Reviews

Synthesis of heterocyclic analogs of isoflavone and homoisoflavone based on 3-formylchromone*

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The review is focused on recent developments of chemistry of synthetic analogs of natural compounds, isoflavone and homoisoflavone. The possible synthetic strategies to access heterocyclic analogs of these compounds starting from readily available 3-formylchromone and its derivatives (3-cyanochromone, 2-amino-3-formylchromone) and products of its condensation with simplest *C*- and *N*-nucleophiles are discussed. The structural features of the reaction products that depend on the nature of the reaction medium, structure of the starting compounds, and reagent ratio are considered. Particular attention is given to the application of the modern strategies of organic synthesis, namely green chemistry approaches, click reactions, domino reactions, *etc*. Examples of compounds of this group most promising for clinical application due to wide and pronounced pharmacological effects are given.

Key words: heterocycles, isoflavone, homoisoflavone, 3-formylchromone.

Introduction

The search for new effective and safe drugs by rational synthesis of biologically active compounds has been a most important aim of modern medicinal chemistry for many years. One of the directions of this search is the modification of natural biologically active substances.[1—4] From this viewpoint, 4*H*-chromen-4-one derivatives that are a subclass of flavonoids, secondary metabolites of plants, are of great interest. The convenient precursors for the synthesis of heterocyclic analogs and homologs of isoflavones are 3-formylchromones (**1**) and, in particular compound **1a** (R = H).

* Dedicated to Academician of the Russian Academy of Sciences V. N. Charushin on the occasion of his 70th birthday.

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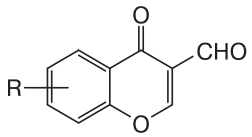

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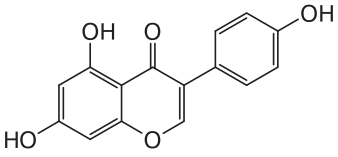
To date, more than 8000 natural and synthetic flavonoids are described.[5] These compounds exhibit a wide range of biological activities along with low toxicity (see, for example, reviews[6—11]). Reviews[12—14] are focused on the potential of different natural compounds, including flavonoids, to combat COVID-19.

In the flavonoid class, derivatives of 3-phenylchromone also called isoflavonoids are of considerable interest.[15,16] The structures of isoflavones and their heterocyclic analogs that are currently used in clinical practice or under clinical trials are shown below.



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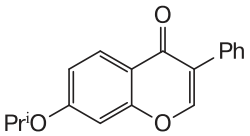

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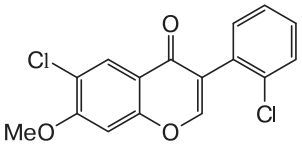

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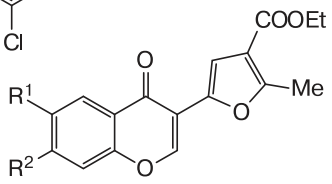

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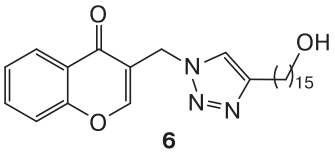

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5: R^1 = H, OMe, OEt; R^2 = H, OMe

Isoflavone genistein **2** is an active ingredient of the dietary supplements (Menoril®) used for alleviating menopausal symptoms.[17] Synthetic isoflavone ipriflavone **3** is used to inhibit bone resorption and to prevent bone and cartilage degeneration.[18] 2′,6-Dichloro-7-methoxyisoflavone (**4**) efficiently induces keratinocyte migration and could be used in wound healing compositions.[19] Furan isoflavone analogs **5** showed antituberculosis activity against reference strain H37Rv of *Mycobacterium tuberculosis*. The authors believe that the cell wall lipoproteins of *M. tuberculosis* are the major target for these compounds.[20] (Chromon-3-yl)triazolylmethane derivative **6** showed antimycobacterial activity similar to that of Rifampicin.[21]

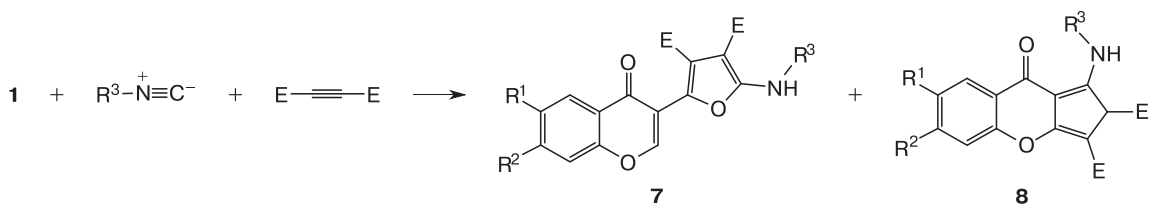
The most known methods for the synthesis of isoflavone heterocyclic analogs involve preliminary synthesis hetaryl desoxybenzoins and their subsequent cyclization.[15,16,22,23] This approach is very time- and labor-consuming when applied for the library synthesis of new isoflavone derivatives. Another strategy is the C—C bond formation between the chromone fragment and 3-positioned cyclic substituent by the cross coupling reactions.[24—28] This is very important to note that 3-formylchromones have three reactive centers, *i.e.*, an aldehyde group, an electrophilic C(2) atom, and a carbonyl group at C(4) that provide possibility to modify the structures of the starting compounds (the reactivity of compounds **1** is discussed in reviews[29—34]). The reactivity of the simplest chromone derivatives, *viz.* 3-cyanochromone[35,36] and 2-aminochromone-3-carboxaldehyde,[37] was reviewed earlier. Depending on the reactive center of the starting compound involved in the reaction with nucleophile, 3-formylchromones can either undergo recyclization to hetaryl-substituted phenols, or produce benzopyran-fused systems, or participate in the reactions occurring with the retention of the initial heterocycle. The present review is mainly focused on this last type of the reactions.

