoic acids **229a–g**. The overall yield of **227**, **228**, and **229** is 55–75%. All three groups of compounds could be easily isolated from the products mixture [89] (**Scheme 64**).



Scheme 64. Reaction products of 3-formylchromones **225** with 2-aryl-4-hydroxy-6*H*-1,3-thiazin-6-ones **226**

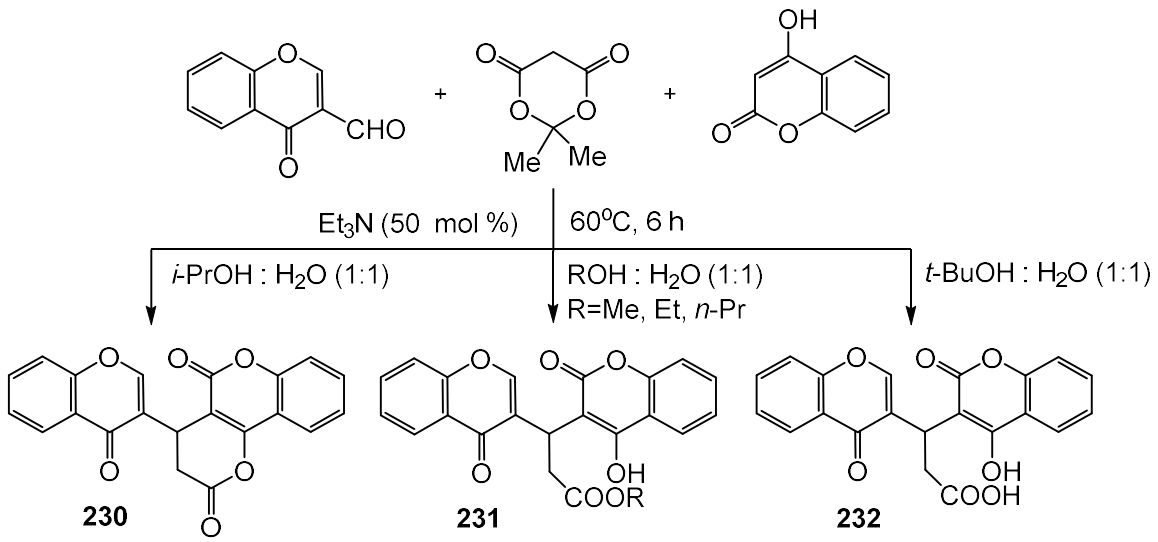
Table 7. Reaction products of 3-formylchromones with 2-aryl-4-hydroxy-6*H*-1,3-thiazin-6-ones

226	Ar	**225**	R	Products (%)		
226a	Ph	**225a**	7-Me	**227a** (33)	**228a** (32)	**229a** (16)
		225b	6-OMe	-	**228b** (32)	**229b** (18)
		225c	6-OH	-	**228c** (48)	**229c** (18)
		225d	6-Me	**227b** (35)	**228d** (31)	**229d** (17)
		225e	H	**227c** (40)	**228e** (29)	**229e** (14)
		225f	6-Cl	**227d** (60)	**228f** (5)	**229f** (17)
		225g	6-Br	**227e** (65)	**228g** (5)	**229g** (14)
		225h	6-NO_2	**227f** (52)	**-**	**-**
226b	4-MeC_6H_4	**225d**	6-Me	**227g** (38)	**228h** (35)	**229d** (13)
		225g	6-Br	**227h** (66)	**-**	**229g** (14)

The yields of these compounds clearly depend on the nature of the substituent in 3-formylchromone **225** and on the reaction conditions. As can be seen from **Table 7**, chromones with electron-withdrawing substituents (Br, Cl, NO_2) form predominantly pyranochromenes **227**, while chromones with a strong electron-donating substituent (MeO) react with thiazines to form pyranothiazines **228**. Unsubstituted and alkylchromones form mixtures of products **227** and **228** in approximately equal yields.

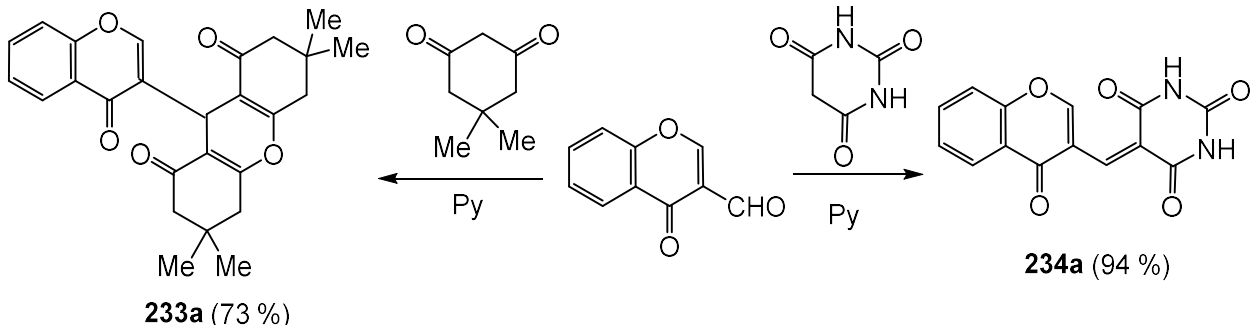
Another important factor affecting the yield was the solvent used. Compounds **227** are formed in the presence of pyridine. The use of THF or MeCN led to a decrease in the yield of **227** and a longer reaction time. Furthermore, when thiazines **226** were reacted with 6-bromo- or 6-chlorochromones **225f,g** in glacial acetic acid, the corresponding pyranothiazines **228f,g** were obtained in 60% yield. Alcohols cannot be used as solvents due to the unstable nature of thiazine under these conditions.

The four-component reaction of 3-formylchromone, Meldrum's acid, 4-hydroxycoumarin and *i*-propanol in aqueous medium in the presence of triethylamine (50 mol%) resulted in the formation of the cyclic product 4-(4-oxo-4*H*-chromen-3-yl)-3,4-dihydropyrano[3,2-*c*]chromene-2,5-dione **230**, in contrast to the reaction products **231** and **232** formed in this reaction with other alcohols (**Scheme 65**). In this case, the OH group of coumarin acts as an intramolecular nucleophile in the presence of base [90].



Scheme 65. The products of the reaction of 3-formylchromone with Meldrum's acid, 4-hydroxycoumarin and alcohols

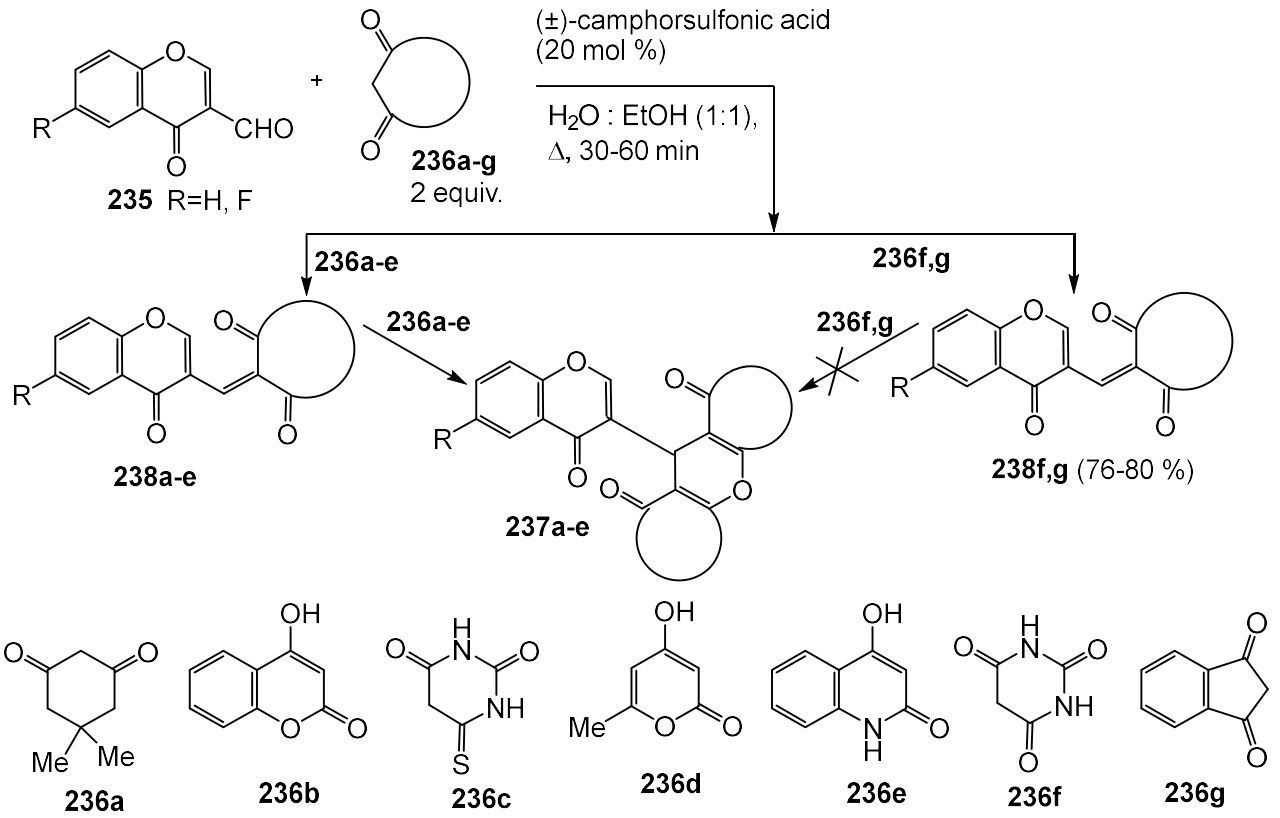
The reaction of 3-formylchromone with 2 equiv. dimedone in pyridine at room temperature followed by treatment with concentrated HCl and recrystallization from EtOH acidified with HCl gave the condensation product 3-(3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthen-9-yl)chromone **233.** A similar reaction with barbituric acid (~ 1.3 equiv.) gave 5-(4-oxo-4*H*-benzopyran-3-ylmethylene)barbituric acid **234** [91] (**Scheme 66**).



