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Isoflavonoids modified with azole heterocycles with three heteroatoms

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Heterocycle modified chromones are attracting increasing attention as novel potential therapeutic agents due to their effective bioactivities and low toxicity. This review describes all strategies and versatile synthons that have been developed to date for the synthesis of isoflavone heterocyclic analogs containing isolated 5-member heterocyclic rings with three different or identical heteroatoms. Their biological activity is also represented.

Introduction

One of the most promising ways to create new biologically active compounds is undoubtedly the synthesis of analogs of natural low molecular weight bioregulators.

In this respect, 3-hetarylchromones, being a combination of such pharmacophores as a chromone and a heterocycle nucleus, are perspective molecular tools based on natural and synthetic (carbo)heterocycles for solving pressing problems in the field of medicine [1-3], agriculture [4-5] and materials chemistry [6]. The interest of researchers in this class of compounds for six decades of historical development (the first publication was on 3-thienylchromones in 1960 [7]) is constantly growing. The use of new technologies in the synthesis of 3-hetarylchromones (e.g., new types of reactions, reagents and catalysts) allows to expand their structural diversity, and opens up new opportunities to create target libraries that are now mandatory in medical chemistry.

We present here the current state of research on isoflavone heterocyclic analogs containing isolated 5-member heterocyclic rings with three different or identical heteroatoms. Relatively few materials on this topic were published before 2000, while the main studies have been in the last two decades, and are not systematized.

Design of target 3-hetarylchromones can be accomplished both by cyclization of synthons containing azole cycle into chromone system or by

introduction of an azole heterocycle to the chromone core.

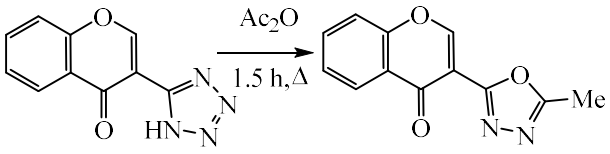
The spectrum of biological action of the target 3-hetarylchromones has been determined.

1. 3-Oxadiazolylchromones

1.1. Synthesis

The oxadiazole ring, which may exist in four isomeric forms, is present in the currently synthesized 3-oxadiazolyl-chromones in the isomeric forms of 1,3,4-oxadiazole and 1,2,4-oxadiazole. The basis of the vast majority of methods presented in the literature for the synthesis of 3-oxadiazolylchromones is the principle of completion of the oxadiazole ring to the chromone system, with the original building blocks being derivatives of 3-formylchromone.

The first representative of 3-(1,3,4-oxadiazolyl)chromones was described in 1977 [8]. This is the only case of transformation of a 3-hetarylchromone into another 3-hetarylchromone. When studying the reactivity of 3-(1*H*-tetrazol-5-yl)chromone (**1**) in boiling acetic anhydride for 1.5 h, 3-(2-methyl-1,3,4-oxadiazol-5-yl)chromone (**2**) was obtained (**Scheme 1**).

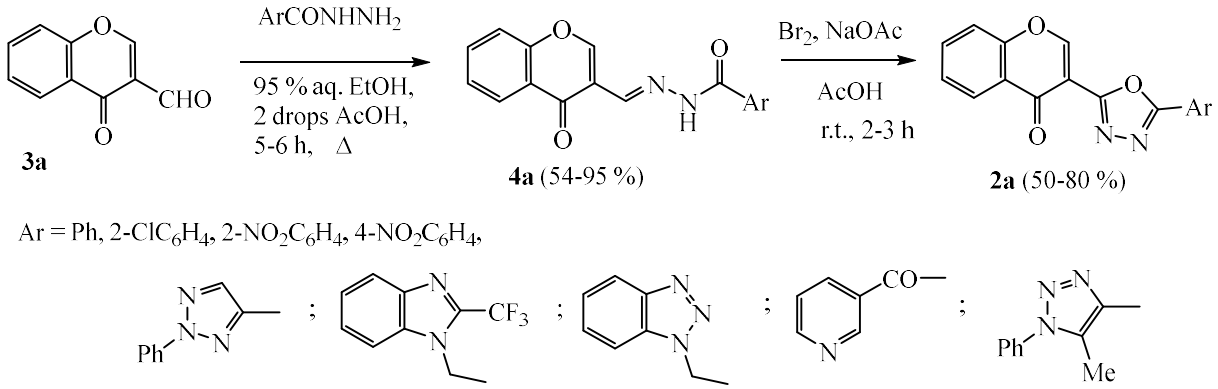


1 **2** (72 %)

Scheme 1. Transformation of 3-(1*H*-tetrazolyl-5)chromone into 3-(2-methyl-1,3,4-oxadiazol-5-yl)chromone

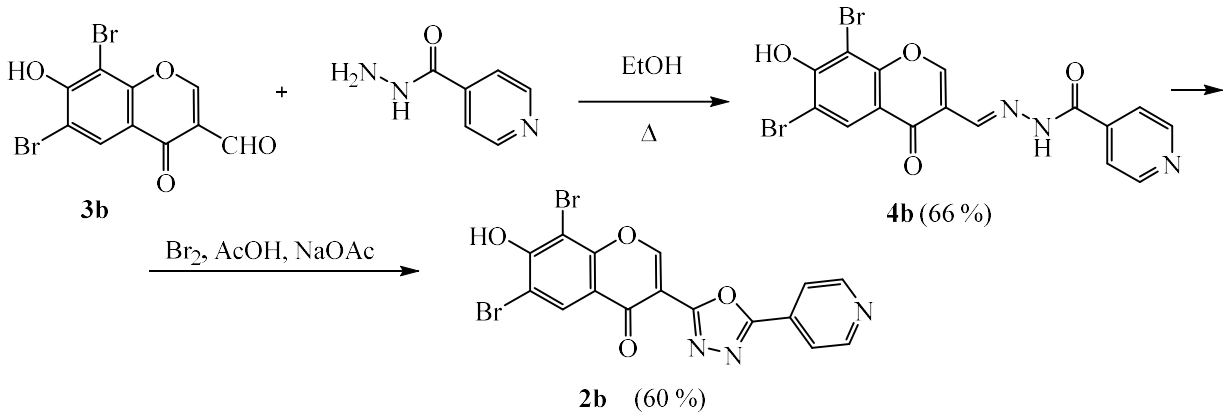
Current trends in the production of 3-(5-R-1,3,4-oxadiazol-2-yl)chromones are based on oxidative heterocyclization reactions of condensation products of 3-formylchromone derivatives with 1,2-*N,N*-dinucleophiles.

A general procedure for the synthesis of 3-(5-aryl-1,3,4-oxadiazol-2-yl)chromones **2a** by the reaction of 3-formylchromone **3a** with aroylhydrazines (molar ratio 1:1) and the conversion of the corresponding aroylhydrazones **4a** in 1,3-dipole under the action of bromine in the presence of sodium acetate, followed by intramolecular cyclization was proposed in works [9, 10] (**Scheme 2**).



Scheme 2. The synthesis of 3-(5-aryl-1,3,4-oxadiazol-2-yl)chromones by the reaction of 3-formylchromone with aroylhydrazines followed by intramolecular cyclization

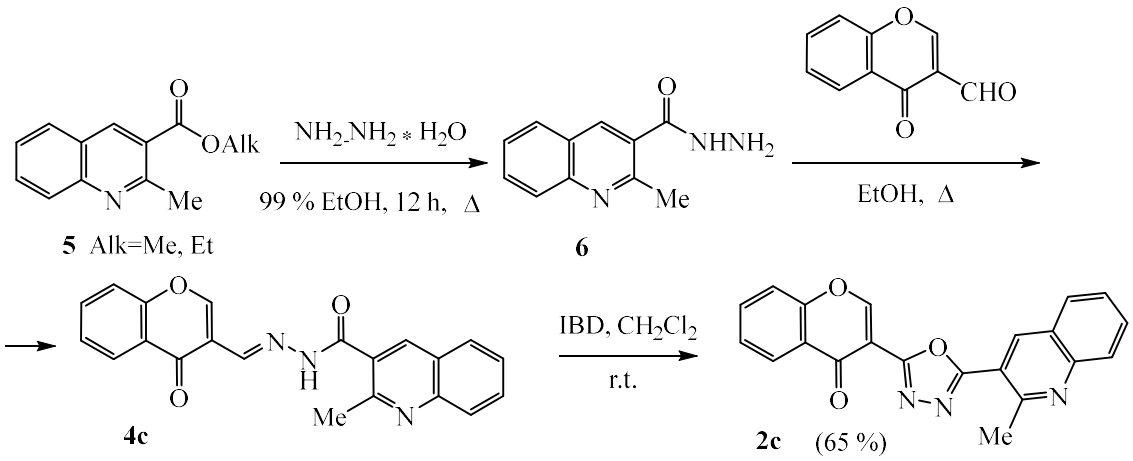
By the same principle, the reaction of substituted 3-formylchromone **3b** with pyridine-4-carbohydrazine in boiling ethanol affords the corresponding hydrazone **4b** in 66% yield. Treatment of hydrazone **4b** with bromine in acetic acid with freshly melted sodium acetate gave 3-[5-(4-pyridyl)-1,3,4-oxadiazol-2-yl]-6,8-dibromo-7-hydroxychromone (**2b**) in 60% yield [11] (**Scheme 3**).