1. Synthetic approaches to heterocyclic analogs of isoflavone

1.1. Isoflavone hetero analogs with five-membered heterocycles

Three-component reaction of 3-formylchromones **1**, alkyl isocyanides, and acetylenedicarboxylates gave the furan-substituted isoflavones **7**, cyclopenta[*b*]chromene-

Scheme 1



7 **8**

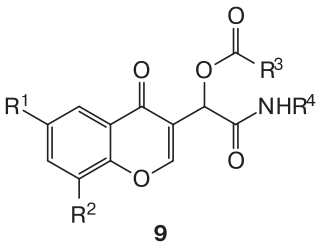
R^1 = H, Me, Pr^i, NO_2, Cl; R^2 = H, Me; R^3 = Bu^t, *cyclo*-C_6H_{11}; E = CO_2Me, CO_2Et

Conditions: benzene, 40—55 °C, 12 h.

dicarboxylates **8** or their mixtures (Scheme 1).[38] The direction of the reaction depends on both the nature of the substituents in 3-formylchromone **1** and the structure of acetylenedicarboxylate. The presence of electron-releasing substituents in the chromone ring system and the use of methyl acetylenedicarboxylate both facilitated the formation of isoflavone hetero analogs **7**. In contrast, the presence of electron-withdrawing substituents in chromone and the use of ethyl acetylenedicarboxylate led to predominant formation of the fused derivatives **8**.

The reaction of 3-formylchromones **1** (R^1 = H, Me; R^2 = H), alkyl isocyanides (R^3 = Bu^t, *cyclo*-C_6H_{11}), and methyl acetylenedicarboxylate in polyethylene glycol 400 (PEG-400) at room temperature gave selectively furan isoflavone analogs **7** in 75—90% yields.[39]

When acetylenedicarboxylate was replaced with cinnamic and benzoic acids, 2-acyloxy-2-(chromon-3-yl)-acetamides **9** were obtained.[40]



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R^1 = H, Me, Cl; R^2 = H, Cl, R^3 = Ph, 2,4-$Cl_2C_6H_3$, 4-$O_2NC_6H_4$, Bn, $ClCH_2$, *etc.*; R^4 = Bn, *cyclo*-C_6H_{11}, Bu^t, *etc.*

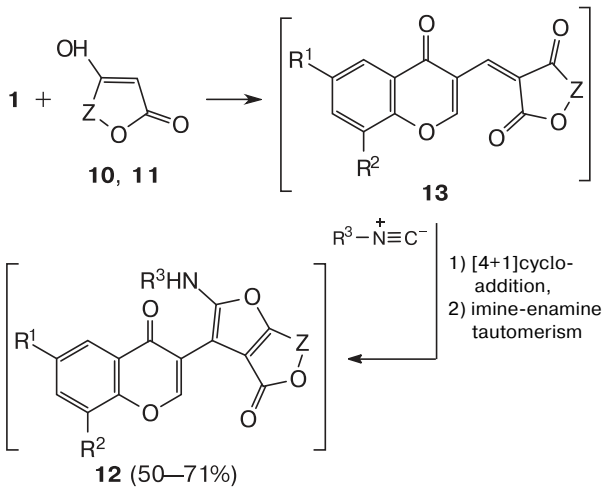
Three-component reaction of 3-formylchromones **1**, isocyanide, and either 4-hydroxycoumarin (**10**) or 4-hydroxy-6-methylpyran-2-one (**11**) in refluxing toluene for 2 h gave furocoumarin and furopyranone isoflavone derivatives **12** (Scheme 2).[41] The authors suggest that the reaction proceeded as [4+1] cycloaddition of isocyanide to the Knoevenagel adduct **13** that generated in the reaction of 3-formylchromones **1** with compounds **10** and **11**.[41] Product **12** exists in the more stable enamine form.

If primary aromatic amines were employed in this reaction instead of isocyanides, 5-oxofuran derivatives **14** were synthesized (Scheme 3).[42] The authors believed the reaction proceeds as follows. Initially, acetylenedicarboxylate reacted with amine to give dimethyl (*E*)-2-anilinobut-2-enedicarboxylate that further added to the aldehyde group of 6-formylfurochromone **1b**.