Scheme 66. The products of the reaction of 3-formylchromone with dimedone and barbituric acid

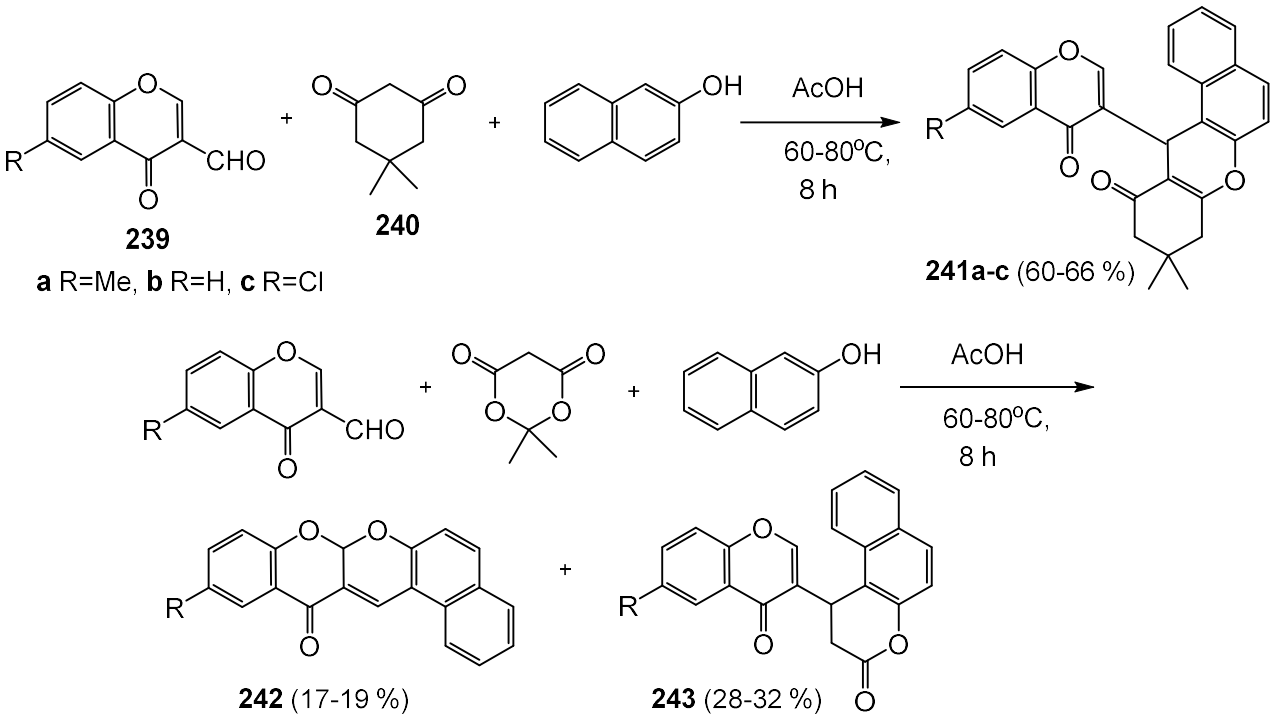
The study of the reaction of (un)substituted 3-formylchromones **235** with (hetero)cyclic 1,3-dicarbonyl compounds **236a-g** (at a ratio of 1:2) in 50% aqueous EtOH in the presence of (±)-camphorsulfonic acid as a catalyst showed that the structure of the final product is precisely influenced by the nature of the cyclic 1,3-diketones. The reaction of 3-formylchromones **235** with active methylene compounds **236a–e** gave pyran-functionalized

isoflavone analogues **237a–e**, while the reaction with barbituric acid (**236f**) and 1,3-indanedione (**236g**) led only to the corresponding Knoevenagel adducts **238f** and **238g**, which do not react with the second molecule of the active methylene compound [92] (**Scheme 67**).



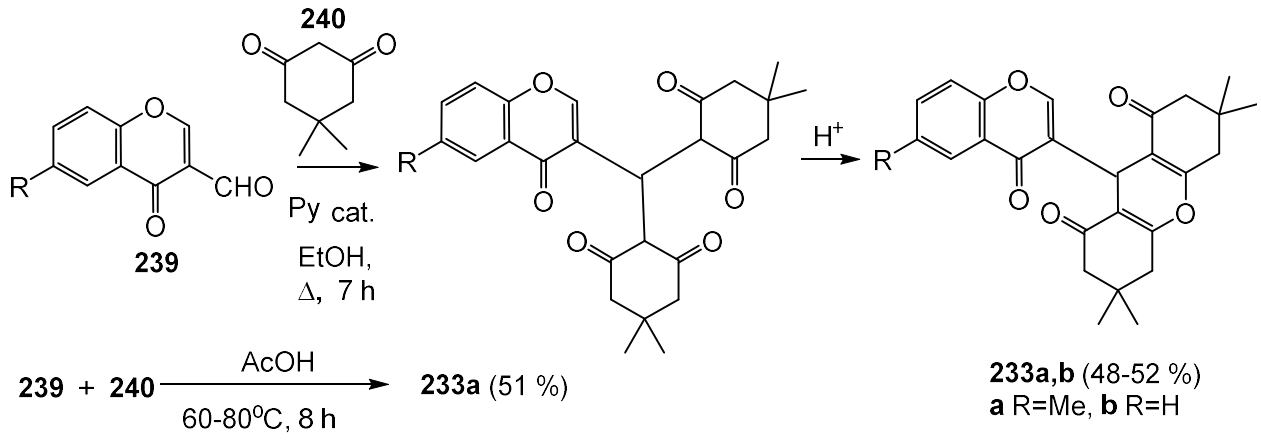
Scheme 67. The products of the reaction of 3-formylchromone with (hetero)cyclic 1,3-dicarbonyl compounds **236a-g** in the presence of (±)-camphorsulfonic acid as a catalyst

When an equimolar mixture of 6-substituted 3-formylchromones **239**, β-naphthol, and dimedone **240** is heated in AcOH, 3,3-dimethyl-11-(4-oxo-4*H*-1-benzopyran-3-yl)-1,2,3,4-tetrahydronaphtho[2,1-*b*]-1-benzopyran-11*H*-1-ones **241a-c** are formed, while under similar conditions, when Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) is used instead of dimedone, a mixture of 1-benzopyrano[2,3-*b*]naphtho[1,2-e]pyran-7*H*,13*H*-13-ones **242a-c** and 3,4-dihydro-4-(4-oxo-4*H*-1-benzopyran-3-yl)naphtho[2,1-*b*]pyran-2*H*-2-ones **243a-c** is formed [93] (**Scheme 68**).



Scheme 68. The products of three component reactions of 3-formylchromones and β-naphthol with dimedone or Meldrum's acid

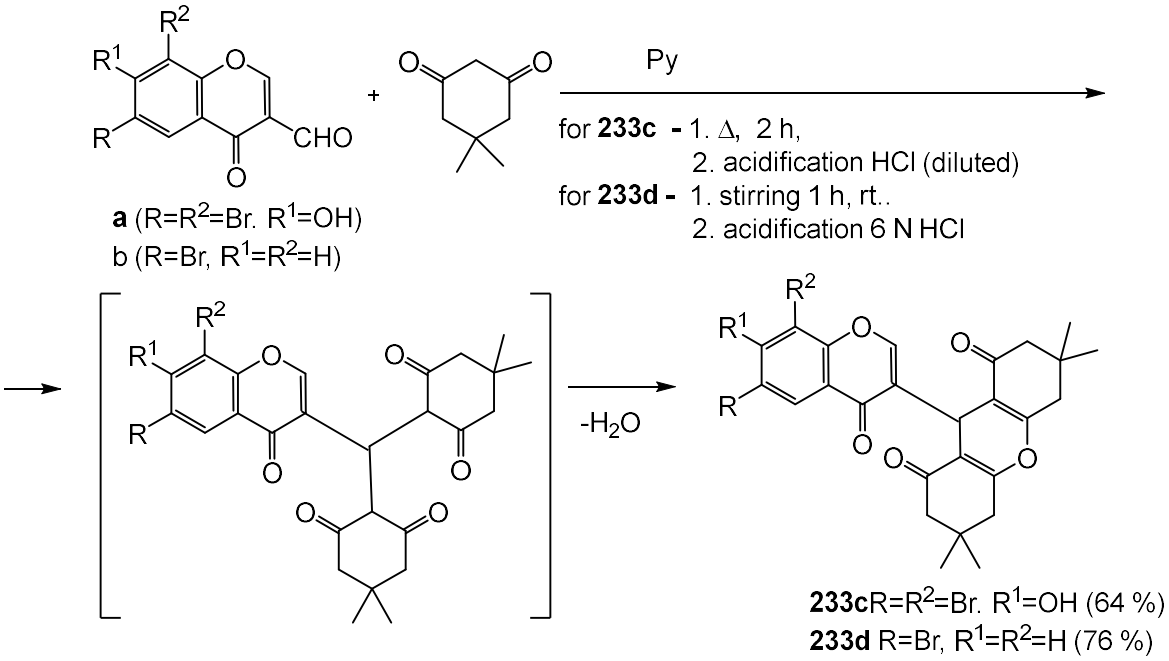
Heating an equimolar mixture of 6-substituted 3-formylchromones **239** and dimedone **241** in ethyl alcohol with catalytic amounts of pyridine or in acetic acid produces 1,2,3,4,5,6,7,8-octahydro-3,3,6,6-tetramethyl-9-(4-oxo-4*H*-1-benzopyran-3-yl)-9*H*-xanthene-1,8-diones (**233a,b**) [93] (**Scheme 69**).