Scheme 3. The synthesis of 3-[5-(4-pyridyl)-1,3,4-oxadiazol-2-yl]-6,8-dibromo-7-hydroxychromone

This approach was also used in the synthesis of a library of different quinolinyloxadiazoles, although under other conditions of oxidative cyclization [12]. **Scheme 4** reproduces the synthesis of one of the representatives of this library - 3-[5-(2-methylquinolin-3-yl)-1,3,4-oxadiazol-2-yl]-4*H*-chromen-4-one (**2c**). According to the protocol, esters of 2-methylquinoline **5** were boiled with hydrazine hydrate to give the corresponding

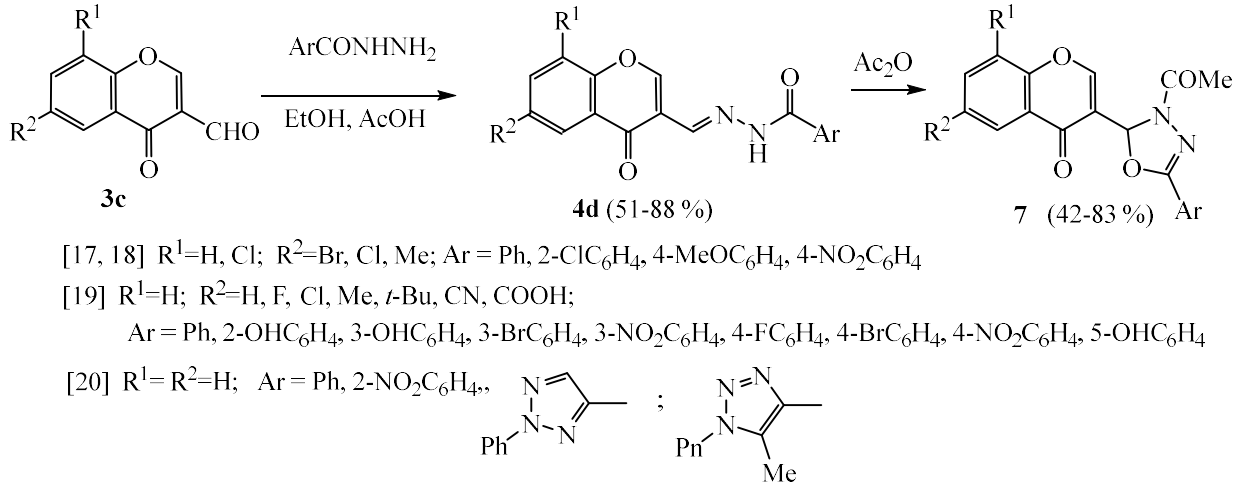
acylhydrazide **6**, which forms acylhydrazone **4c** by condensation with 3-formylchromone. Oxidative cyclization of acylhydrazone **4c** in the presence of iodobenzene diacetate (IBD) finally gives the target product **2c**.



Scheme 4. The synthesis of 3-[5-(2-methylquinolin-3-yl)-1,3,4-oxadiazol-2-yl]-4*H*-chromen-4-one

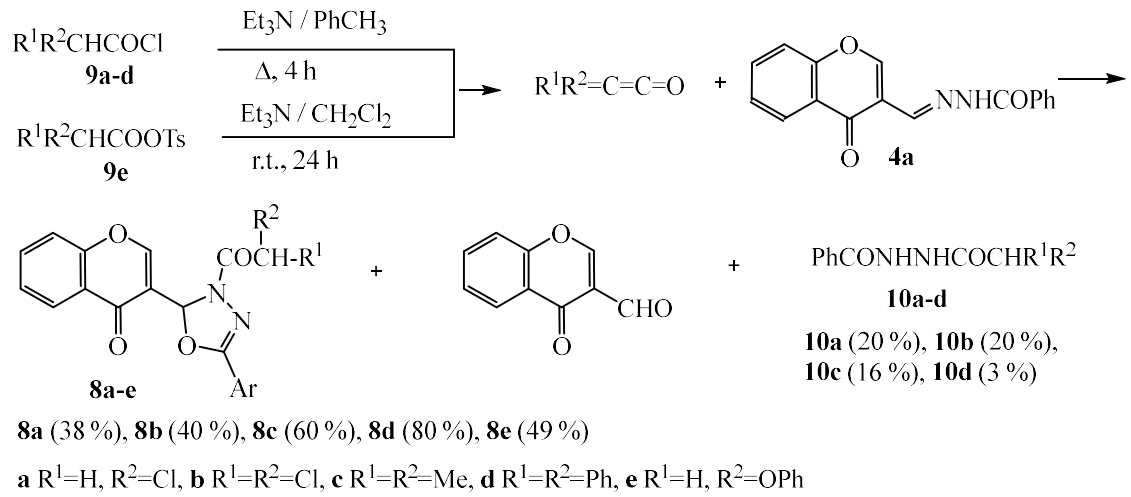
Following the same principle series of 6-R-3-(5-R^1-1,3,4-oxadiazol-2-yl)-4*H*-chromen-4-ones wherein 6-R=H, Me; 5-R^1=Ph, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 3-BrC_6H_4, 4-FC_6H_4, 3-FC_6H_4, pyridin-3-yl and pyridin-4-yl [13, 14] and wherein 6-R=H, Cl, Br, F; 5-R^1=Ph, 3-BrC_6H_4, 3-$NO_2C_6H_4$, 4-FC_6H_4, 4-BrC_6H_4, 4-$CF_3C_6H_4$ [15] were obtained by oxidative cyclization of the corresponding acylhydrazones using CH_2Cl_2 as a solvent and iodobenzene diacetate as a multifunctional oxidizing agent. Crystal structure of 6-methoxy-3-(5-(3-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-4*H*-chromen-4-one-methanol (1/1), $C_{20}H_{18}N_2O_6$ is considered in [16].

The synthesis of 3-(3'-acetyl-5'-aryl-1',3',4'-dihydrooxadiazol-2'-yl)chromones **7**, described in [17-20], was performed according to **Scheme 5** by reaction of the corresponding hydrazones of chromone **4d** with acetic anhydride, which in this case is both a cyclizing reagent and a solvent. The phenolic hydroxyl groups present in an aryl radical [19] can be acetylated at the same time of ring closing, and the acetyl phenol ester is generated. The use of microwave irradiation was shown to significantly speed up the reaction compared to conventional heating [20].



Scheme 5. The synthesis of 3-(3'-acetyl-5'-aryl-1',3',4'-dihydrooxadiazol-2'-yl)chromones

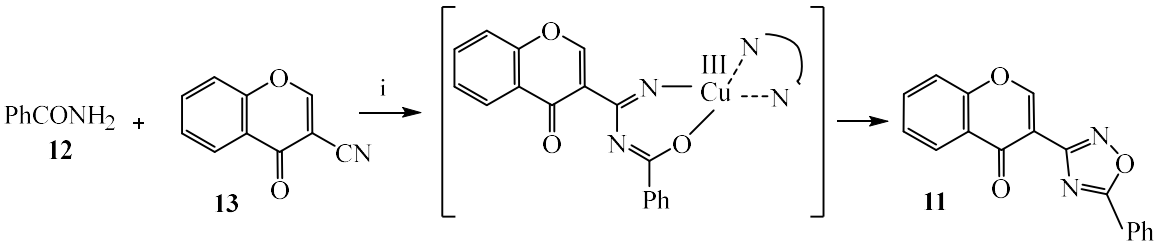
A method for the synthesis of 3-(3'-acetyl-5'-phenyl-1',3',4'-dihydrooxadiazol-2'-yl)chromones **8a-e** by the reaction of 3-formylchromone-N-benzoylhydrazone **4a** with ketenes was proposed in [17]. 3-Formylchromone-N-benzoylhydrazone **4a**, obtained by condensation of 3-formylchromone with benzohydrazide, reacts with ketenes obtained *in situ* by dehydrohalogenation of the corresponding chlorides of acids **9a-d** in the presence of triethylamine to give derivatives of 3-(1,3,4-oxadiazolinyl)chromones **8a-d**. In the case of chloro- and dichloroketene, 3-(1,3,4-oxadiazolinyl)chromones **8a** and **8b** were isolated with moderate yield (~40%), while in the case of dimethyl- and diphenylketene compounds 3-(1,3,4-oxadiazolinyl-chromones **8c** and **8d** were obtained with good yields (60 and 80%, respectively). During the reaction, a part of the 3-formyl-N-benzoylhydrazone **4a** decomposes into 3-formylchromone and benzohydrazide, which reacts with ketenes to form the corresponding N-benzohydrazides **10a-d**. In addition, the reaction of 3-formylchromone-N-benzoylhydrazone **4a** with mixed anhydride **9e,** synthesized from phenoxyacetic acid and *p*-toluenesulfonyl chloride in the presence of triethylamine in dichloromethane at room temperature, was studied. Under mild conditions the reaction proceeded to give the corresponding 3-(1,3,4-oxadiazolinyl)chromone **8e** in 49% yield (**Scheme 6**).



Scheme 6. The synthesis of 3-(3'-acetyl-5'-phenyl-1',3',4'-dihydrooxadiazol-2'-yl)chromones by the reaction of 3-formylchromone-N-benzoylhydrazone with ketenes

The synthesis of 3-(1,2,4-oxadiazolyl)chromones is described in only two publications.

A high-modulus single-step method for the synthesis of 1,2,4-oxadiazole derivatives from stable, sufficiently non-toxic and readily available amides and organic nitriles was described by Cu-catalyzed oxidative cyclization due to uncommon oxidative formation of N–O bonds using O_2 as the sole oxidant [18]. According to this method, 3-(5-phenyl-1,2,4-oxadiazol-3-yl) chromone (**11**) was synthesized with a yield of 40% from benzamide (**12**) and 3-cyanochromone (**13**) under optimized standard conditions (**Scheme 7**).

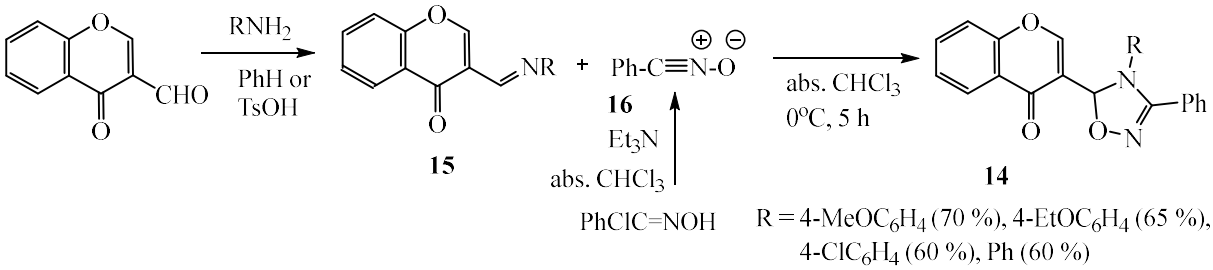


i: **12** (1 equiv.), **13** (2 equiv.), CuI (10 mol %),
ligand - 1,10-phenanthroline (batophenanthroline), K_2CO_3 (2 equiv.),
ZnI_2 (10 mol %) MS (4 A°) 300 mg in $ClCH_2CH_2Cl$, 130°C, O_2 (1 atm.), 24 h

Scheme 7. The synthesis of 3-(5-phenyl-1,2,4-oxadiazol-3-ylchromone from amide and nitrile by Cu-catalyzed oxidative cyclization

The synthesis of 3-(3-phenyl-1,2,4-oxadiazolin-5-yl)chromones **14**, which took place regio-specifically, is presented in [19]. The two remarkable reagents of this synthesis are imines of

chromone **15**, which were obtained without by-products by the reaction of 3-formylchromone with aromatic amines in boiling benzene with a catalytic amount of *p*-toluenesulfonic acid, and benzonitrile oxide **16**, formed *in situ* from benzhydroxaminoyl foundations. The reaction of equimolecular amounts of imines of chromone **15** and benzonitrile oxide **16** in anhydrous chloroform at 0°C and stirring took place for 5 hours afforded the 3-(3-phenyl-1,2,4-oxadiazolin-5-yl)chromones **14** (**Scheme 8**).