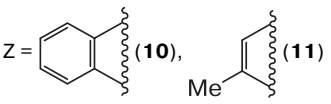
Some furochromone derivatives **14** demonstrated *in vitro* cytotoxicity against hepatocellular carcinoma (HEPG2) and breast cancer (MCF7) cell line similar to that of the commonly used chemotherapeutic agents, 5-Fluorouracil and Doxorubicin, and *in vivo* against *N*-methyl-*N*-nitrosourea-induced breast cancer in rats.[42]

Four-component condensation of 3-formylchromones **1**, Meldrum′s acid, alkyl isocyanide, and alcohol resulted in succinimide derivatives **15** (Scheme 4).[43] The reaction

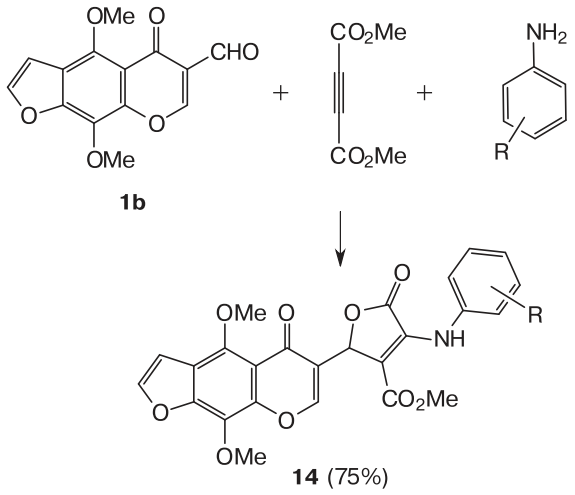
Scheme 2



R^1 = H, Me, Cl; R^2 = H, Cl; R^3 = Alk, Ar

Z =  (**10**), (**11**)

Scheme 3



R = 3-NO_2, 4-Me, 2-OH, 2-OMe, 4-OMe

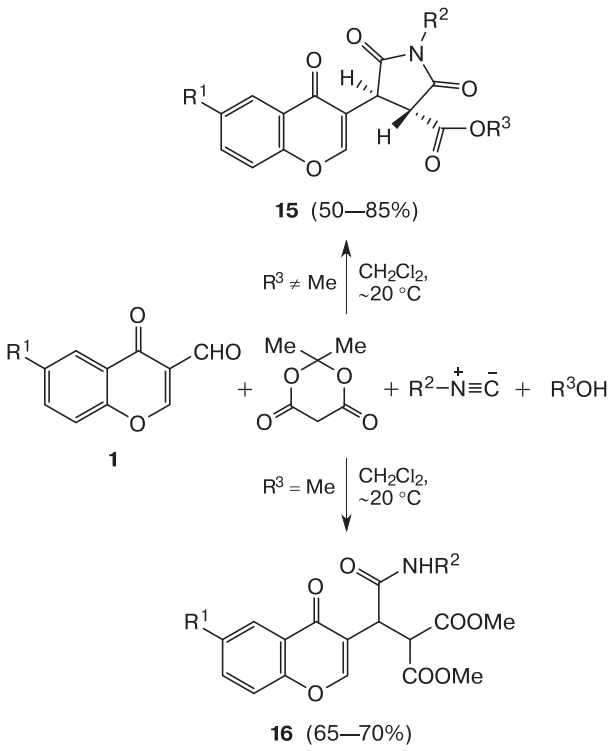
Conditions: TsOH, toluene, reflux.

proceeded at room temperature chemo- and regioselectively to give products **15** in reasonable yields.

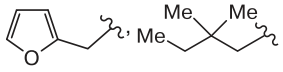
This approach is tolerated to a wide variety of the substituents R^2 and R^3, while the use of methanol promoted the pyrrolidone ring opening to give amido diesters **16**[43] (see Scheme 4).

Pseudo three-component reaction of 3-formylchromones **1** and isocyanides afforded furo[3,4-*b*]chromones **17** in high yields (Scheme 5).[44] The authors suppose that

Scheme 4



R^1 = H, Me; R^2 = *cyclo*-C_6H_{11}, Bn, 1,1,3,3-tetramethylbutyl, 2-morpholinoethyl; R^3 = Me, Et, Bu, $(CH_2)_5$, *cyclo*-C_6H_{11}, 4-$ClC_6H_4CH_2$, 2-adamantyl,

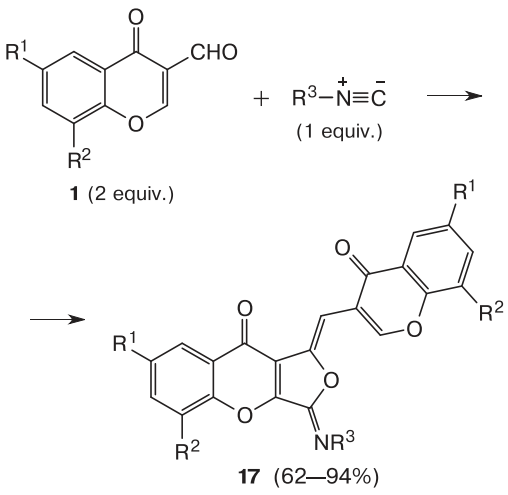


this reaction is a cascade transformation involving [1+4] cycloaddition of isocyanide to the position 2 of formylchromones **1** followed by condensation of the generated adduct with the second molecule of aldehyde **1**.