Scheme 69. The synthesis of 1,2,3,4,5,6,7,8-octahydro-3,3,6,6-tetramethyl-9-(4-oxo-4*H*-1-benzopyran-3-yl)-9*H*-xanthene-1,8-diones **233a,b**

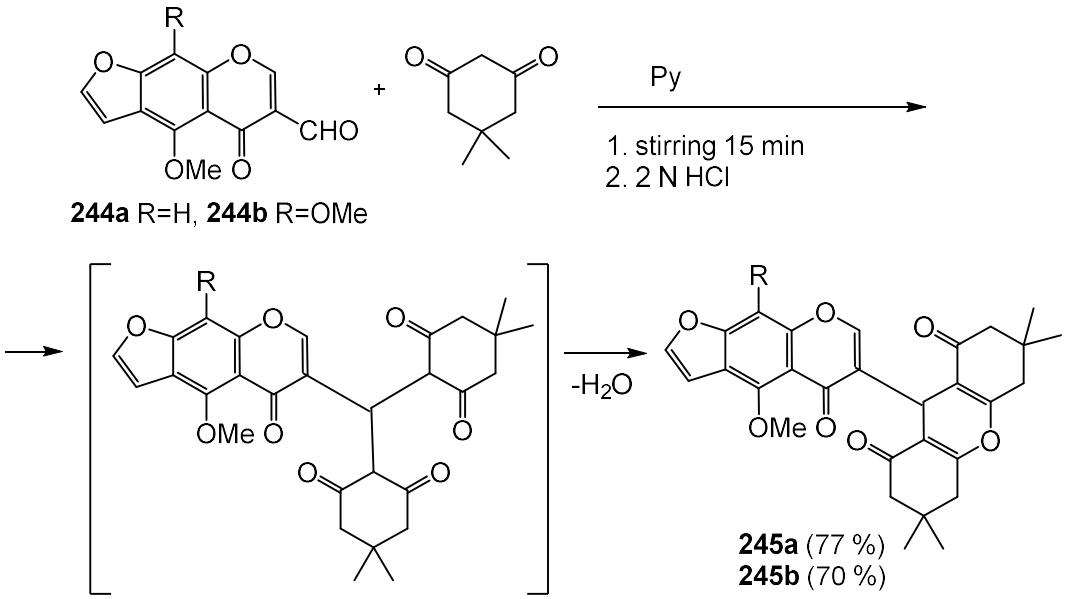
A structural analogue of compounds **233** - 1,2,3,4,5,6,7,8-octahydro-3,3,6,6-tetramethyl-9-(5,7-dimethyl-4-oxo-4*H*-1-benzopyran-3-yl)-9*H*-xanthene-1,8-dione is claimed in a patent [94] as a compound modulating a transcription factor. When a microbial cell is contacted with a compound modulating a transcription factor, the resistance of the specified cell to antibiotics decreases.

New derivatives of 9-(chromon-3-yl)-3,3,6,6-tetramethylxanthene-1,8-dione **233c,d** were obtained by condensation of substituted 3-formylchromones with dimedone (molar ratio 1:2) in pyridine under the conditions given in **Scheme 70** [95, 96].



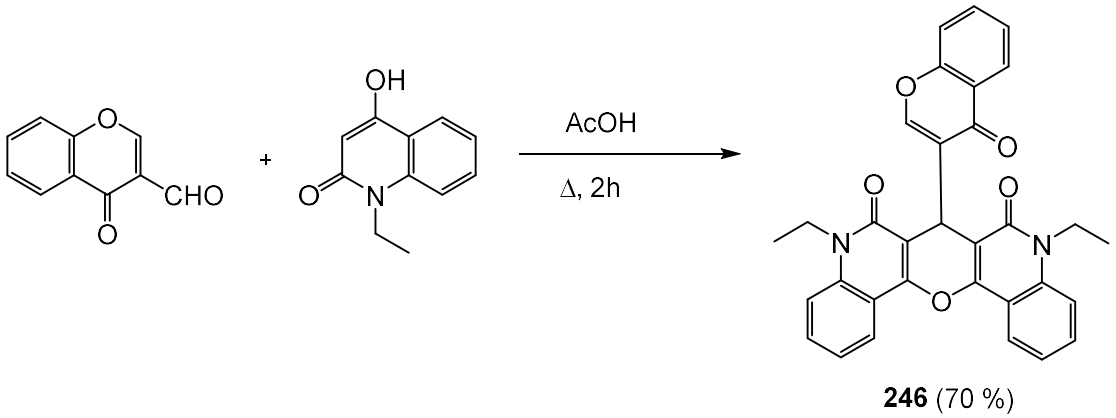
Scheme 70. The synthesis of 9-(chromon-3-yl)-3,3,6,6-tetramethylxanthene-1,8-dione derivatives **233c,d**

By carrying out a similar condensation with 4-methoxy/4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*][l]benzopyran-6-carbaldehydes (**244a,b**), 4-methoxy/4,9-dimethoxy-6-(3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthen-9-yl)-5-oxo-5*H*-furo[3,2-*g*][1]benzopyrans (**245a,b**) were obtained [97] (**Scheme 71**).



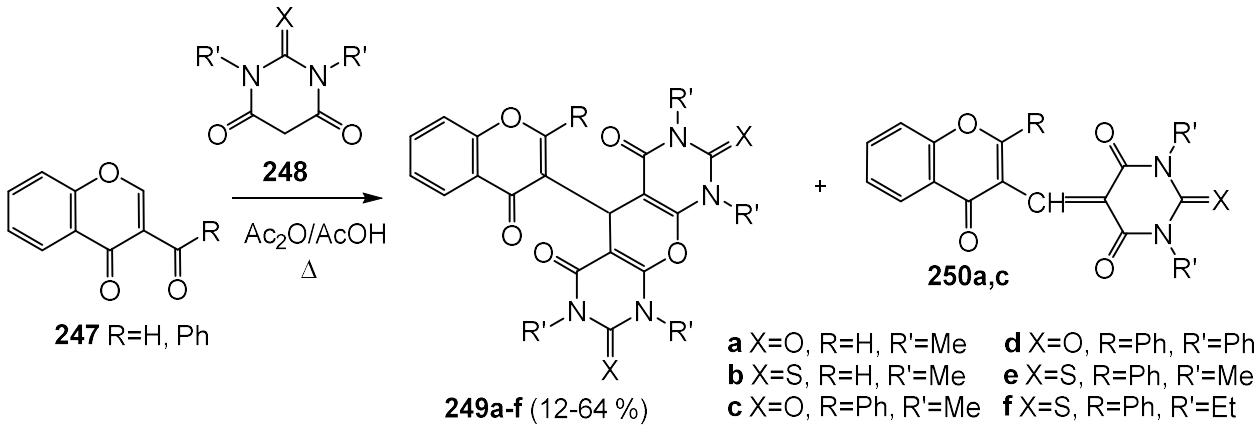
Scheme 71. The synthesis of 4-methoxy/4,9-dimethoxy-6-(3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthen-9-yl)-5-oxo-5*H*-furo[3,2-*g*][1]benzopyrans (**245a,b**)

The reaction of 3-formylchromone with 1-ethyl-4-hydroxyquinolin-2(1*H*)-one in glacial acetic acid did not lead to the expected condensation product (molar ratio 1:1), but a new 5,9-diethyl-7-(chromon-3-yl)-7*H*-quinolino[3′,4′:5,6]pyrano[3,2-*c*]quinoline-6,8(5*H*,9*H*)-dione **246** was isolated (molar ratio 1:2) [98] (**Scheme 72**).



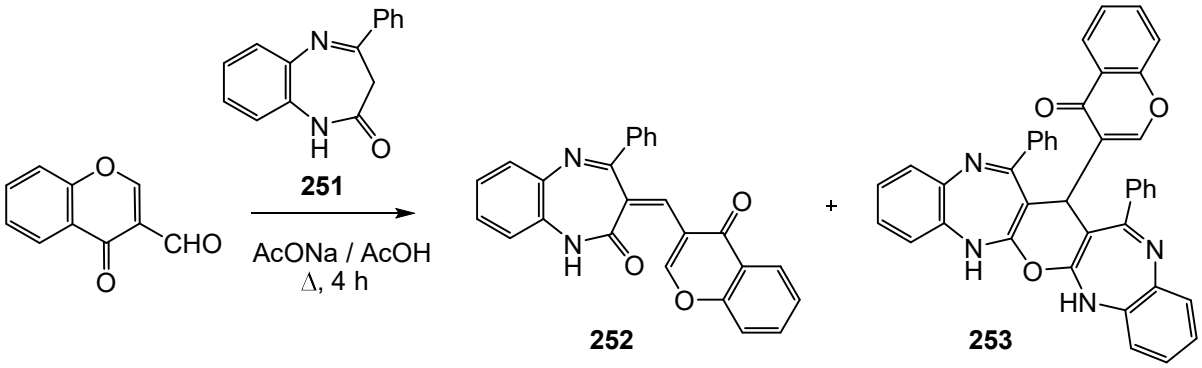
Scheme 72. The synthesis of 5,9-diethyl-7-(chromon-3-yl)-7*H*-quinolino[3′,4′:5,6]pyrano[3,2-*c*]quinoline-6,8(5*H*,9*H*)-dione **246**

3-Acylchromones **247** react with CH-acidic compounds **248** upon boiling in an Ac_2O/AcOH mixture to form 3-pyrimidopyranylchromone derivatives **249** alone or in a mixture with 3-pyrimidinylidenemethylchromone derivatives **250** [99] (**Scheme 73**).