Scheme 8. The synthesis of 3-(3-phenyl-1,2,4-oxadiazolin-5-yl)chromones from chromone imines and benzonitrile oxide

1.2. Biological activity

The study of antiallergic activity of compounds 3-(1*H*-tetrazol-5-yl)chromone (**1)** and 3-(2-methyl-1,3,4-oxadiazol-5-yl)chromone **(2)** allowed to evidence the importance of tetrazole ring acidity for antiallergic activity in the absence of antiallergic activity in 3-(2-methyl-1,3,4-oxadiazol-5-yl) chromone [8].

3-[5-(4-Pyridyl)-1,3,4-oxadiazol-2-yl]-6,8-dibromo-7-hydroxychromone (**2b**) showed weak or moderate antibacterial activity *in vitro* against *Staphylococcus aureus* (ATCC 25923) and *Bacillus subtilis* (ATCC 6635) as examples of gram-positive bacteria and *Escherichia coli* (ATCC 25922) and *Salmonella typhimurium* (ATCC 14028) as examples of gram-negative bacteria and *Candida albicans* (ATCC 10231) as yeasts, but was found completely inactive against *Asperigillus fumigatus* [11].

Antimycobacterial activity of different quinolinyloxadiazoles was evaluated against *M. Smegmatis*, which is a fast-growing non-pathogenic strain. Among the studied compounds, 3-[5-(2-methylquinolin-3-yl)-1,3,4-oxadiazol-2-yl]-4*H*-chromen-4-one (**2c**) proved to be the most effective. To determine the cytotoxic effect of compounds on human lung epithelial cells, the compounds were tested against A549 epithelial lung cancer cell line, and compound **2c** showed a low cytotoxicity with IC50> 100 μM, thus emphasizing its potential as an anti-TB agent [12].

6-R-3-[5-R^1-1,3,4-oxadiazol-2-yl]-chromones [13, 14] may be useful as an anticancer agent. The cancer may be a colorectal cancer, a breast cancer, a pancreatic cancer, a bone marrow cancer, and the like, preferably a colon cancer. At four different concentrations (0, 10, 20 and 40 μM) these compounds showed an inhibitory effect on the growth of human cancer cells HCT116 with values of half maximum inhibitory concentration (GI_{50}) from 17.6 to 102.8 μM.

6-R-3-[5-R^1-1,3,4-oxadiazol-2-yl]-chromones [15] have wide research prospects in the research of new medicines, and can be particularly used as a blue algae inhibitor/killing agent. 6-R-3-[5-R^1-1,3,4-oxadiazol-2-yl]chromones (R=H, R^1=3-BrC_6H_4; R=F, R^1=3-BrC_6H_4; R=H, R^1=Ph; R=Br, R^1=Ph) inhibit Cy-FBP/SBPase.The IC_{50} value of 27.41-38.23 muM show that the compounds have good inhibition effect on FBP/SBPase in the blue algae. It is possible to mix these 4 compounds with acceptable diluents or carriers in water and formulate them into commonly used formulations such as aqueous solvents, hydrating agents, emulsions, etc. for use as algistats.

6-Substituted-3-(3'-acetyl-5'-aryl-1',3',4'-dihydrooxadiazol-2'-yl)chromones [19] were declared as promising in the research of new medicines and can be particularly used as a blue algae inhibitor agent. 6-R-3-(3'-acetyl-5'-aryl-1',3',4'-dihydrooxadiazol-2'-yl)chromones (R=NO_2, Ar=Ph; R=*t*-Bu, Ar=4-BrC_6H_4; R=H, Ar=3-BrC_6H_4; R=H, Ar=4-$AcOC_6H_4$) inhibit Cy-FBP/SBPase. The IC_{50} value of 26.71-38.68 muM show that the compounds have good inhibition effect on FBP/SBPase in the blue algae.

Presented in the patent specification [24] 2-[[(1*R*)-1-[2-isoindolin-2-yl-6-methyl-3-(1,3,4-oxadiazol-2-yl)-4-oxo-chromen-8-yl]ethyl]amino]benzoic acid is a representative of allosteric chromenone inhibitors of phosphoinositide 3-kinase (PI3K) useful in the treatment of diseases or disorders associated with PI3K (e.g., CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome), PIK3CA-related overgrowth syndrome (PROS), breast cancer, brain cancer, prostate cancer, endometrial cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, or head and neck cancer).

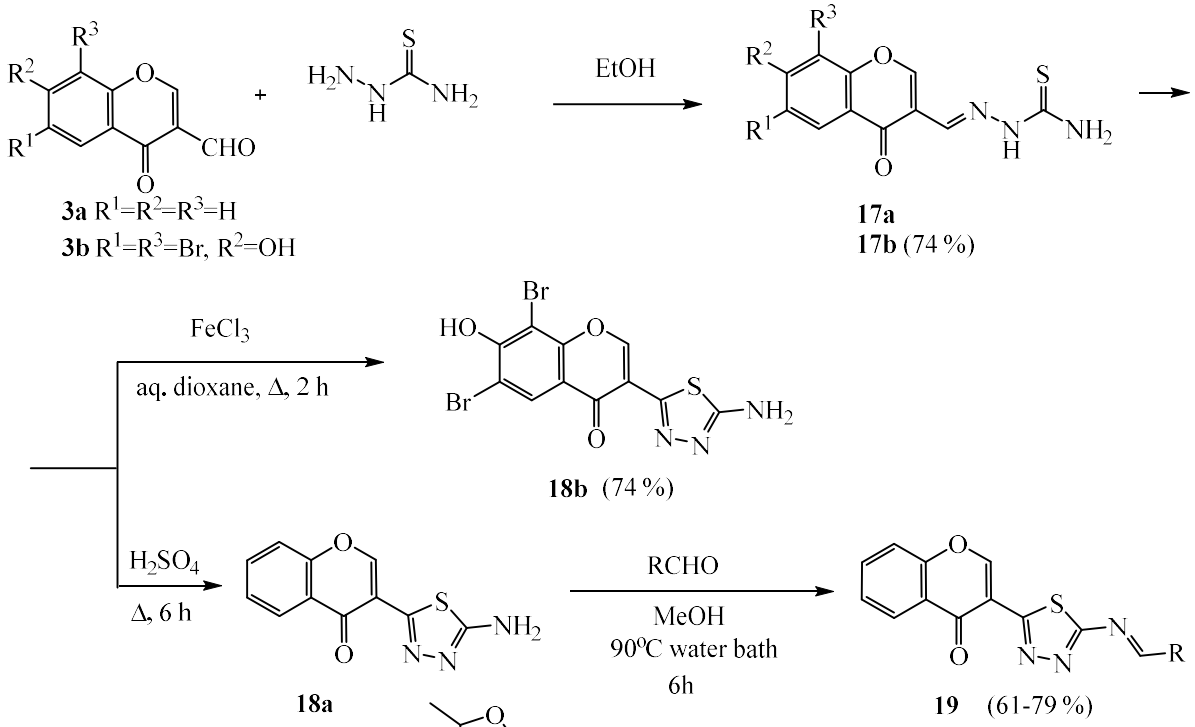
2. 3-Thiadiazolylchromones

The thiadiazole ring, which may exist in four isomeric forms, is present in the currently synthesized 3-thiadiazolyl chromones only in the isomeric form of 1,3,4-thiadiazole. The strategy for the synthesis of 3-(1,3,4-thiadiazolyl)chromones is based on two main principles: completion of the azaheterocycle ring

to the chromone system; or the formation of a pyrone ring from azaheterocycle-containing precursors, using 3-formylchromone or α-hetaryl-2-hydroxyacetophenone derivatives as the main building blocks, respectively.

The synthesis of 3-(1,3,4-thiadiazol-2-yl)- and 3-(3,4-dihydro-1,3,4-thiadiazol-2-yl)chromones according to the first principle was carried out in two stages by the heterocyclization of the condensation products of 3-formylchromone derivatives with 1,2-N,N-binucleophiles.

The reaction of 3-formylchromone **3a** with thiosemicarbazide followed by cyclization of appropriate thiosemicarbazone derivative **17a** at refluxing in concentrated sulphuric acid for 6 hours led to 3-(5-amino-1,3,4-thiadiazol-2-yl)chromone (**18a**). Subsequent modification of 3-(5-amino-1,3,4-thiadiazol-2-yl)chromone (**18a**) at amino group of the 1,3,4-thiadiazole ring with the help of diferent aromatic benzaldehydes in the presence of methanol made it possible to obtain a new series of 1,3,4-thiadiazole linked chromone hybrids **19** [25] (**Scheme 9**).