3-Formylchromone **1a** reacted with glycine derivatives in refluxing toluene in the presence of catalytic amounts of *p*-toluenesulfonic acid (TsOH) to give either pyridine derivatives **18** or substituted pyrroles **19—21** (Scheme 6).[45] The reaction of 3-formylchromone **1a** with ethyl glycinate afforded a mixture of compounds **18a** and **19a**. When α-aminoacetonitrile was used instead of ethyl glycinate, the reaction selectively gave compound **18b**. Both alanine ethyl ester and phenylglycine ethyl ester reacted with 3-formylchromone **1a** to give pyrrole **20**. Under these conditions, *N*-methylglycine afforded pyrrole **21**.

The authors suggested the mechanisms leading to compounds **18—21**.[45] In particular, they proposed almost all possibilities of formation of compounds **18a** and **19a** *via* successive addition of both nucleophilic centers of ethyl glycinate to the position 2 and the aldehyde group of 3-formylchromone **1a**. The authors believe that pyrrole **20** is resulted from the following reaction sequence. The reaction of the starting amine with aldehyde **1a** gave the

Scheme 5



R^1 = H, Me, Cl; R^2 = H, Cl; R^3 = Alk, Ar

Conditions: *i*. CH_2Cl_2, ~20 °C, 4 days.

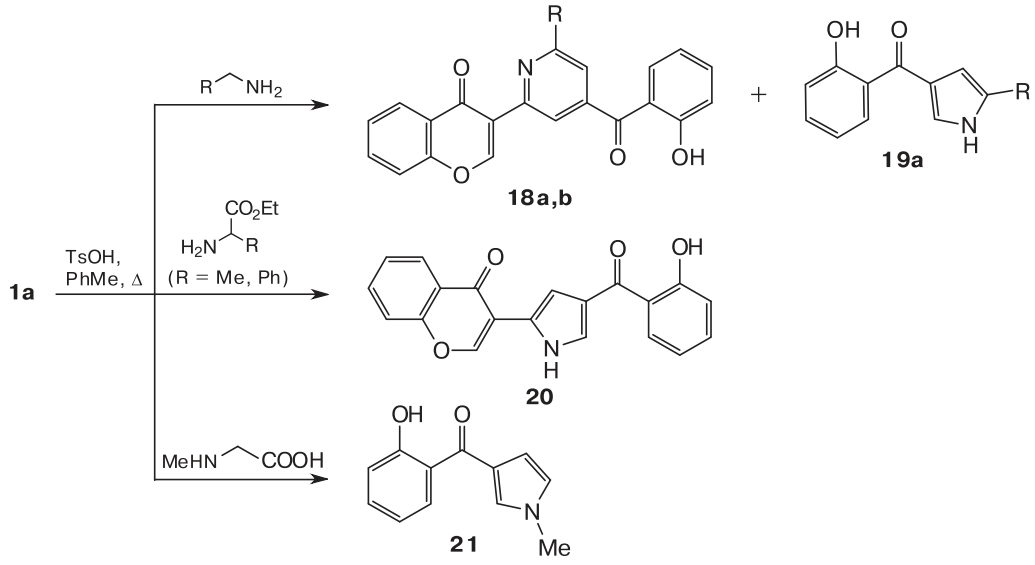
Schiff base that eliminated α-keto acid and afforded 3-aminomethylchromone, the last compound further reacted with the second molecule of aldehyde **1a** to give **20**.

Later,[46] the results obtained and the mechanisms of the reactions of 3-fromylchromone **1a** with amino acid derivatives proposed by Suschitzky and coworkers[45] were revised.

The reaction of compound **1a** with methyl glycinate hydrochloride (**22**) in the presence of K_2CO_3 at a ratio **1a** : **22** : K_2CO_3 of 1 : 1 : 0.5 in refluxing toluene afforded 3-aza-9-xanthene **23** (12%) along with salicyloylpyridine **18c** (21%) and salicyloylpyrrole **19b** (R = COOMe) (8%) (Scheme 7).[46] No product **23** is formed in this reaction performed with excesses of hydrochloride **22** and K_2CO_3 (5 equiv. each).