Scheme 73. The products of the reaction of 3-acylchromones **247** with CH-acidic compounds **248**

Condensation of equimolar amounts of 4-phenyl-1*H*-[1,5]benzodiazepin-2(3*H*)-one (**251**) with 3-formylchromone in acetic acid in the presence of freshly melted sodium acetate gives a mixture of 3-(chromenylmethylene)[1,5]benzodiazepinone **252** and 4-chromenylbenzodiazepino[2,3:6,5]-pyrano[2,3-*b*]benzodiazepine **253**, with the yield of both compounds depending on the molar ratio of the reactants [100] (**Scheme 74**).

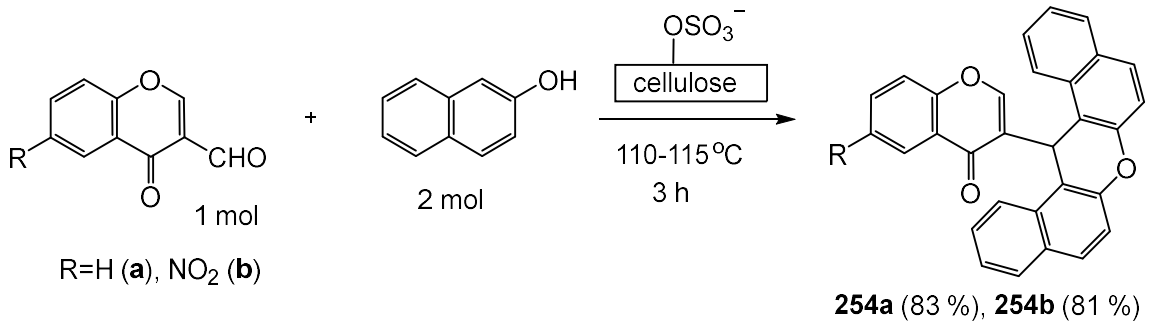


Molar ratio of diazepinone / 3-formylchromone	Yields of compounds % 252	253
1/2	90	05
1/1	60	33
2/1	20	60

Scheme 74. The products of the reaction of 4-phenyl-1*H*-[1,5]benzodiazepin-2(3*H*)-one (**251**) with 3-formylchromone

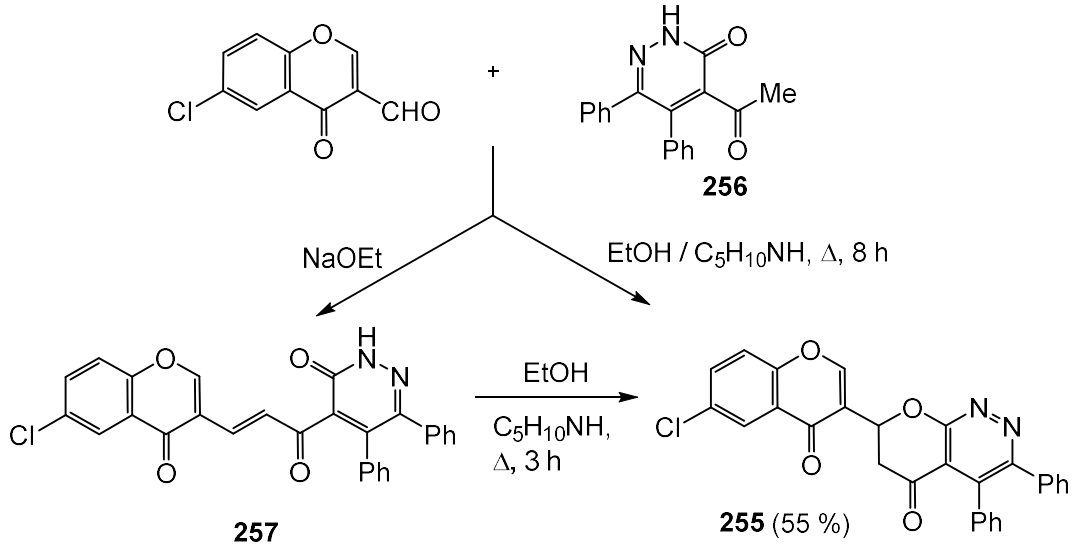
The synthesis of biologically important aryl-14*H*-dibenzo[*a.j*]xanthenes **254a,b** was carried out by the condensation of β-naphthol with 3-formylchromone derivatives in the absence of a solvent using an efficient, environmentally friendly, solid acid catalyst cellulose sulfuric acid (CSA) (**Scheme 75**). The main advantages of this new methodology are the multiple use of the catalyst, ease of operation, and high product yields. The regenerated catalyst can be reused at least three additional times in subsequent reactions without significant loss of

product yield. Cellulose sulfuric acid is obtained by the reaction of cellulose with chlorosulfonic acid; the number of acidic (H^+) sites in CSA is 0.50 meq/g [101].



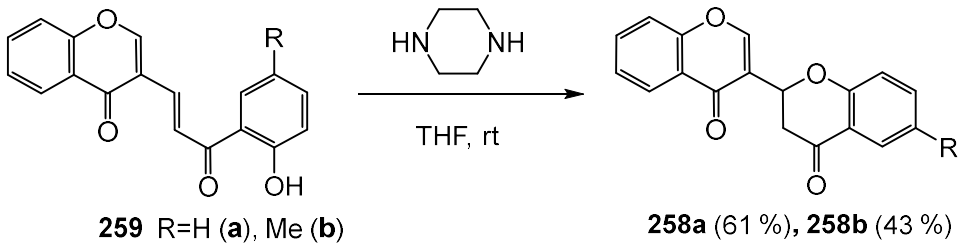
Scheme 75. The synthesis of aryl-14*H*-dibenzo[*a.j*]xanthenes **254a,b** in the presence of cellulose sulfuric acid (CSA)

Two approaches were implemented in the synthesis of 7-(6-chloro-4-oxochromen-3-yl)-3,4-diphenyl-6,7-dihydropyrano[2,3-*c*]pyridazin-5-one (**255**) [102]. As can be seen from **Scheme 76**, compound **255** was obtained directly by heating 4-acetyl-5,6-diphenylpyridazin-3(2*H*)-one (**256**) with 6-chloro-3-formylchromone in ethanol, containing a catalytic amount of piperidine, in 55% yield. The second approach consisted in the condensation of compound **256** with 6-chloro-3-formylchromone in a solution of sodium ethoxide to form 4-[3-(6-chlorochromen-3-yl)prop-2-enoyl]-5,6-diphenylpyridazin-3(2*H*)-one (**257**) and subsequent heating of compound **257** in boiling ethanol, containing a catalytic amount of piperidine, through intramolecular Michael addition of the lactam OH group to the olefinic CH=CH bond to form the ring tautomer of compound **257**–product **255**.



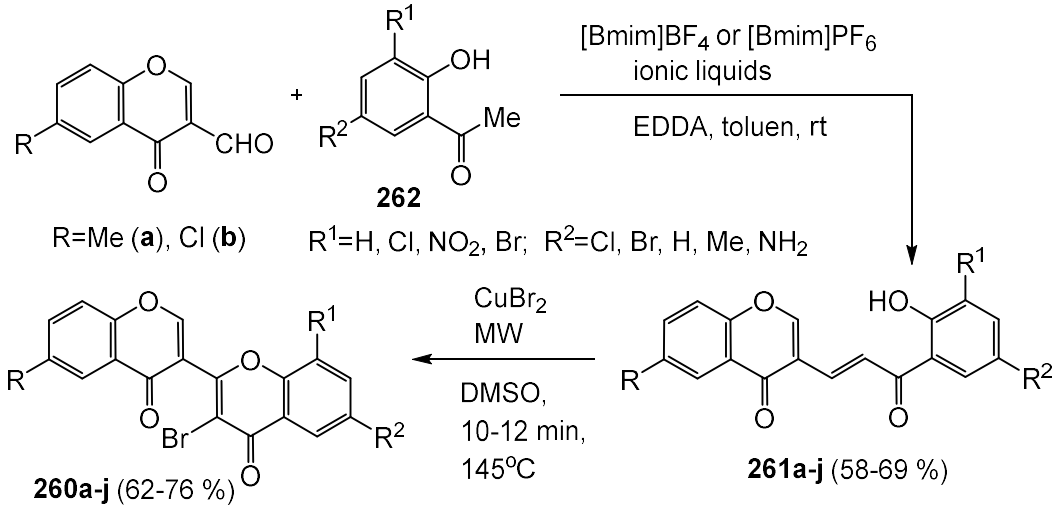
Scheme 76. Two approaches to the synthesis of 7-(6-chloro-4-oxochromen-3-yl)-3,4-diphenyl-6,7-dihydropyrano[2,3-*c*]pyridazin-5-one (**255**)

Chromone-chromanone derivatives, 3-(4-oxochroman-2-yl)-4*H*-chromen-4-ones **258a,b** were obtained as a result of the reaction of (*E*)-3-[3-(2-hydroxyaryl)-3-oxoprop-1-en-1-yl]chromones **259** with the secondary cyclic diamine piperazine in tetrahydrofuran at room temperature [103] (**Scheme 77**).