Scheme 9. The synthesis of 3-(5-amino-1,3,4-thiadiazol-2-yl)chromones from (un)substituted 3-formylchromones and thiosemicarbazide followed by intramolecular oxidative cyclization. Subsequent modification of 3-(5-amino-1,3,4-thiadiazol-2-yl)chromone (**18a**) at amino group of the 1,3,4-thiadiazole ring

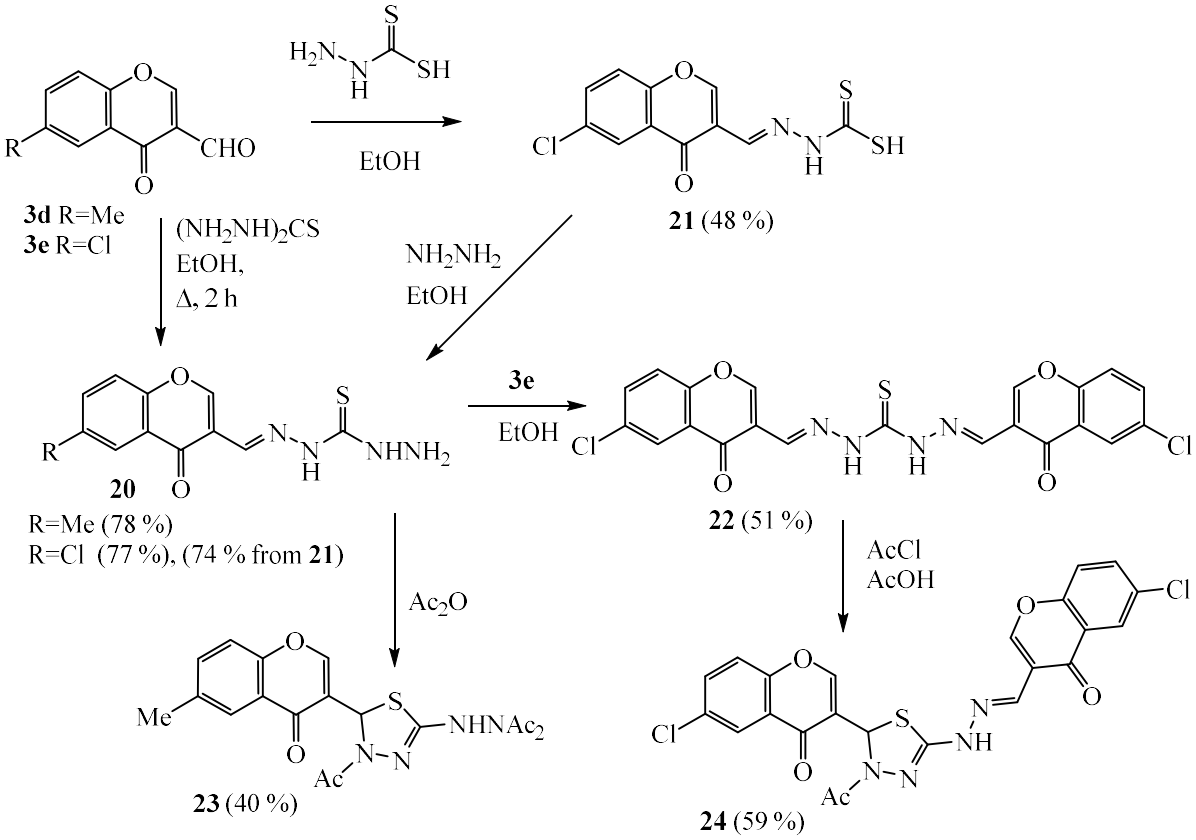
The reaction of substituted 3-formylchromone **3b** with thiosemicarbazide in refluxing ethanol gave the appropriate thiosemicarbazone derivative **17b** in 74% yield. Subsequent intramolecular oxidative cyclization of product **17b** with iron chloride in aqueous dioxane at reflux for 2 hours led to 3-(5-amino-1,3,4-thiadiazol-2-yl)-6,8-dibromo-7-hydroxychromone (**18b**) in 74% yield [11] (**Scheme 9**).

As a result of the condensation of 3-formylchromone derivatives **3d,e** with 1 equivalent of thiocarbohydrazide, monothiocarbohydrazones **20** are formed upon refluxing in ethanol for 2 hours (method A). Another variant of the synthesis of monothiocarbohydrazone **20** (R=Cl) is the condensation of 3-formylchromone **3e** with hydrazinecarbodithioic acid subsequent reaction of the formed hydrazonecarbodithioic acid **21** with hydrazine hydrate in alcohol (Method B). Condensation of monothiocarbohydrazone **20** (R=Cl) with 3-formylchromone **3e** in absolute alcohol in 5 hours affords the bisthiocarbohydrazone **22**. Boiling of monothiocarbohydrazone **20** (R=Me) with acetic anhydride gave N-acetyl-N'-[4-acetyl-5-(6-methyl-4-oxo-4*H*-chromen-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]acetohydrazide (**23**).

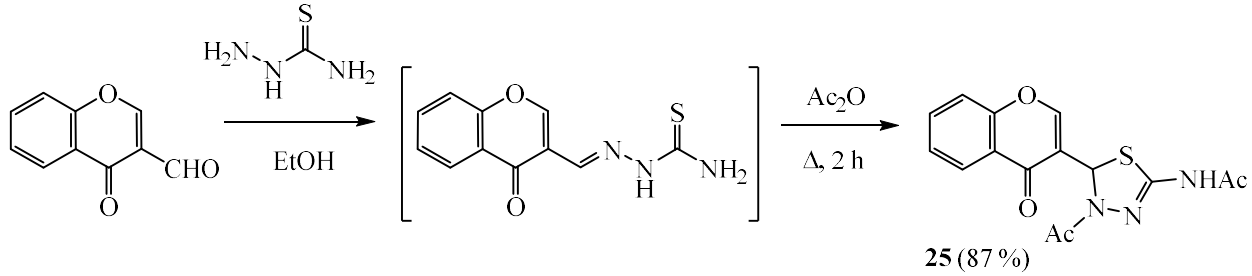
Compound **23** is formed by acetylation of the amino group followed by cyclization of the thiol form of monothiocarbohydrazone **20** (R=Me) in acidic medium and NH-acetylation in the 4,5-dihydrothiadiazole ring. 6-Chloro-4-oxo-4*H*-chromen-3-carbaldehyde[4-acetyl-5-(6-chloro-4-oxo-4*H*-chromen-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]hydrazone (**24**) was obtained by refluxing bisthiocarbohydrazone **22** with acetyl chloride in glacial acetic acid [26] (**Scheme 10**).

N-4-(Acetyl-5-(4-oxo-4*H*-chromen-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)acetamide (**25**) was synthesized using a similar protocol reported in [27] (**Scheme 11**).

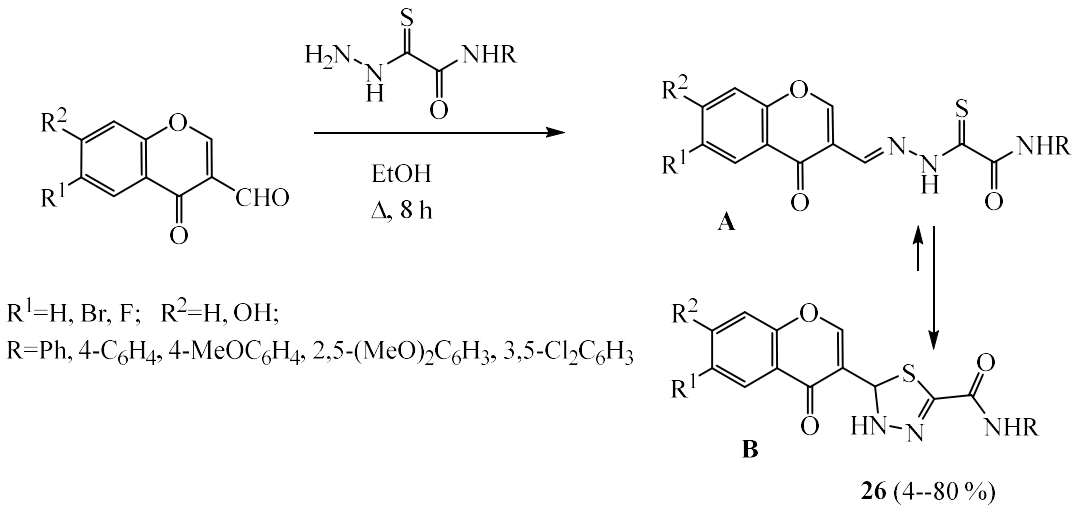
A series of new organic ligands was synthesized from substituted 3-formylchromones and oxamic acid thiohydrazides. Based on spectroscopic studies, unexpectedly, the cyclic forms of the ligands, namely 5-(4-oxo-4*H*-chromen-3-yl)-4,5-dihydro-1,3,4-thiadiazole-2-carboxamides (**26**, form B) have been identified as the preferred tautomers in solution and solid state. The binuclear complexes of copper (II), cobalt (II), and nickel (II) were obtained by reaction of metal chlorides with the ligands in boiling ethanol for 1 hour. The $(L\text{-}H)_2M_2Cl_2$ complexes turned out to be stable and soluble in DMF and DMSO [28] (**Scheme 12**).



Scheme 10. The synthesis of [4-acetyl-5-(6-R-4-oxo-4*H*-chromen-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]hydrazine derivatives

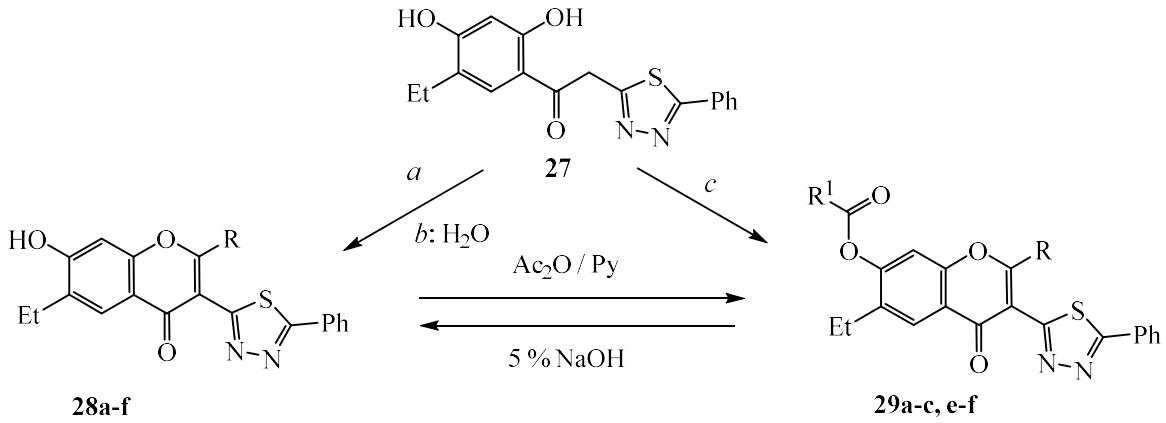


Scheme 11. The synthesis of N-4-(acetyl-5-(4-oxo-4*H*-chromen-3-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)acetamide



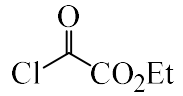
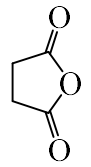
Scheme 12. The synthesis of 5-(4-oxo-4*H*-chromen-3-yl)-4,5-dihydro-1,3,4-thiadiazole-2-carboxamides from substituted 3-formylchromones and oxamic acid thiohydrazides

According to the second principle of the strategy of 3-hetarylchromones synthesis by the formation of a pyrone ring from azaheterocycle-containing precursors, the synthesis of 3-(1,3,4-thiadiazol-2-yl)chromones by cyclization of α-(5-phenyl-1,3,4-thiadiazolyl-2)-5-ethyl-2,4-dihydroxyacetophenone (**27**) was realized in [29] (**Scheme 13**). The cyclizing reagents, reaction conditions, and the resulting products with yields are listed in Table 1.