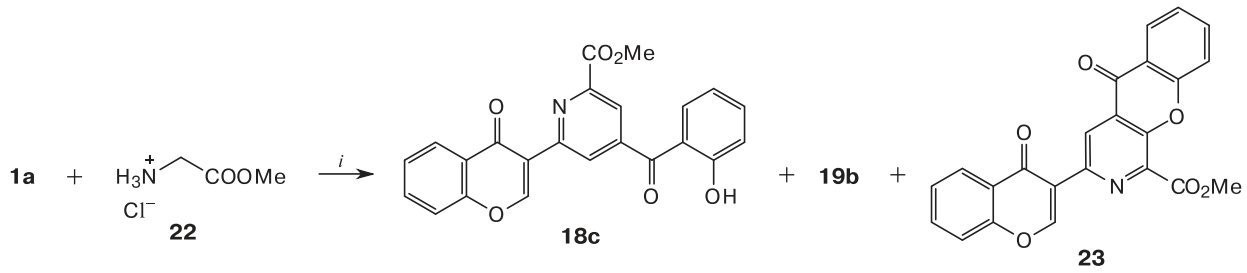
The key intermediate in the reaction of 3-formylchromone **1a** with *N*-methylglycine is azomethine ylide. Formation of intermediate **24** was supported by the synthesis of a series of *N*-methylpyrrolidine derivatives by 1,3-dipolar cycloaddition of different dipolarophiles (Scheme 8).[46—48] The reaction in refluxing toluene with *N*-phenylmaleimide as a dipolarophile gave a mixture of *cis*/*trans* diastereomers **25** and pyrrole **21**.[46] Under similar conditions, the three-component condensation of 3-formylchromone **1a**, *N*-methylglycine, and fullerene C_{60} resulted in unique fullerene—chromone dyad **26**.[47] Tomé and coworkers assumed that combining two structural moieties with antioxidant activity, namely, fullerene and chromone cores, is a promising approach to pharmacologically active compounds. The reaction of 3-formylchromones **1** with *N*-methylglycine in a ratio of 1 : 1 in refluxing DMF gave a mixture of 1-methyl-2,5-dihydropyrrol-2-ylchromones **27** and the products of deformylation of the starting 3-formylchromones, compounds

Scheme 6



R = COOEt (**18a**, **19a**), CN (**18b**)

Scheme 7



Reagents and conditions: *i*. K_2CO_3, toluene, reflux.

28 (see Scheme 8).[48] No increase in the yield of compounds **27** was achieved when 2 equiv. of formylchromones **1** were used. The authors believe that products **27** are resulted from [3+2] cycloaddition of compounds **1** to intermediates **24**.

Dimethyl fumarate, 1,4-naphthoquinone, and dimethyl acetylenedicarboxylate were found unreactive in 1,3-dipolar cycloaddition reaction with intermediates **24**. Under these conditions, only 1-methyl-3-salicyloylpyrrole **21** was formed.[46]

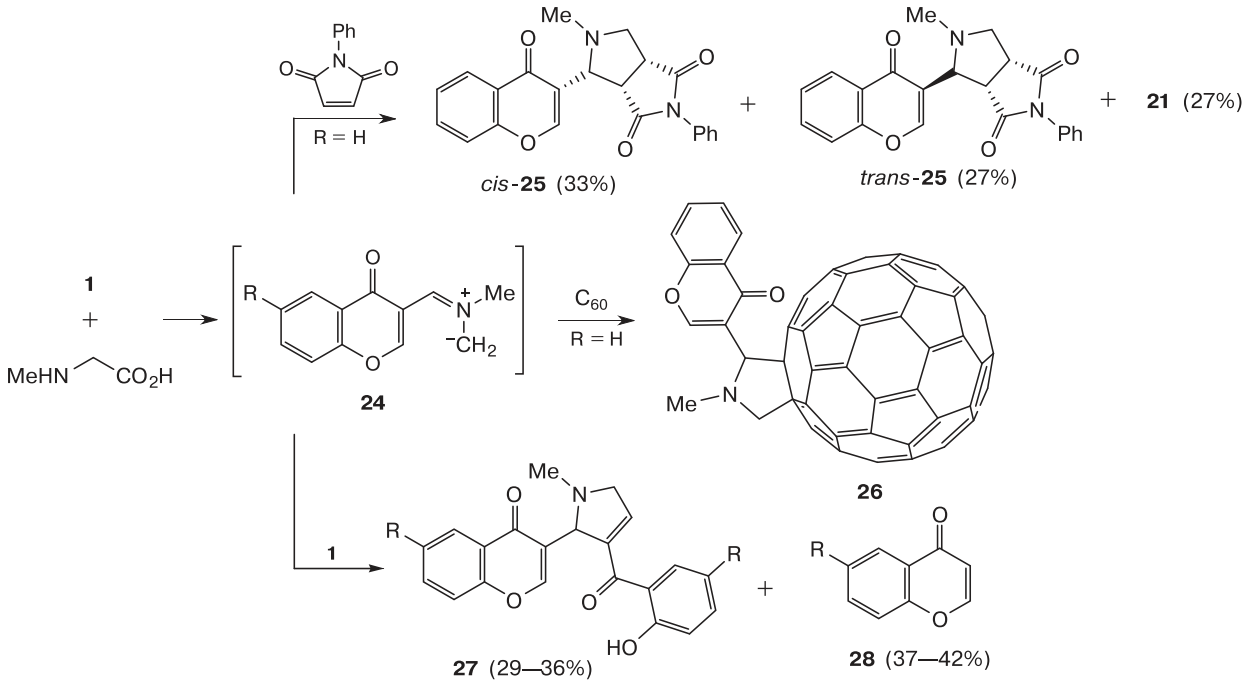
In the absence of dipolarophile, the main product in the reaction of 3-formylchromone **1a** with *N*-methylglycine (2.5 equiv.) was pyrrole **21** (80%).[46] Apparently, the formation of **21** is a result of 1,5-electrocyclization of azomethine ylide **24** followed by the pyranone ring opening. The minor product in this reaction was chromonopyrrole **29** (Scheme 9). The authors suggested that compound **29** is formed *via* the 1,3-cycloaddition of ylide **24** to compound **1a**. The yield of product **29** could be increased to 50% reacting 3-formylchromone **1a** with *N*-methylglycine in a 10 : 1 ratio.[46]