Scheme 77. The synthesis of 3-(4-oxochroman-2-yl)-4*H*-chromen-4-ones **258a,b**

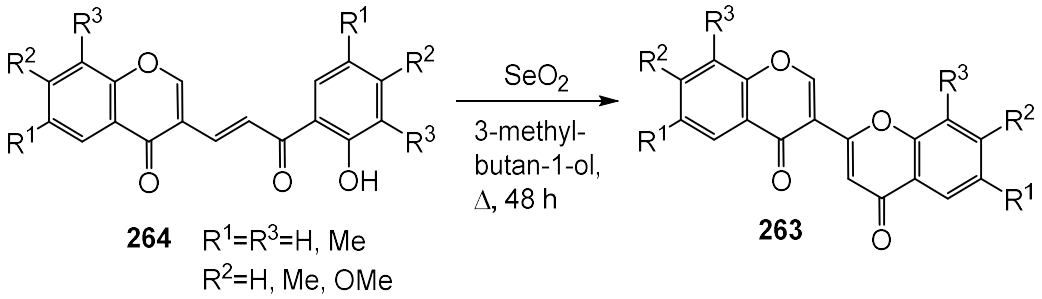
A series of substituted 3-(3-bromo-4-oxo-4*H*-chromen-2-yl)-4*H*-chromen-4-ones **260a-j** were obtained as a result of intramolecular cyclization of 3-(3-(2-hydroxyphenyl)-3-oxoprop-1-enyl)-4*H*-chromen-4-one derivatives **261a-j** in the presence of copper bromide and DMSO, which was carried out both by conventional heating and by microwave irradiation, observing under irradiation conditions a very significant reduction in reaction time and an increase in product yields [104] (**Scheme 78**). The starting 3-(3-(2-hydroxyphenyl)-3-oxoprop-1-enyl)-4*H*-chromen-4-ones **261a-j** were obtained by condensation of acetophenones **262** with 6-R-3-formylchromones in the presence of a catalytic amount of ethylenediammonium diacetate (EDDA) using various ionic liquids at room temperature. The advantages of this method compared to the classical variant (alcohol/piperidine at 35-40°C) are generality, high yields, short reaction time, and ease of product isolation.



Scheme 78. The synthesis of 3-(3-bromo-4-oxo-4*H*-chromen-2-yl)-4*H*-chromen-4-ones **260a-j**

Compounds **260a-j** were tested for antimicrobial activity *in vitro* against clinical isolates of Gram-positive bacteria *Staphylococcus aureus*, Gram-negative bacteria *P. fluores, Escherichia coli* and *Candida albicans*. Doxycycline and fluconazole were used as standards. All synthesized compounds showed moderate to resistant activity against all microbes. A moderate zone of inhibition was observed against *E. coli, P. fluores* and *S. aureus* strains, while compounds **260b** (R=Me, R^1=H, R^2=Cl), **260c** (R=R^1=Cl, R^2=Br), **260e** (R=Cl, R^1=NO_2, R^2=Me), **260j** (R=R^2=Me, R^1=H) showed significant activity against *Candida albicans* strains [104].

Substituted 2,3′-bischromones **263** were synthesized by prolonged boiling of chromonyl chalcone **264** with selenium dioxide in isoamyl alcohol [105] (**Scheme 79**).

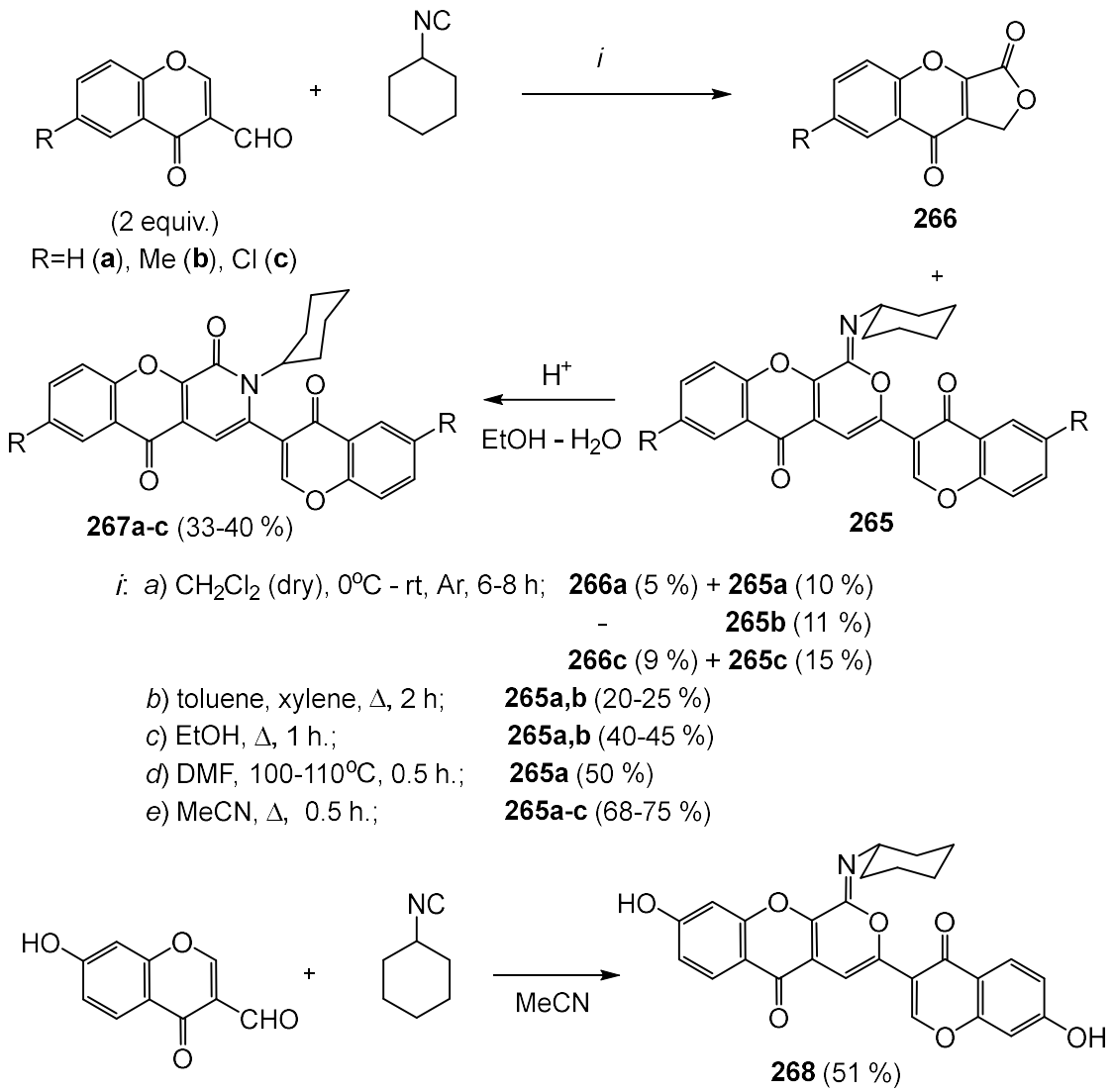


264 R^1=R^3=H, Me; R^2=H, Me, OMe

263

Scheme 79. The synthesis of 2,3′-bischromones **263** from chromonyl chalcones **264**

The synthesis of 1-(cyclohexylimino)pyrano[3,4-*b*]chromones **265** by the reaction of (un)substituted 3-formylchromones (2 equiv) with cyclohexylisocyanide was carried out under different conditions [106]. As can be seen from **Scheme 80**, the course of this reaction (its selectivity, product yields, and time) is significantly influenced by the solvent and temperature. In case of carrying out the reaction in CH_2Cl_2, in addition to the products **265**, furochromones **266** were also isolated. The synthesis of 1-(cyclohexylimino)pyrano[3,4-*b*]chromones **265a-c** proceeded selectively in a short time with the highest yields of 68-75% when boiling in acetonitrile.



Scheme 80. The synthesis of 1-(cyclohexylimino)pyrano[3,4-*b*]chromones **265** and **268**

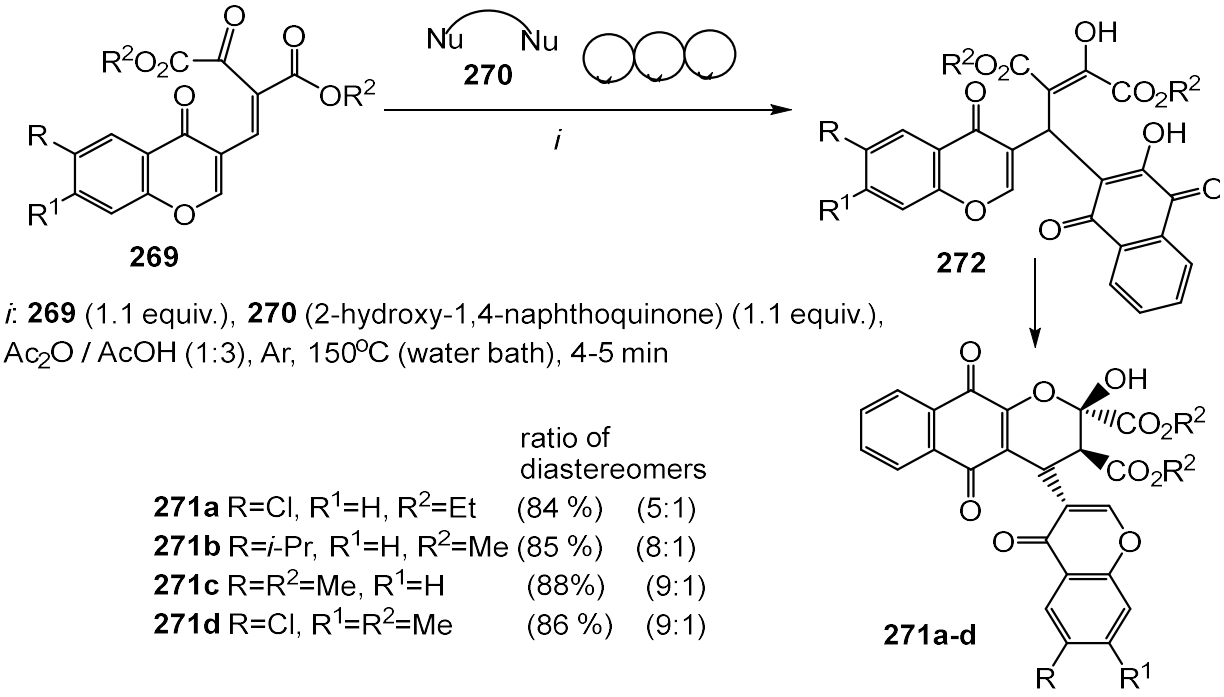
Compounds **265** have a chromone moiety linked to a pyrano[3,4-*b*]-1-benzopyran moiety, forming a conjugated ***π***-system that can undergo intramolecular charge transfer upon excitation and can act as a fluorophore.