Scheme 13. The synthesis of 2-R-6-ethyl-3-(5-phenyl-1,3,4-thiadiazol-2-yl)chromones **28a-d** and **29e-g**

Table 1. The synthesis of 2-R-6-ethyl-3-(5-phenyl-1,3,4-thiadiazol-2-yl)chromones **28a-d** and **29e-g**, their yields and reaction conditions

N	R	R^1	Yield, %	Reaction conditions
28a	H		46 71	*a*: A: $CH(OEt)_3$, Py, Pip, 100°C, 45 min B: DMF, $BF_3{*}Et_2O$, PCl_5, 50°C, 15 min
28b	CF_3		86	*a*: $(CF_3CO)_2O$, Py, r.t., 48 h
28c	CO_2Et		82	*a*:  , Py, r.t., 48 h
28d	$(CH_2)_2COOH$		72	*a*:  , Py, r.t., 12 h
29e	Me	Me	86	*c*: Ac_2O, Et_3N, r.t., 12 h
29f	Et	Et	89	*c*: $(EtCO)_2O$, Et_3N, r.t., 12 h
29g	$ClCH_2$	$ClCH_2$	89	*c*: $ClCH_2COCl$, Py, dioxane, Δ, 6 h

Terminal 6-ethyl-7-hydroxy-3-(5-phenyl-1,3,4-thiadiazol-2-yl)chromone (**28a**) was prepared in two ways. According to the Venkataraman method, the cyclization of ketone **27** was performed with ethyl orthoformate (molar ratio 1:6) in pyridine in the presence of a catalytic amount of piperidine by heating at 100°C for 45 minutes, and gave a yield of 46% (method A). Wilsmeyer formylation was performed by dropwise addition of $BF_3{*}Et_2O$ to a suspension of ketone **27** in DMF followed by the addition of phosphorus pentachloride in portions (molar ratio 6:1:1,2), heating for 15 minutes at 50°C, addition of water and boiling for another 5 minutes, and gave the product in 71% yield. Following the second method, both the purity and yield of chromone **28a** are higher, and may be due to the milder reaction conditions. It should be noted that another method for the synthesis of terminal 3-aryl/hetarylchromones by cyclization of α-(hetaryl)-2,4-dihydroxyacetophenone with acetic formic anhydride turned out to be inefficient in the case of 3-(5-phenyl-1,3,4-thiadiazole-2-yl)chromones [30].

In order to obtain 2-R-6-ethyl-7-hydroxy-3-(5-phenyl-1,3,4-thiadiazol-2-yl)chromones with electron-donating and electron-withdrawing substituents at position 2 of the chromone system ketone **27** was cyclized with carboxylic acid chlorides and anhydrides such as ethoxalyl

chloride, chloroacetyl chloride, succinic, acetic, propionic and trifluoroacetic anhydrides.

The reaction of ketone **27** with an excess of trifluoroacetic acid anhydride (in a molar ratio of 1:4) or ethyloxalyl chloride (in a molar ratio of 1:2,3) was carried out in pyridine at 0°C and kept at room temperature. After treatment of the reaction mixture with water, 2-trifluoromethyl- or 2-ethoxycarbonyl-6-ethyl-7-hydroxy-3-(5-phenyl-1,3,4-thiadiazolyl-2)chromones (**28b,c**), respectively, were isolated.

The reaction of ketone **27** with succinic anhydride (in a molar ratio of 1:6) in pyridine gave 2-(*β*-carboxyethyl)-6-ethyl-7-hydroxy-3-(5-phenyl-1,3,4-thiadiazol-2-yl)chromone (**28d**) by a short heating (until the reagents dissolve) followed by stirring at room temperature for 12 hours.

For the condensation of ketone **27** with acetic and propionic anhydrides in triethylamine (in a molar ratio of 1:5:5), heating is necessary only to dissolve the reagents (further heating only leads to a blackening of the product and a decrease in yield), and then holding at room temperature for 2 hours. Treatment of the reaction mixture with water did not remove the acyl group at position 7; as a result of the reaction, 2-methyl- or 2-ethyl-substituted 7-acyloxy-6-ethyl-3-(5-phenyl-1,3,4-thiadiazol-2-yl)chromones (**29e,f**) were formed. The 7-hydroxy derivatives **28e,f** were obtained by boiling 7-acyloxy derivatives **29e,f** with 5% sodium hydroxide solution in alcohol for a short time.

The reaction of ketone **27** with chloroacetyl chloride in pyridine proceeded extremely vigorously even at low temperature and gave a resinous product. Chromatographically pure 7-chloroacetoxy-2-chloromethyl-6-ethyl-3-(5-phenyl-1,3,4-thiadiazol-2-yl)chromone (**29g**) is formed in high yield by refluxing ketone **27** with about a twofold excess of chloroacetyl chloride and pyridine in absolute dioxane.

7-Hydroxychromones **28a,b,c** are easily acylated with acetic anhydride in pyridine in the cold, to obtain 7-acetoxy derivatives **29a,b,c** in high yield. However, the acylation of product **28d** under the same conditions was unsuccessful.

2.2. Biological activity

New 1,3,4-thiadiazole linked chromone hybrids **19** [25] were screened for their *in vitro* anticancer activity against MDA-MB-231, MCF-7, and Vero cancer cell lines. Among them, compounds **19c** and **19j** emerged to be the most active against MDA-MB-231 cell line (IC_{50} = 38.12 and 56.53), **19c** and **19e** - the most active against MCF-7 cell line (IC_{50}=41.21 and 66.54) and **19c**, **19j** and **19a** - the most active against Vero cell line (IC50=30,21, 42.43 and 47.93). Designed chromone-1,3,4-thiadiazole scaffold is an interesting anticancer pharmacophore and

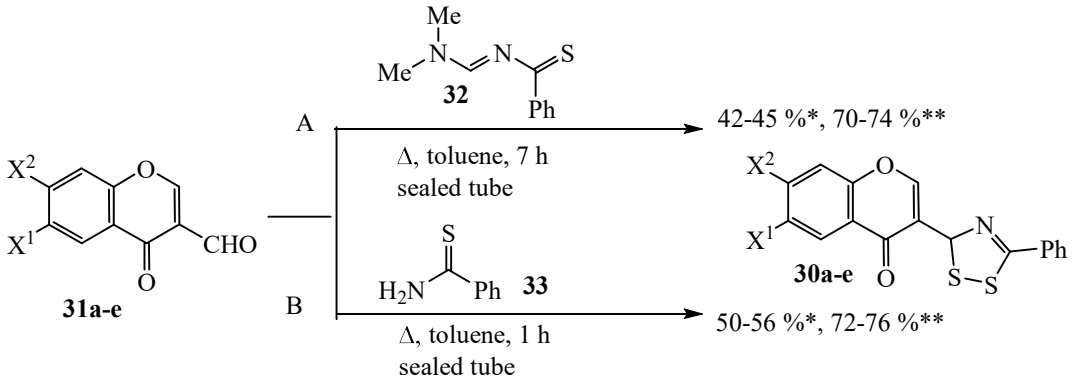
considered as novel lead scaffold for any future optimization.

3. 3-Dithiazolylchromones

3.1. Synthesis

The dithiazole ring, which may exist in two isomeric forms, is present in the 3-dithiazolylchromones in the 1,2,4-dithiazole isomeric form. The method for the synthesis of 3-dithiazolylchromones described in the literature is based on the achievement of the dithiazole ring onto the chromone system, 3-formylchromone derivatives acting as initial building blocks.

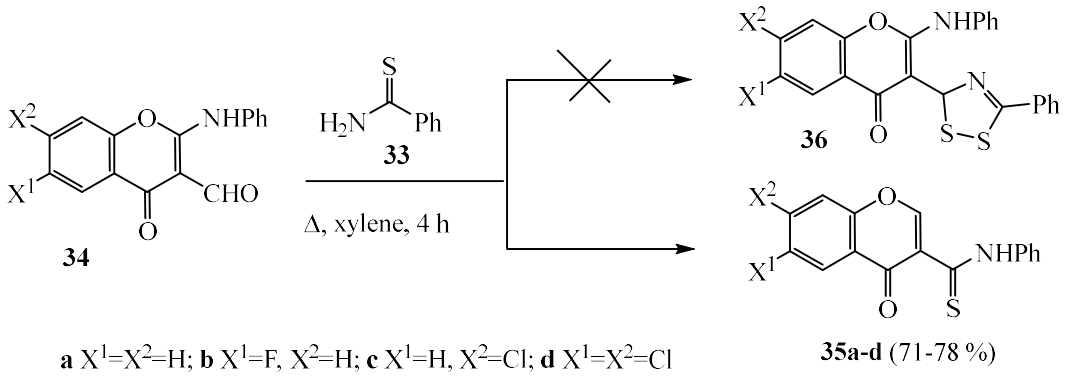
Simple and efficient synthesis of 3-(5-phenyl-3*H*-[1,2,4]dithiazol-3-yl)chromones **30a-e**, consisting in the reaction of substituted 3-formylchromones **31a-e** with 2-phenyl-4-dimethylamino-1-thia-3-azabuta-1,3-diene (**32**) or thiobenzamide (**33**) was described by heating their solution in toluene in a sealed tube [31] (**Scheme 14**). It was shown that the yields of the reaction increase by 1.5 times if the amount of 2-phenyl-4-dimethylamino-1-thia-3-azabuta-1,3-diene (**32**) or thiobenzamide (**33**) is not 1M equivalent*, but 2M equivalents.**



a X^1=X^2=H; **b** X^1=Cl, X^2=H; **c** X^1=F, X^2=H; **d** X^1=F, X^2=Cl; **e** X^1=Me, X^2=H

Scheme 14. The synthesis of 3-(5-phenyl-3*H*-[1,2,4]dithiazol-3-yl)chromones from substituted 3-formylchromones and 2-phenyl-4-dimethylamino-1-thia-3-azabuta-1,3-diene or thiobenzamide

The mechanism of formation and biological activity of 3-(5-phenyl-3*H*-[1,2,4]dithiazol-3-yl)chromones **30a-e** are reported in [32]. The conversion of 2-anilino-3-formylchromones **34a-d** by the reaction with thiobenzamide (**33**) to the corresponding thioamides **35a-d** and not to 3-dithiazolylchromones **36** establishes that this reaction proceeds through the attack of a more electrophilic C2 atom (**Scheme 15**).