The reaction of 3-formylchromone **1a**, DL-alanine, and dimethyl fumarate in MeOH in the presence of catalytic amounts of AcOH selectively gave diastereomer **30**. When fumaronitrile was used as a dipolarophile, a 4.5 : 1 mixture of diastereomers **31a** and **31b** was obtained in 61% yield (Scheme 10).[49]

The course of the reaction of primary hetaryl methaneamines with 3-formylchromone **1a** in the presence of TMSCl strongly depends on the reagent ratio. 5-Hetaryl-3-(2-hydroxybenzoyl)-1*H*-pyrrols **32** were obtained using a molar ratio **1a** : amine of 1 : 2, while at a molar ratio **1a** : amine of 2 : 1 the only reaction products were chromenopyrrole isoflavone analogs **33** (Scheme 11).[50]

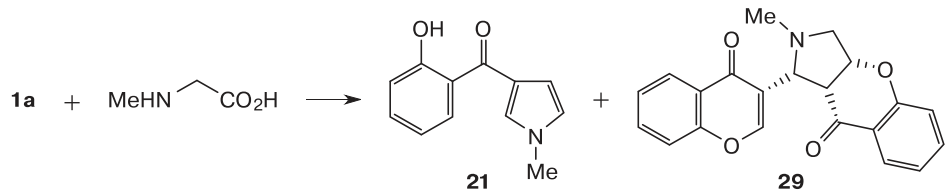
The reaction of 3-formylchromone **1a** with secondary hetarylmethaneamines is independent of the reagent molar ratio and gives *N*-substituted salicyloylpyrroles **34** in 61—99% yields (Scheme 12).[50]

Scheme 8



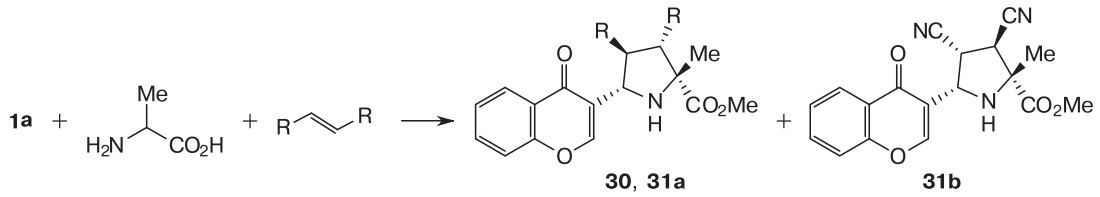
R = H, Me, Cl

Scheme 9



Conditions: toluene, N_2, reflux, 7.5 h.

Scheme 10



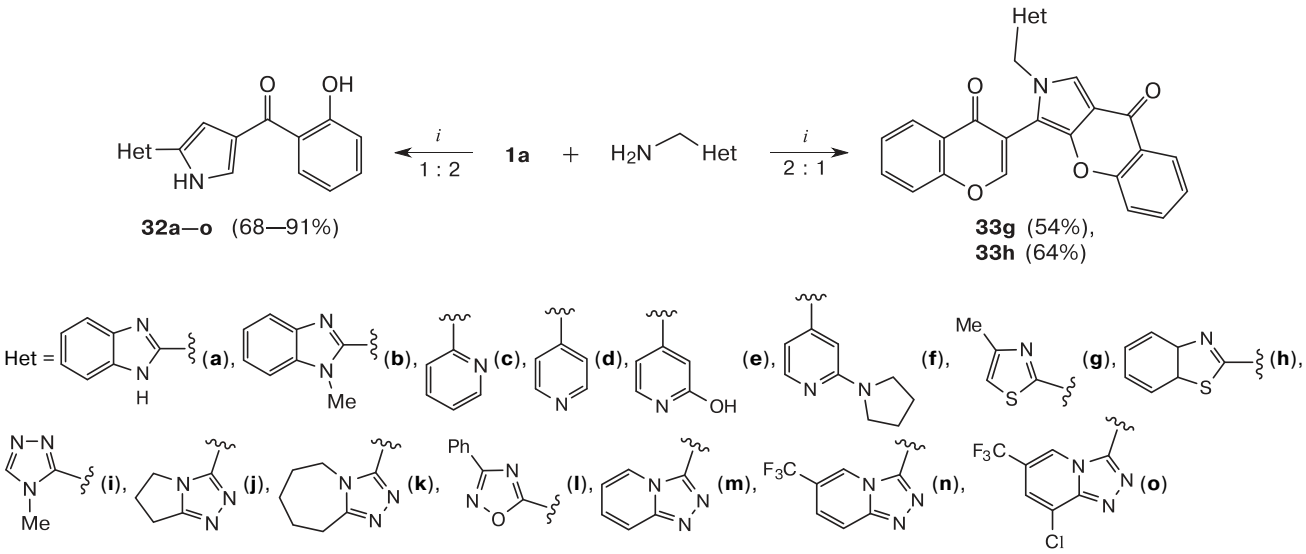
R = COOMe (**30**), CN (**31a,b**)

Conditions: AcOH (cat.), MeOH, reflux, 1 h (for **30**) or ~20 °C, 2 days (for **31**).