Upon heating in EtOH in the presence of HCl, imine **265** undergoes rearrangement to lactam **267**. An attempt to hydrolyze imines **265** and isolate the corresponding pyrano[3,4-*b*]chromenediones was unsuccessful.

The pyrano[3,4-*b*]chromone core is the central component of rotenone, a natural compound with a broad spectrum of biological activity. For the synthesis of rotenone analogues, the presence of a hydroxyl group in the 7-position of compound **265** is necessary. The synthesis of 2-(7-hydroxy-4-oxo-4*H*-1-benzopyran-3-yl)-7-hydroxy-4-(N-cyclohexylimino)pyrano[3,4-*b*]-1-benzopyran-10-one (**268**) was carried out according to the above protocol from 7-hydroxy-3-

formylchromone with a yield of 51% [106] (**Scheme 80**).

Chromone-substituted pyranonaphthoquinones **271a-d** were obtained with good diastereoselectivity as a result of a cascade reaction sequence from ketoester substrates **269** (1.1 equiv.) with the *O,C*-bisnucleophile 2-hydroxy-1,4-naphthoquinone (**270**) (1 equiv.) in the presence of a mixture of acetic anhydride/acetic acid (1:3) in an argon atmosphere at 150°C (oil bath) for 4–5 min [12] (**Scheme 81**).

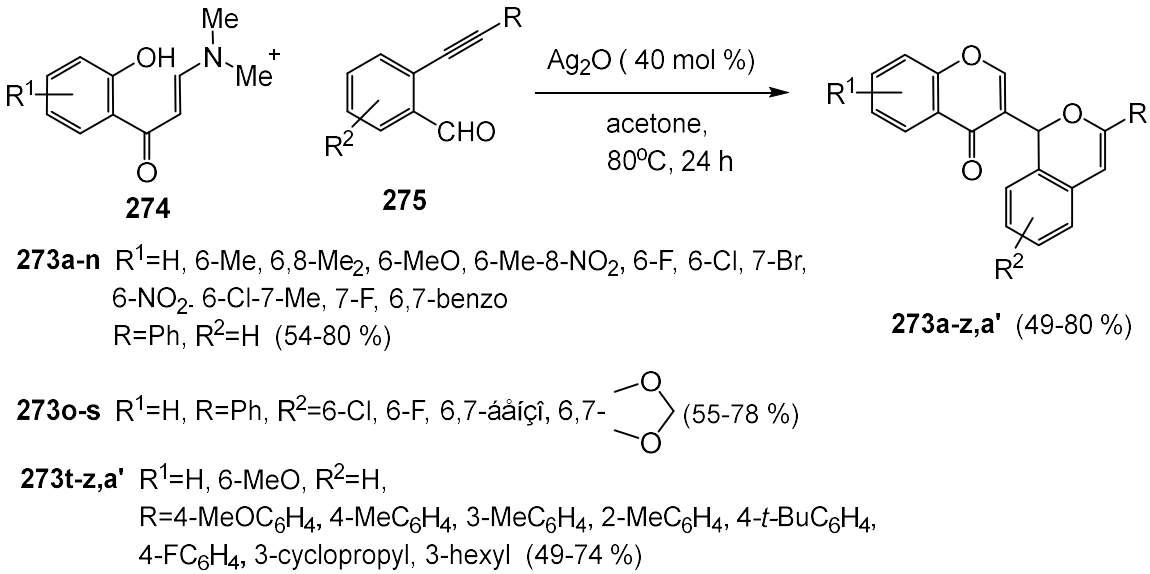


		ratio of diastereomers
271a R=Cl, R^1=H, R^2=Et	(84 %)	(5:1)
271b R=*i*-Pr, R^1=H, R^2=Me	(85 %)	(8:1)
271c R=R^2=Me, R^1=H	(88%)	(9:1)
271d R=Cl, R^1=R^2=Me	(86 %)	(9:1)

Scheme 81. The synthesis of chromone-substituted pyranonaphthoquinones **271a-d**

In the case of the bisnucleophile *o*-hydroxynaphthoquinone (**270**), addition of the conjugate to ketoester substrates **269** leads to intermediate **272**, which undergoes cyclization to form anomerically stabilized tricyclic acetals **271** via a branched cascade.

The synthesis of a series of functionalized 3-(1*H*-isochromene)-chromones **273a-z,a'** was carried out by Ag_2O-catalyzed cascade cyclization reaction of *o*-hydroxyaryleneaminones **274** with *o*-alkynylbenzaldehydes **275** (molar ratio **274**:**275**=5:1) in Ace Glass tubes under pressure at 80°C for 24 hours [107] (**Scheme 82**).



Scheme 82. The synthesis of functionalized 3-(1*H*-isochromene)-chromones **273a-z,a'**

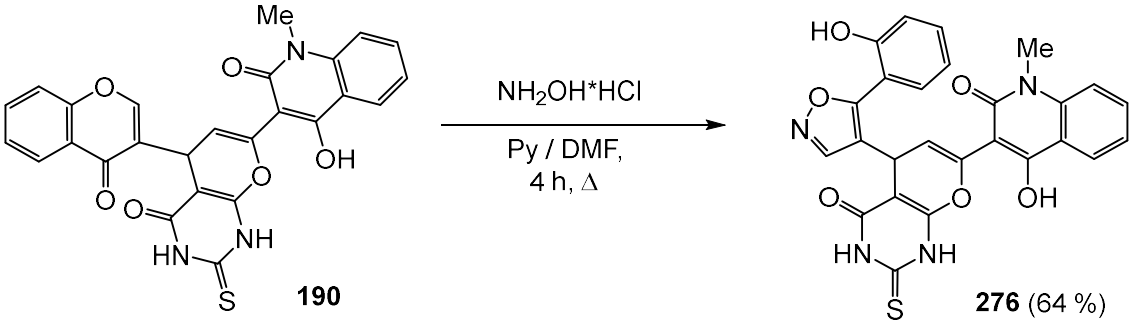
This is the only example found in the literature of the synthesis of pyran-functionalized isoflavone analogs, carried out by closing the precursor-substrates into a chromone ring. All other syntheses presented in this subsection were carried out by completing the *O*-heterocycle to the chromone ring.

3.2. Chemical properties

Previously, chemical transformations (modifications and heterocyclizations) carried out on the pyrano[2,3-*c*]pyrazole fragment of 6-amino-4-(4-oxo-4*H*-chromen-3-yl)-3-phenyl-1,4-dihydropyrano-[2,3-*c*]pyrazole-5-carbonitrile (**191**), which led to the synthesis of new 3-hetarylchromones with functionalized pyrano[2,3-*c*]pyrazole, pyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidine and pyrazolo[4',3':5,6]pyrano[2,3-*d*]oxazine rings[81] were presented in **Schemes 52-56** [81].

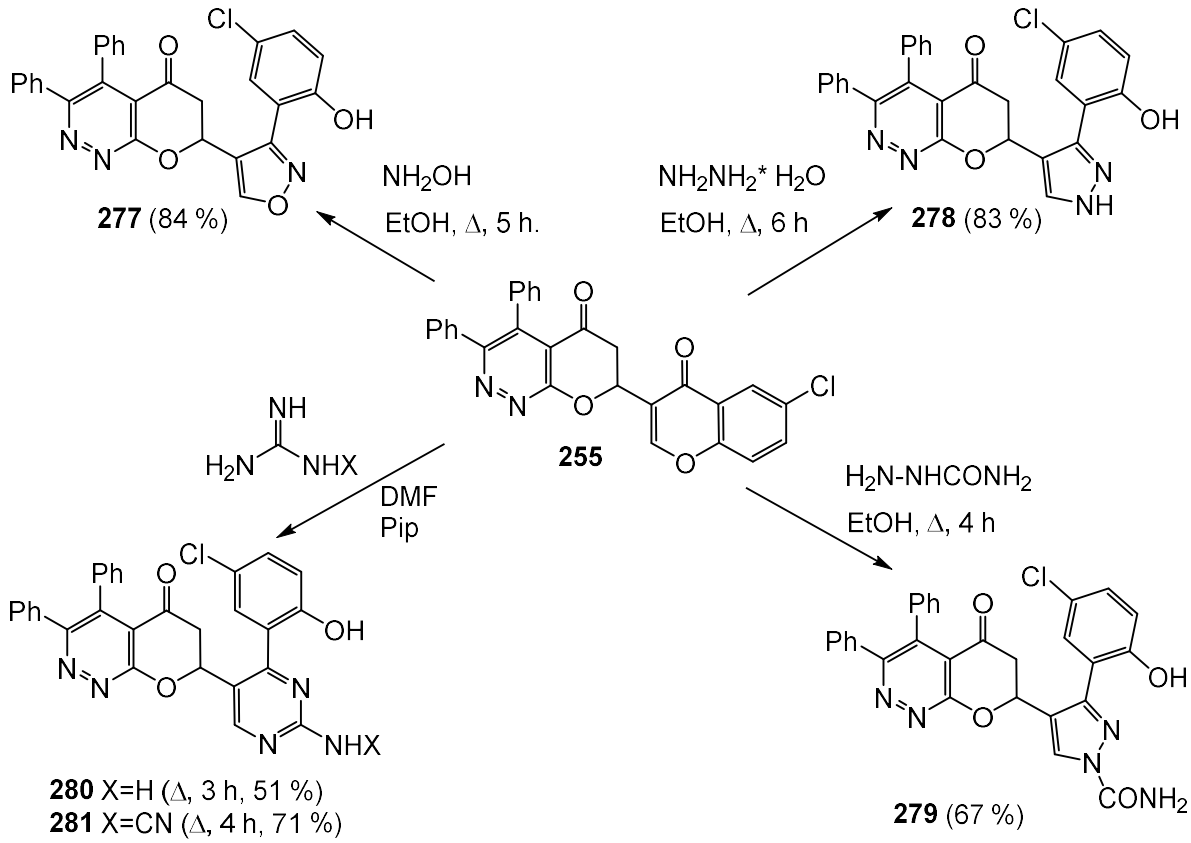
Reactions with nucleophilic reagents of pyranoannelated analogs of isoflavones were studied in [80, 98, 102, 108].