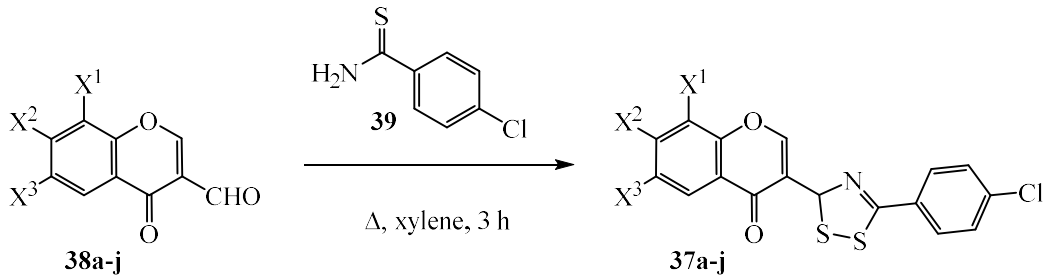


Scheme 15. Interaction of 2-anilino-3-formylchromones with thiobenzamide

And in light of the failure of benzaldehyde and 2-N-methylanilino-3-formylchromone to react with thiobenzamide or thiazadiene, it is concluded that the thionation of 3-formylchromones also proceeds through an initial attack on the more electrophilic C2 but not on the aldehyde carbon, thereby establishing the mechanism of thionation and, consequently, the formation of 3-(5-phenyl-3*H*-[1,2,4]dithiazol-3-yl)chromen-4-ones **30a–e**.

Compounds of the 3-(5-phenyl-3*H*-[1,2,4]dithiazol-3-yl)chromen-4-one series **30a-e** [31] and additionally synthesized **30f** (X^1=X^2=Cl) and **30g** (X^1=Cl, X^2=H) according to option B of **Scheme 14** (in boiling toluene for 5-7 hours with a yield of 70-74%) were studied for cytotoxic activity [33].

The synthesis of a new series of 3-(5-aryl-3*H*-[1,2,4]dithiazol-3-yl)chromen-4-one derivatives **37a-j** with lipophilic electron-withdrawing groups at positions C6 and C7 (F, Cl, Br) and C8 (Cl) of the chromone ring and an introduced chlorine substituent in the 4' position of the phenyl ring of 3-(5-phenyl-3*H*-[1,2,4]dithiazol-3-yl)chromen-4-one was reported in [34]. Substituted 3-(5-aryl-3*H*-[1,2,4]dithiazol-3-yl)chromen-4-ones **37a–j** were prepared by the reaction of 3-formylchromones **38a-j** with two equivalents of *p*-chlorothiobenzamide **39** in dry xylene for 3-3.5 hours in 40-85.5% yields (**Scheme 16).**



a X^1=X^2=X^3=H; **b** X^1=X^2=H, X^3=Me; **c** X^1=X^3=H, X^2=Cl; **d** X^1=X^3=H, X^2=F; **e** X^1=X^3=H, X^2=Br; **f** X^1=X^2=H, X^3=F; **g** X^1=X^2=H, X^3=Cl; **h** X^1=X^2=H, X^3=Br; **i** X^1=X^3=Cl, X^2=H; **j** X^1=Cl, X^2=X^3=H

Scheme 16. The synthesis of 3-(5-aryl-3*H*-[1,2,4]dithiazol-3-yl)chromen-4-ones from substituted 3-formylchromones and *p*-chlorothiobenzamide

3.2. Biological activity

3-(5-Phenyl-3*H*-[1,2,4]dithiazol-3-yl)chromones **30a-e** tested for antifungal and antibacterial activity in [26] have a high potential and are covered in the review in *Current Medicinal Chemistry* [35] .

In vitro studies of the antifungal activity of 3-(5-phenyl-3*H*-[1,2,4]dithiazol-3-yl)chromones **30a-e** were carried out on fungal strains of *Aspergillus niger* (MTCC-281), *Geotrichum candidum* (MTCC-3993), *C. albicans* (MTCC-227) and *Candida tropicalis* (MTCC-230) using fluconazole as a positive control. The inhibitory potential of the compounds was determined in terms of MIC (mg/ml) using the turbidimetry method. Compound **1c** (X^1=F, X^2=H) showed maximum inhibition (MIC 50) against *A. niger*, on par with fluconazole (MIC 49). Compound **30d** (X^1=F, X^2=Cl) showed a very high level of inhibition (MIC 5 μg/ml), which is greater than that of fluconazole (MIC 9) against *G. candidum*. Compounds **30b** (X^1=Cl, X^2=H) (MIC 28) and **30a** (X^1=H, X^2=H) (MIC 30) were the most active against *C. albicans* compared to fluconazole (MIC 24). Compounds **30b,d** showed maximum activity (MIC 28) against *C. tropicalis* compared with fluconazole (MIC 25) [32].

In vitro studies of the antibacterial activity of 3-(5-phenyl-3*H*-[1,2,4]dithiazol-3-yl)chromones **30a-e** were carried out on gram-negative and gram-positive bacterial strains by the disk diffusion method. All compounds **30a-e** showed notable antibacterial activity, although significantly lower than the activity of ciprofloxacin and chloramphenicol, which were used as positive controls. In the case of the anaerobic gram-negative bacterium *E. coli*, compound **30a** showed significant activity at 56.68% ($5x10^{-5}$ mg/ml, MIC 88). In the case of *S. flexneri*, a maximum growth inhibition of 98.55%

(MIC 52) and 85.50% (MIC 58) was observed for **30d** and **30a**, respectively, at the same concentration. For the gram-positive bacterium *S. aureus*, a maximum growth inhibition of 92.72% ($5x10^{-5}$ mg/ml, MIC 54) was observed for **30e** (X^1=Me, X^2=H). At the same time, all studied compounds were inactive against aerobic gram-negative bacteria *P. aeruginosa* [32].

The results of the cytotoxic activity studies of 3-(5-phenyl-3*H*-[1,2,4]dithiazol-3-yl)chromen-4-ones **30a-g** against human cancer cell lines indicated that in most experiments the maximum activity was observed in the presence of electron-withdrawing groups at positions C6 and C7 of the chromone ring (**30b** (X^1=Cl, X^2=H), **30g** (X^1=H, X^2=Cl), **30d** (X^1=F, X^2=Cl)) or unsubstituted variant (**30a** (X^1=X^2=H)). Among the studied compounds **30b** (X^1=Cl, X^2=H) (IC_{50}=10 μM), **30c** (X^1=F, X^2=H) (IC_{50}=14.6 μM) and **30a** (X^1=X^2=H) (IC_{50}=10.5 μM) showed maximum activity against neuroblastoma cell lines, **30g** (X^1=H, X^2=Cl) (IC_{50} =10.5 μM) - against ovarian cancer cell lines, **30g** (X^1=H, X^2=Cl), **30f** (X^1= X^2=Cl), **30b** (X^1=Cl, X^2=H), **30d** (X^1=F, X^2=Cl) - against prostate cancer cell lines, **30g** (X^1=H, X^2=Cl) - against lungs cancer cell lines; no significant activity was observed against liver and colon cancer cell lines. These molecules are useful prototypes of "lead compounds" for further development [33].

The antimicrobial activity of 3-(5-aryl-3*H*-[1,2,4]dithiazol-3-yl)chromen-4-ones **37a-j** with lipophilic electron-withdrawing substituents at positions C6 and C7 (F, Cl, Br) and C8 (Cl) of the chromone ring and the introduced Cl substituent in the 4' position of the phenyl ring of 1,2,4-dithiazole against various pathogenic bacteria and fungal strains was described in [34].

The antibacterial activity of 3-(5-aryl-3*H*-[1,2,4]dithiazol-3-yl)chromen-4-ones **37a-j** was studied *in vitro* against five human pathogenic bacteria *Staphylococcus aureus* (MTCC96), *Bacillus subtilis* (MTCC 2451), *Escherichia coli* (MTCC 82), *Pseudomonas aeruginosa* (MTCC 2642) and *Salmonella typhimurium* (MTCC 1251). The inhibitory potential of the synthesized compounds was determined in terms of the minimum inhibitory concentration (MIC) in μg/ml by the turbidity method. Compound **37c** showed high inhibitory activity against *B. subtilis* with a MIC of 0.78, comparable to gentamicin-positive control, compound **37h** with MIC 1.56 and compound **37f** with MIC 3.12 had slightly lower activity. Compounds **37a**, **37c** and **37e** showed promising activity against *S. aureus* with MIC 6.25. Compound **37h** showed relatively high inhibitory activity against *Escherichia coli* with MIC 1.56, lower activity of compounds **37c** and **37g** with MIC 3.12 and compounds **37f** and **37i** with MIC 6.25. Compounds **37h** and **37c** showed

good inhibitory activity against *P. aeruginosa* and *S. Typhi* with MIC 6.25 and 12.5, respectively.