Ryabukhin and coworkers postulated two possible mechanisms of the TMSCl-activated reaction.[50] First, TMSCl can activate 3-formylchromone **1a** *via* addition to the carbonyl oxygen at C(4). This reaction after some transformation may result in salicyloylpyrroles **32** and **34**. Another possible activation route involves addition of TMSCl to the aldehyde group of compound **1a**. This reaction pathway could give rise to derivatives **33** as well as to salicyloylpyrroles **32** and **34**.

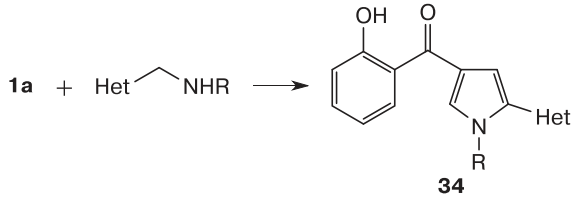
Pyrazoline and pyrazole derivatives of isoflavone analogs can be synthesized by cyclization of chromones bearing 3-positioned α,β-unsaturated moiety with either di-

Scheme 11



Reagents and conditions: *i*. Me_3SiCl (4 equiv.), DMF, 100 °C, 6—15 h.

Scheme 12



R = Me, Et, Pr^i, Bu^n, Bu^s, $(CH_2)_2OMe$, $(CH_2)_2NMe_2$, Bn, (tetrahydrofuran-2-yl)methyl

Reagents and conditions: Me_3SiCl (4 equiv.), DMF, 100 °C, 6—15 h.

azomethane[51] or hydrazine[52—54] (Scheme 13). Thus, Shanker *et al*. reported[52] the synthesis of pyrazoline isoflavone analog **36** by treatment of chromone analog of chalcone **35** with hydrazine hydrate in AcOH. The use of hydrazine hydrate excess enabled recyclization of the pyrone ring of chromone to give pyrazolopyrazoline **37**.[52] The reaction of ketone **35** with hydrazine hydrate in DMF[53] and the reaction of α,β-dihalo carbonyl derivatives of chromone **38** with hydrazine[54] both afforded 3-(pyrazol-5-yl)chromone derivatives **39** (see Scheme 13).

Some pyrazolylchromone derivatives **39** were active against Gram-positive (*Staphylococcus aureus*, *Bacillus subtilis*) and Gram-negative (*Escherichia coli*, *Salmonella typhimurium*) bacteria and fungi strains (*Candida albicans*, *Aspergillus niger*, and *Aspergillus fumigatus*).[53,54]

The treatment of nitrovinylchromones **40** with the generated *in situ* aromatic aldehyde *N*-methylhydrazones gave pyrazole isoflavone analogs **41** (Scheme 14).[55] The starting compounds **40** were synthesized by the $SnCl_2$-catalyzed reaction of 3-formylchromones **1** with bromonitromethane followed by acetylation and β-elimination reactions.

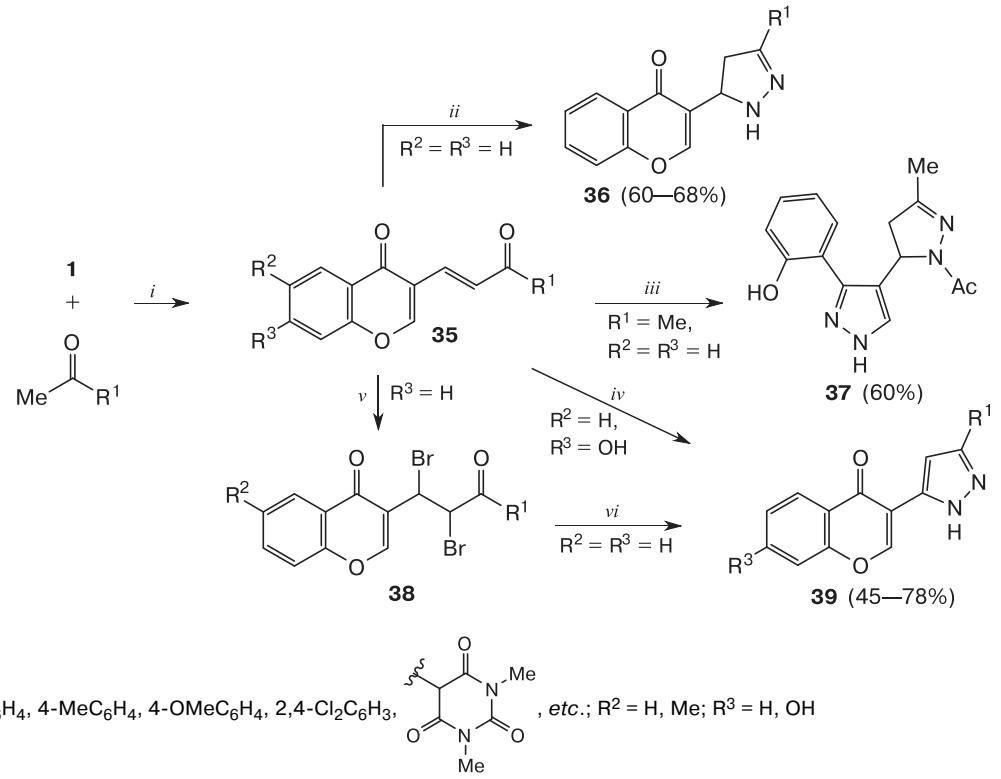
Compound **41** bearing the pyrocatechol moiety (R^1 = = R^2 = H, R^3 = R^4 = OH) showed antioxidant activity comparable with that of tocopherol and α-glucosidase inhibitory activity. It was found that introduction of the hydroxy groups into the chromone core did not significantly increase free radical scavenging activity.[55]