7-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-5-(4-oxo-4*H*-chromen-2-yl)-2-thioxo-1,2,3,5-tetrahydropyrano[2,3-*d*]pyrimidin-4-one (**190**) reacted with hydroxylamine hydrochloride in boiling DMF to form 7-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-5-[5-(2-hydroxyphenyl)-isoxazol-4-yl]-2-thioxo-1,2,3,5-tetrahydropyrano[2,3-*d*]pyrimidin-4-one (**276**) [80] (**Scheme 83**).



Scheme 83. Recyclization of **190** under the action of hydroxylamine hydrochloride

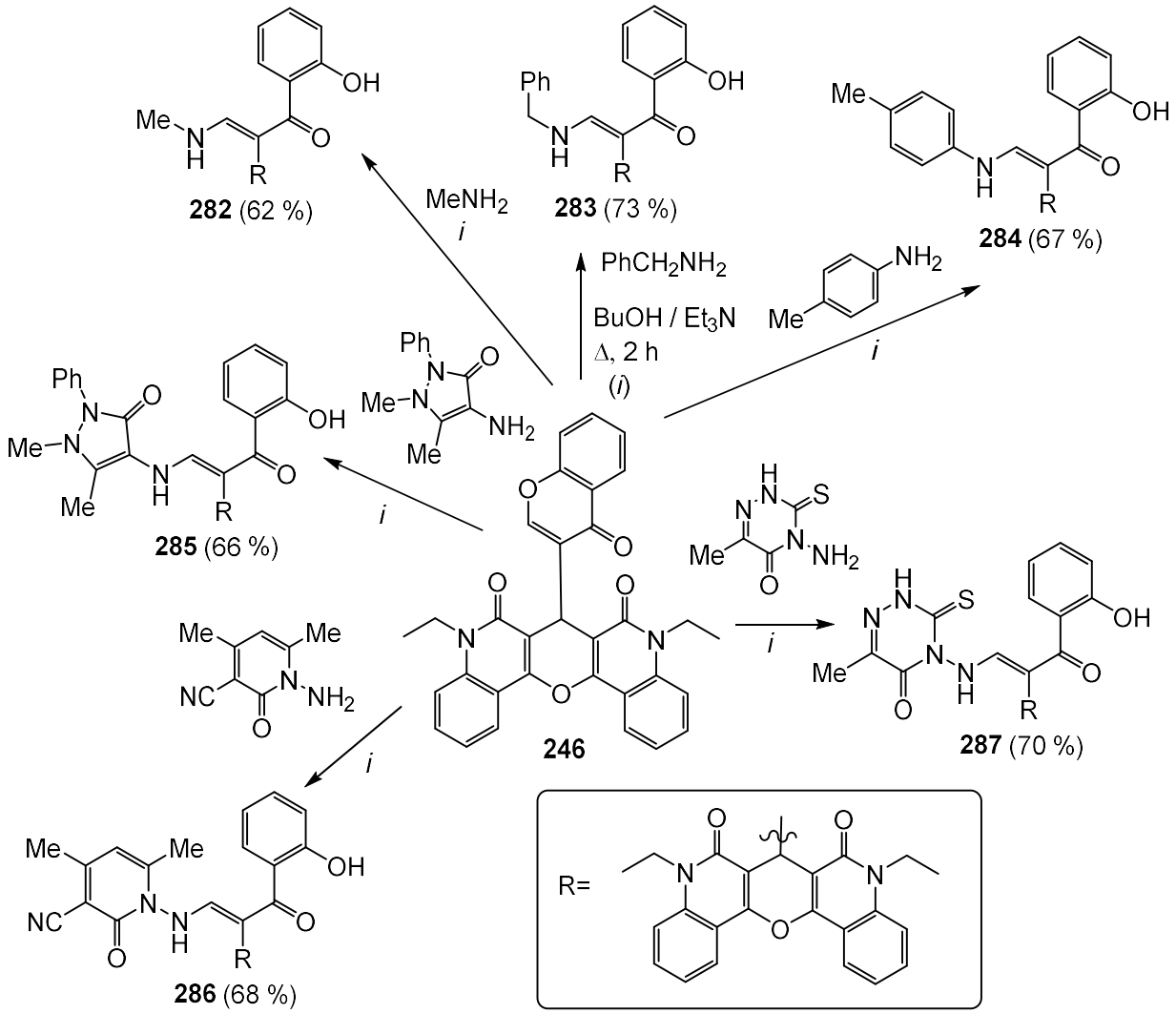
The reactions of 7-(6-chloro-4-oxochromen-3-yl)-3,4-diphenyl-6,7-dihydropyrano[2,3-*c*]pyridazin-5-one (**255**) with nucleophilic reagents – hydroxylamine, hydrazine hydrate, semicarbazide hydrochloride, guanidine hydrochloride and cyanoguanidine were studied in [102]. Under the action of these nucleophilic reagents, compound **255** is recycled into isoxazolylpyranopyridazine derivatives **277**, pyrazolylpyranopyridazines **278** and **279**, pyrimidinylpyranopyridazines **280** and **281**, respectively (**Scheme 84**).



Scheme 84. Recyclizations of **255** under the action of binucleophiles

The chemical behavior of the electron-deficient substrate 5,9-diethyl-7-(chromon-3-yl)-7*H*-quinolino[3′,4′:5,6]pyrano[3,2-*c*]quinoline-6,8(5*H*,9*H*)-dione **246** was investigated in [98, 108].

Reactions of the substrate **246** with various primary amines, which proceed with the opening of the γ-pyrone ring, lead to the quinolino[3′,4′:5,6]pyrano[3,2-*c*]quinoline-linked propenones **282-284** and **285-287**, which exist in the *E*-configuration, in 62-73% yields [98] (**Scheme 85**).



Scheme 85. The opening of the γ-pyrone ring in **246** under the action of primary amines

The antimicrobial activity of compounds **282-287** was investigated *in vitro* against a panel of pathogenic microorganisms, including Gram-positive bacteria [*Staphylococcus aureus* (G + 1) and *Bacillus subtilis* (G + 2)] and Gram-negative bacteria [*Escherichia coli* (G-1) and *Salmonella*

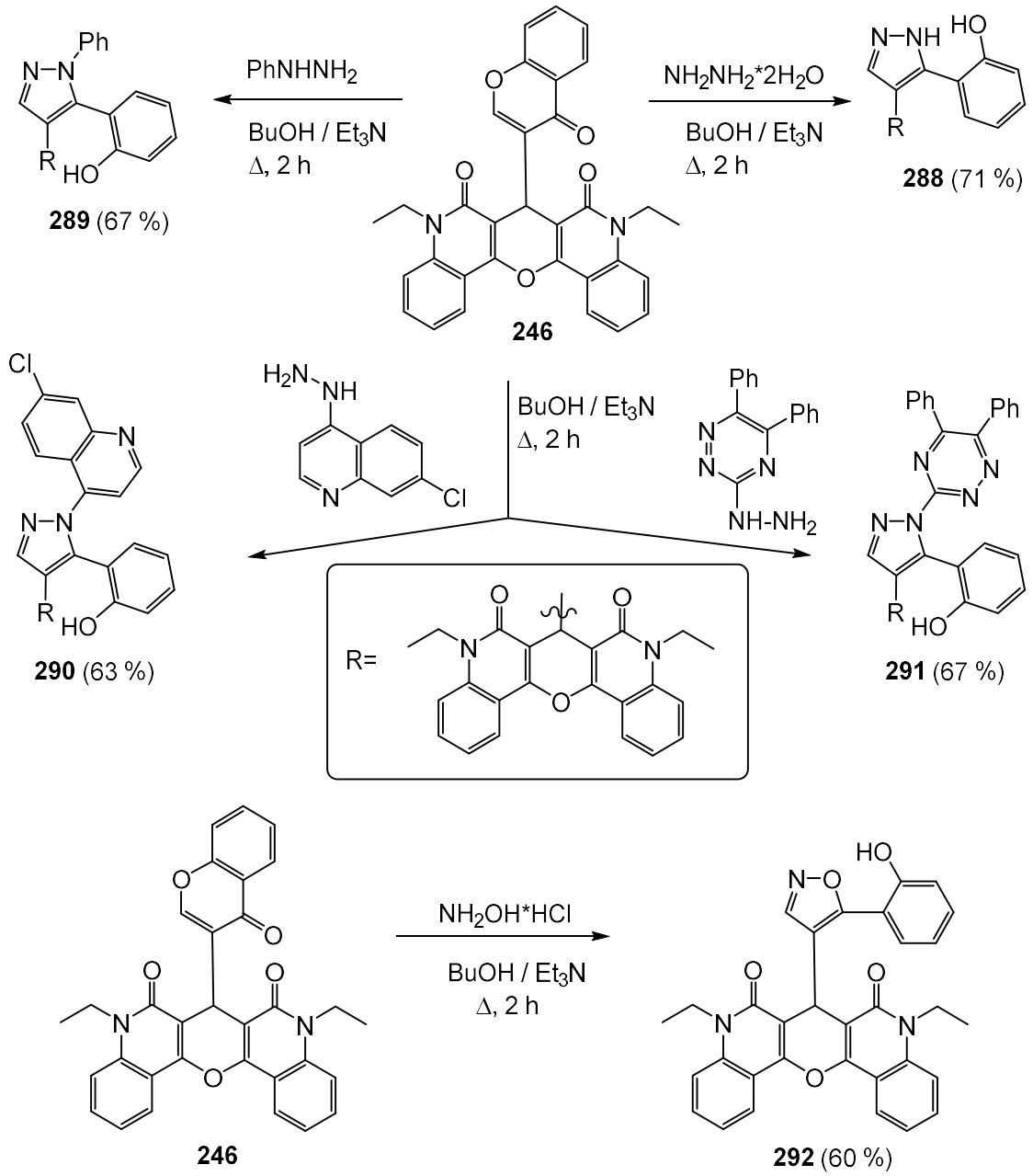
typhimurium (G-2)], as well as the yeast *Candida albicans* (F1) and the fungus *Aspergillus fumigatus* (F2) [98]. The results showed that the test substances had moderate to high inhibitory activity. Compounds **282**, **284** and **287** were highly potent antibacterial candidates against all tested organisms. Compounds **283**, **285** and **286** are more potent antibacterial candidates against the Gram-positive bacteria *B. subtilis*, compounds **283** and **285** showed higher inhibitory effect against two species of Gram-negative bacteria (*S. typhimurium* and *E. coli*), yeast *C. albicans*) and fungi (*A. fumigatus*). Compound **286** showed high activity against yeast (*C. albicans*).