The antifungal activity of compounds **37a-j** was studied *in vitro* against three fungal strains, *Saccharomyces cerevisiae* (MTCC 172), *Candida albicans* (MTCC 3018) and *Cryptococcus gastricus* (MTCC 1715). In the case of the fungal strain *S. cerevisiae*, compound **37h** showed very high inhibitory activity with a MIC of 0.78, which is greater than that of fluconazole (MIC 1.9), used as a positive control under similar conditions, a lower activity was observed for compound **37g** with MIC 3.12 and compound **37a** with MIC 6.25. The inhibitory activity of compound **37c** against *C. albicans* with MIC 3.12 exceeded the standard positive control (MIC 3.9), a lower activity was observed for compounds **37a**, **37e** and **37h** with MIC 6.25. Compound **37h** showed better inhibitory activity against *C. gastricus* (MIC 6.25) than fluconazole (MIC 7.8), and a lower activity was obtained for compound **37c** with MIC 12.5.

According to the results of the studies, it becomes obvious that the introduction of a chlorine into the *para*-position of the phenyl substituent in 1,2,4-dithiazole and the introduction of electron-withdrawing substituents (F, Br) into the C6 and C7 positions of the chromone ring enhanced the inhibitory activity of the compounds against various bacterial and fungal strains, especially against *B. subtilis, E. coli* and *S. cerevisiae*. Electron donor substituents (CH_3) reduce the inhibitory activity against both bacterial and fungal strains. These molecules are also useful prototypes for "lead compounds". system, 3-formylchromone derivatives most often act as the main building block.

4. 3-Triazolylchromones

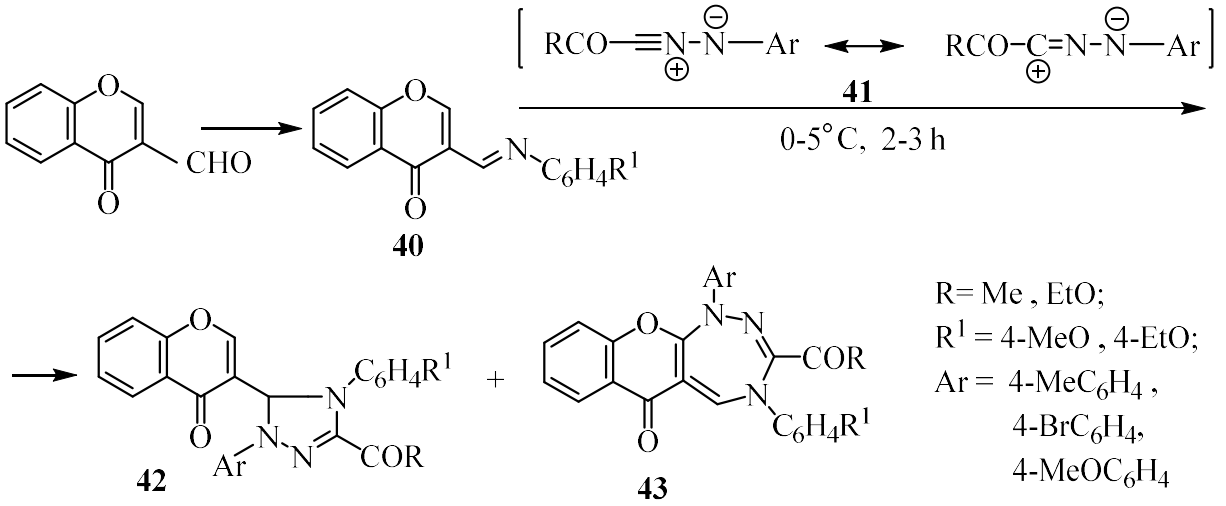
4.1. Synthesis

The triazole ring is present in the 3-triazolylchromones in the isomeric forms of 1,2,3-triazole and 1,2,4-triazole. Methods for the synthesis of 3-triazolylchromones are based both on the principle of completion of the triazole ring to the chromone system and on the formation of a pyrone ring from precursors containing an azaheterocycle.

When implementing the principle of completion of the triazole ring to the chromone

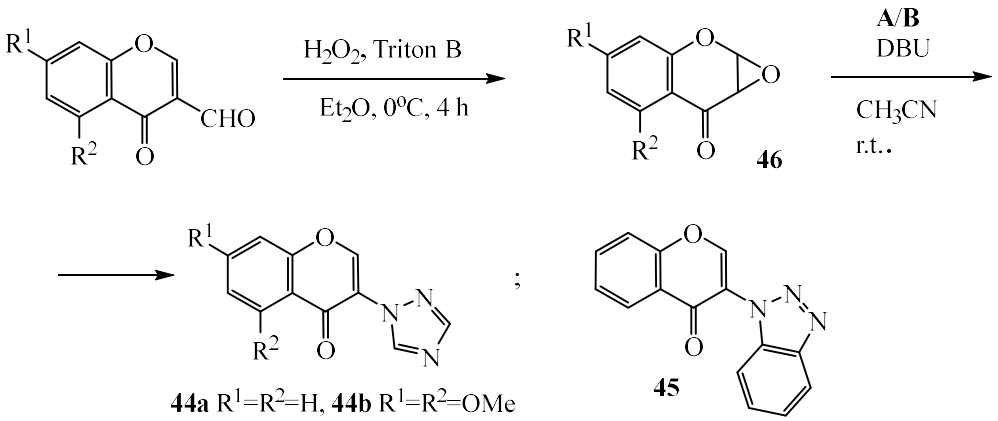
The reaction of chromone imines **40** and nitrilimines **41** in dry chloroform at low temperature gives both types of adducts ([2+3] and [4+3]), 3-(1,2,4-triazolinyl)chromones **42** and condensed triazepinochromones **43 (Scheme 17**). The starting chromone imines **40** are formed by condensation of 3-formylchromone with *p*-anisidine or *p*-phenitidine in boiling benzene. C-Acetyl- and C-ethoxycarbonylnitrilimines **41** were obtained *in situ* from the corresponding arylhydrazonoyl halides in the presence of absolute triethylamine in dry chloroform [36].

Interestingly, this work was the first use of the principle of 1,3-dipolar cycloaddition in chromone chemistry.



Scheme 17. The synthesis of 3-(1,2,4-triazolinyl)chromones from chromone imines and nitrilimines

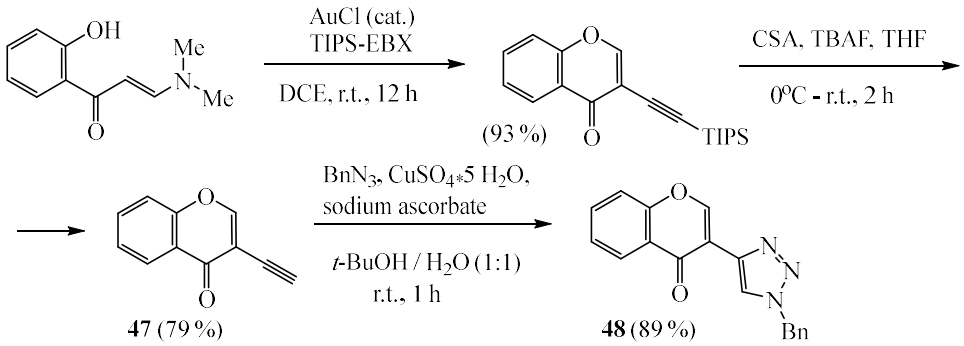
The patent [37] discloses a synthesis of 3-(1,2,4-triazol-1-yl)chromones **44** and 3-(1,2,3-benzotriazol-1-yl)chromone **45** based on 2,3-epoxychromones **46**, 1,2,4-triazole (**A**) or 1,2,3-benzotriazole (**B**) and DBU occurring at room temperature in about 90% yields (**Scheme 18**)



Scheme 18. The synthesis of 3-(1,2,4-triazol-1-yl)chromones and 3-(1,2,3-benzotriazol-1-yl)chromone from 2,3-epoxychromones and 1,2,4-triazole (**A**) or 1,2,3-benzotriazole (**B**)

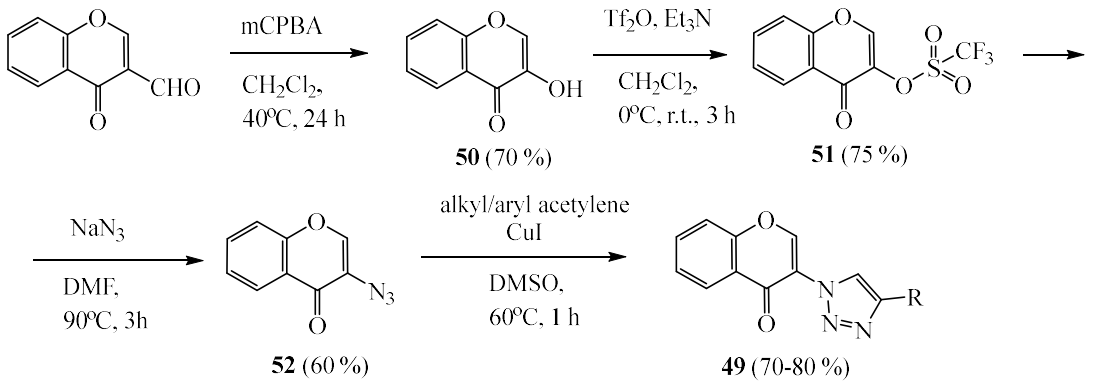
Using a strategy based on the *o*-hydroxyarylaminones, a method for the preparation of structurally diverse 3-alkynylchromones, including gold-catalyzed alkynylation of the enamine moiety using TIPS-

EBX (1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one) followed by intramolecular cyclization was proposed in [38]. TIPS deprotection has been found to occur under mild conditions with a combination of TBAF and camphorsulfonic acid. The possibilities of the transformation of 3-alkynylchromones into various functionalized chromones are demonstrated by the example of the transformation of ethenylchromone **47** into 3-(N-Bn-1,2,3-triazol-4-yl)chromone **48** by copper-catalyzed azide-alkyne cycloaddition (CuAAC) (**Scheme 19**).



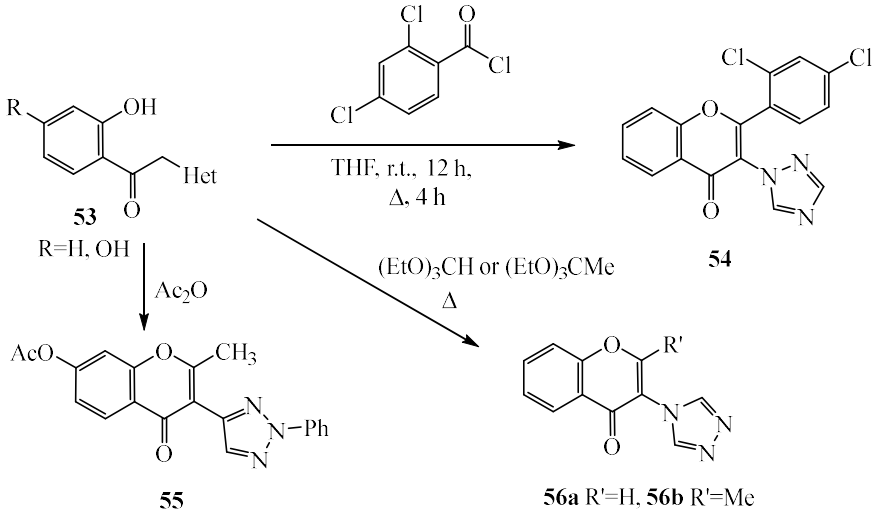
Scheme 19. Transformation of ethenylchromone into 3-(N-Bn-1,2,3-triazol-4-yl)chromone *via* azide-alkyne cycloaddition catalyzed by copper

The principles of click chemistry in the synthesis of 3-(1,2,3-triazol-1-yl)chromones **49** were also used in [39]. By regioselective Baeyer-Villiger oxidation of the starting chromon-3-aldehyde with *m*-CPBA, 3-hydroxy-4*H*-chromen-4-one **50** was obtained. To make the hydroxy group of compound **50** easily displaced (eliminated), it is converted to O-triflate (compound **51**) by treatment with triflate anhydride. Compound **51** was subjected to nucleophilic substitution with azide by reaction with NaN_3 in DMF to form the desired key intermediate 3-azido-4*H*-chromen-4-one **52** in 60% yield. The alternative preparation of compound **52** from 3-bromochromone, even by a long-term reaction with NaN_3 in DMF, proceeded in low yield. Next, the key intermediate **52** underwent a 1,3-dipolar cycloaddition catalyzed by copper with alkyl/aryl alkynes in DMSO to give exclusively 1,4-regioisomeric 3-(4-R-1,2,3-triazol-1-yl) chromones **49** in 70-80% yields (**Scheme 20**).



Scheme 20. The synthesis of 3-(4-R-1,2,3-triazol-1-yl)chromones from 3-formylchromone

An efficient method for the synthesis of 3-(1,2,4-triazolyl)- and 3-(1,2,3-triazolyl)chromones *via* the formation of a pyrone ring from azaheterocycle-containing precursors is the cyclization of the corresponding α-hetaryl-2-hydroxyacetophenones **53** (**Scheme 21**).



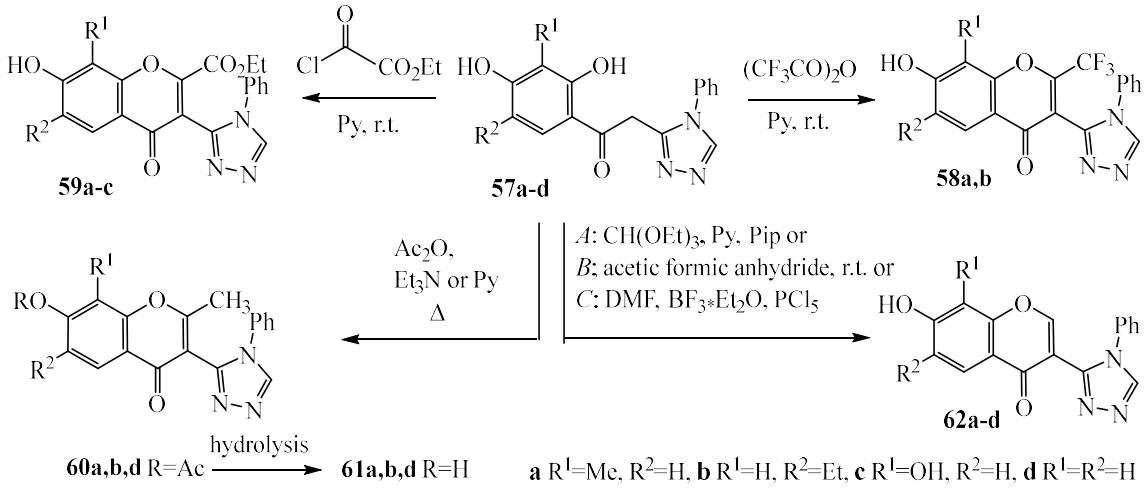
Scheme 21. The synthesis of 3-(1,2,4-triazolyl)- and 3-(1,2,3-triazolyl)chromones from corresponding α-hetaryl-2-hydroxyacetophenones

Cyclization of 2-hydroxy-α-(1,2,4-triazol-1-yl)acetophenone with 2,4-dichlorobenzoyl chloride in THF in the presence of triethylamine afforded 2-(2,4-dichlorophenyl)-3-(1,2,4-triazol-1-yl)chromone (**54**) [4].

Cyclization of 2,4-dihydroxy-α-(2-phenyl-1,2,3-triazol-5-yl)acetophenone with acetic anhydride was completed to obtain 2-methyl-7-acetoxy-3-(2-phenyl-1,2,3-triazol-5-yl)chromone (**55**) [40].

3-(1,2,4-Triazol-4-yl)chromones **56a,b** were obtained by cyclization of 2-hydroxy-α-(1,2,4-triazol-4-yl) acetophenone by boiling with triethylorthoformate or triethylorthoacetate [41].

Synthesis of 7-hydroxy-3-(4-phenyl-1,2,4-triazol-3-yl)chromones with various substituents both in the benzene and pyrone rings by cyclization of α-(4-phenyl-1,2,4-triazol-3-yl)-2-hydroxyacetophenones, structurally including fragments of resorcinol, alkylresorcinols and phloroglucinum was carried out in [42, 43] (**Scheme 22**).



Scheme 22. The synthesis of 7-hydroxy-3-(4-phenyl-1,2,4-triazol-3-yl)chromone derivatives by cyclization of substituted 2-hydroxy-α-(4-phenyl-1,2,4-triazol-3-yl)acetophenones

The ketones **57a-c** react with trifluoroacetic anhydride or ethoxalyl chloride in pyridine at low temperature and cyclize to 6-R^2-8-R^1-7-hydroxy-3-(4-phenyl-1,2,4-triazol-3-yl)chromones with triflurомethyl (**58a,b**) or carbethoxy substituents (**59a-c**) at position 2 of the molecule. Treatment of the ketone **57b** with acetic anhydride in triethylamine at 130°C and subsequent work up of the reaction mixture with water gave 7-acetoxy-6-ethyl-2-methyl-3-(4-phenyl-1,2,4-triazol-3-yl)chromone (**60b**) which is readily hydrolyzed using aqueous alcoholic base to give the target 7-hydroxy derivative **61b**. It was not possible to prepare the pure 7-acetoxy derivatives of 2-methylchromones under the same conditions (A) or in pyridine at 90-95°C [43] (B) from the ketones **57a,d** due to partial hydrolysis when treated with water hence the dry products underwent acid or base hydrolysis to give the 7-hydroxy-2-methylchromones **61a,d.** It should be noted that change of base or increase in temperature did not affect the yield of compound **61d** which was 57%, as reported in [42].

The 7-hydroxy-3-(4-phenyl-1,2,4-triazol-3-yl)chromones unsubstituted at the position 2 had been prepared before using the Venkataraman method by refluxing the starting ketone **57d** with ethyl orthoformate in pyridine [42] or by treatment

with acetoformic anhydride without a catalyst at room temperature [30]. The preparation of chromone **62b** in its pure form by the Venkataraman method proved to be problematic. Synthesis of terminal chromones **62a-d** by Vilsmeyer formylation made it possible to obtain the desired products in good yields within 1 h.

4.2. Biological activity

Compounds **44** and **45**, which are inhibitors of matrix metalloproteinases, can inhibit the production, secretion or activation of extracellular matrix proteinase and be useful for the prevention of metastasis and inhibition of cancer growth [37].

2-(2,4-Dichlorophenyl)-3-(1,2,4-triazol-1-yl)chromone (**54**) showed herbicidal activity against *Erysiphe graminis*: barley powdery mildew, providing over 50% disease control at a concentration of 500 ppm (w/w volume) or less [4].

The results of a screening test for lethal convulsions in mice induced by pentylenetetrazole (PTZ), which is used to characterize potential anticonvulsants, demonstrated the absence of anticonvulsant activity in 3-(1,2,4-triazol-4-yl)chromen-4-ones **56a,b** [41].

As mentioned in patents [44, 45] according to Biacore binding assay results 7-hydroxy-2-methyl-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-4-one and 7-hydroxy-2,8-dimethyl-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4H-chromen-4-one were identified as binders to $A\beta_{(1-42)}$ oligomers/soluble polymers. 7-Hydroxy-2-methyl-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-4-one also bound to $A\beta_{(1-42)}$ synthetic fibrils, although this scaffold was found to bind to oligomers and polymers preferentially over fibrils. 7-Hydroxy-2,8-dimethyl-3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-4*H*-chromen-4-one has been found not to bind to fibrils.

Conclusions

In conclusion, it should be noted that synthesis strategies focused on diversity, accessible and highly reactive synthons open up new prospects for the development of the chemistry of heterocyclic analogues of isoflavones presented in this review.

The results of screening for biological activity showed directions for further search of promising objects for medicinal chemistry, the so-called medicinal candidates for the developement of drugs in the future. As an example, the potential of 3-[5-(2-methylquinolin-3-yl)-1,3,4-oxadiazol-2-yl]-4*H*-chromen-4-one as an anti-TB agent allows it to be used as a starting point for the development of potent anti-tuberculosis agents, and 3-(5-aryl-3*H*-[1,2,4]dithiazol-3-yl)chromones, which demonstrate promising antifungal, antibacterial and cytotoxic activities are the original prototypes of "lead compounds" for

further development.

In order to identify attractive representatives, it is necessary to increase the volume of the library of 3-hetarylchromones. This problem should be solved not only by synthesizing new analogues, but also by implementing various possible modifications in the structure of existing representatives both on the benzene and on the pyran ring, which has already been carried out to a certain extent in the works [46-52].

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