Cytotoxicity testing *in vitro* against HepG-2 cell lines showed that compounds **282-287** had greater activity against HepG-2 cell lines than cis-platinum [98]. Growth inhibitory activity was determined by IC_{50}, which is the concentration of the screened compound in micromoles per liter that inhibits tumor cell growth by 50%. Screening of the selected compounds against HepG-2 cell lines showed that all compounds exhibited potent or moderate activity against HepG-2 cell lines with an IC_{50} range of 5.76–24.27 μM. In addition, compounds **282-284** and **285-287** had greater activity against HepG-2 cell lines compared to the positive control (Cis-platin). This may be due to the presence of an enaminone group conjugation system in compounds **282-286**. Furthermore, compound **287** was the most active compound (IC_{50} = 5.76 μM), which may be due to the presence of a thioxo group (C–S) and a triazine ring in addition to the conjugation system, compound **246** showed significant cytotoxic activity with IC_{50} values (24.27 μM) in HepG-2 cell lines. Considering these results, the researchers believe that some of these compounds can be used in antibiotic formulation as drugs to increase antibiotic sensitivity, which stimulate cancer treatment and induce apoptosis of human hepatocellular carcinoma.

The first hyperpolarizability of the obtained compounds was also calculated, which turned out to be higher than that of urea. Therefore, these compounds are ideal candidates for nonlinear optical applications [98].

Lipinski's rules ("rule of five") indicate that there are no problems with the oral bioavailability of the obtained compounds [98]

Reactions of substrate **246** with hydrazine derivatives, namely hydrazine hydrate, phenylhydrazine, 7-chloro-4-hydrazinoquinoline and 3-hydrazino-5,6-diphenyl-1,2,4-triazine, led to 7-pyrazolylquinolinopyranoquinolines **288**, **289**, **290** and **291**, respectively. Reaction of compound **246** with hydroxylamine hydrochloride afforded 7-isoxazolylquinolino[3′,4′:5,6]pyrano[3,2-*c*]quinoline **292**. These reactions proceed via γ-pyrone ring opening, followed by closure of the intermediates into pyrazole or isoxazole rings [108] (**Scheme 86**).



Scheme 86. Recyclizations of **246** under the action of binucleophiles

The antimicrobial activity of the synthesized compounds was investigated using the agar diffusion method. The compounds were tested for their ability to inhibit the growth of Gram-positive bacteria [*Staphylococcus aureus* (G+1) and *Bacillus subtilis* (G+2)] and Gram-negative bacteria [*E. coli* (G-1) and *S. typhimurium* (G 2)], as well as the yeast *Candida albicans* (F1) and the fungus *Aspergillus fumigatus* (F2), using chloramphenicol for Gram-positive bacteria, cephalothin for Gram-negative bacteria and cycloheximide for yeast and fungi as reference compounds. The results showed that the tested compounds exhibited moderate to high inhibitory activity. Compound **291** was the most potent candidate against all

tested organisms. Furthermore, compound **289** is a more potent antibacterial candidate against two species of Gram-negative bacteria (*S. typhimurium* and *E. coli*), yeast (*C. albicans*), and fungi (*A. fumigatus*). This may be due to the presence of a benzene ring that increases the conjugation system [108].

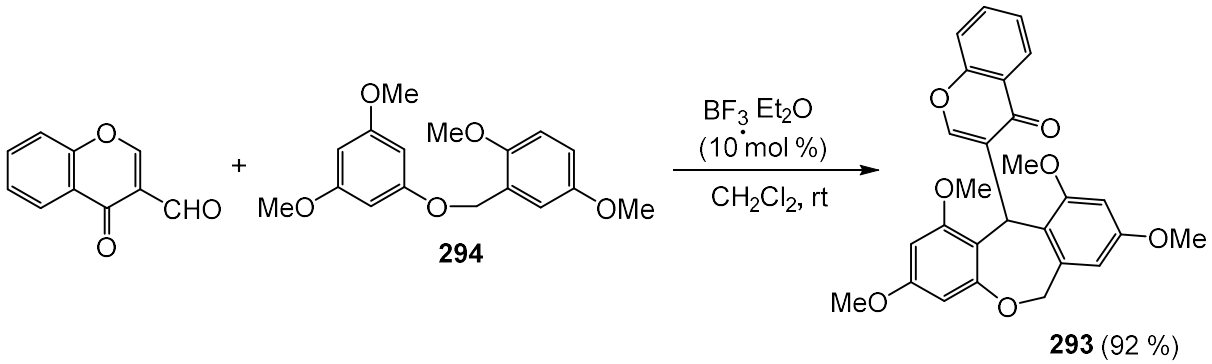
Colorimetric analysis of antitumor activity was carried out *in vitro* for 24 h on compounds against hepatocellular carcinoma (HepG-2) cells [108]. Cis-platin was chosen as the reference drug, which has high efficacy as an antitumor agent. All synthesized compounds showed potential or moderate growth inhibitory activity on the tested cell line with IC_{50} ranging between 13.62 and 30.25 μM. Compounds **289** and **291** were more active against HepG-2 cells than the positive control (Cis-platin). This may be due to the presence of benzene rings that enhanced conjugation in the system. Meanwhile, compounds **246**, **288**, **290** and **292** showed significant cytotoxic activity with IC_{50} values ranging from 24.27 to 30.25 μM in HepG-2 cell lines. Therefore, some of these compounds may become more effective in promoting the therapy of human hepatocellular carcinoma and inducing apoptosis.

The calculated first hyperpolarizability of the resulting compounds was in the range of 1.49×10-30–3.02×10-30 Fr and demonstrated that the current compounds can be used for nonlinear optical (NLO) applications such as photonics, fiber optic communication, optical computing, data storage, dynamic holography and photodynamic therapy.

The synthesized substances could theoretically be potentially suitable for oral administration according to Lipinski's rules [108].

4. 3-(Dibenzo[*b,e*]oxepinyl)chromone

Dibenzoxepin scaffolds are important structural motifs in pharmaceuticals with diverse biological activities and are found in bioactive natural products. The synthesis of 3-*O*-hetarylchromone, where hetaryl is a tricyclic dihydrodibenzoxepine - a 7-membered oxygen-containing oxepine ring dibenzo-annelated at the *b,e* faces, is reported in [109]. 3-(1,3,8,10-Tetramethoxy-6,11-dihydrodibenzo[*b,e*]oxepin-11-yl)-4*H*-chromen-4-one (**293**) was synthesized by $BF_3 \cdot Et_2O$-catalyzed tandem cyclization of the electron-rich substrate 1-(3,5-dimethoxybenzyloxy)-3,5-dimethoxybenzene **294** with 3-formylchromone. The reaction proceeded in 1 h in 92% yield (**Scheme 87**). The mild reaction conditions and operational simplicity make this approach an interesting method.



Scheme 87. The synthesis of 3-(1,3,8,10-tetramethoxy-6,11-dihydrodibenzo[*b,e*]oxepin-11-yl)-4*H*-chromen-4-one

Conclusions

The review outlines the development and achievements in the chemistry of isoflavonoids modified with oxygen-containing heterocycles with one oxygen atom, which have a wide range of biological activities and therapeutic potential.

Successful synthetic methodologies have been used to synthesize a fairly large array of natural and synthetic 3-hetarylchromones with oxygen-containing heterocycles of different sizes and structures. The undoubted prestige of these biomolecules as interesting research targets for further developments in the design, discovery and promotion of new drug molecules with multidimensional pharmaceutical applications.

Acknowledgements

Funding for this research was provided by Ministry of Education and Science of Ukraine (grant for the perspective development of the scientific direction “Mathematical sciences and natural sciences“ at the Taras Shevchenko National University of Kyiv.

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