The imidazole isoflavone analogs **42** were synthesized by condensation of 3-formylchromones **1** with 1,2-dicarbonyl compounds in glacial AcOH in the presence of ammonium acetate.[56—63] Scheme 15 exemplifies the synthesis of imidazolyl chromones **42**.[56,57]

The role of 1,2-dicarbonyl compound could be played by *o*-quinones (1,2-naphthoquinone, 9,10-phenanthrenequinone, and substituted isatines) (Scheme 16).[64] The synthesized compounds **43** and **44** were evaluated for their antimicrobial, antifungal, and antioxidant activities. It was shown that glucosidated derivatives **44** are more active than their analogs **43** unsubstituted at the position 7 of the chromone ring.

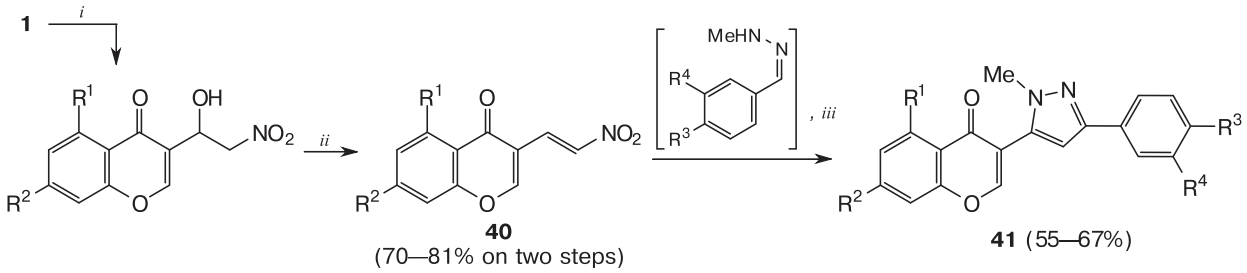
2-(6-Methyl-3-chromonyl)imidazo[4,5-*f*][1,10]phenanthrolines **45** were synthesized by condensation of 3-formylchromones **1** with 1,10-phenanthroline-5,6-dione. Compounds **45** were used as the ligands for the synthesis of ruthenium(II) complexes **46** (Scheme 17).[60—63,65] It was found that ruthenium complexes **46** can intercalate into DNA base pairs and cleave DNA upon irradiation. Thus, complexes **46** after incubation with pBR322 DNA plasmid and irradiation at 365 nm efficiently cleave supercoiled form of the circular plasmid DNA to nicked-circular form.[60—63,65]

Scheme 13



Reagents and conditions: *i.* EtOH, pyridine, reflux, 7—7.5 h or microwave irradiation;[54] *ii.* $N_2H_4 \cdot H_2O$ (1 equiv.), AcOH, reflux, 8 h;[52] *iii.* 1) $N_2H_4 \cdot H_2O$ (2 equiv.), EtOH, reflux, 30 min, 2) AcOH, reflux, 6 h;[52] *iv.* $N_2H_4 \cdot H_2O$ (1 equiv.), DMF, reflux, 18 h;[53] *v.* Br_2, $CHCl_3$, ~20 °C;[54] *vi.* $N_2H_4 \cdot H_2O$ (1 equiv.), pyridine, ~20 °C, 20 h or microwave irradiation.[54]

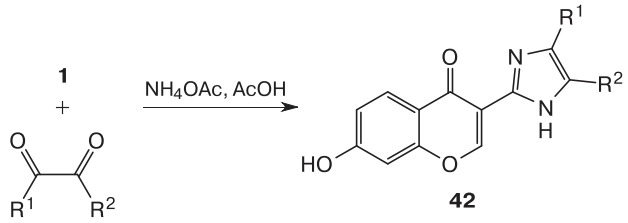
Scheme 14



R^1 = H, OH, OMe, OBn; R^2 = H, OMe, OBn; R^3 = OH, OMe, OBn, Hal; R^4 = H, OMe, OBn

Reagents and conditions: *i.* $BrCH_2NO_2$, $SnCl_2$, THF, ~20 °C, 4 h; *ii.* Ac_2O, pyridine, $CHCl_3$, ~20 °C, 10 h; *iii.* TFA, MeOH, ~20 °C, 24 h.

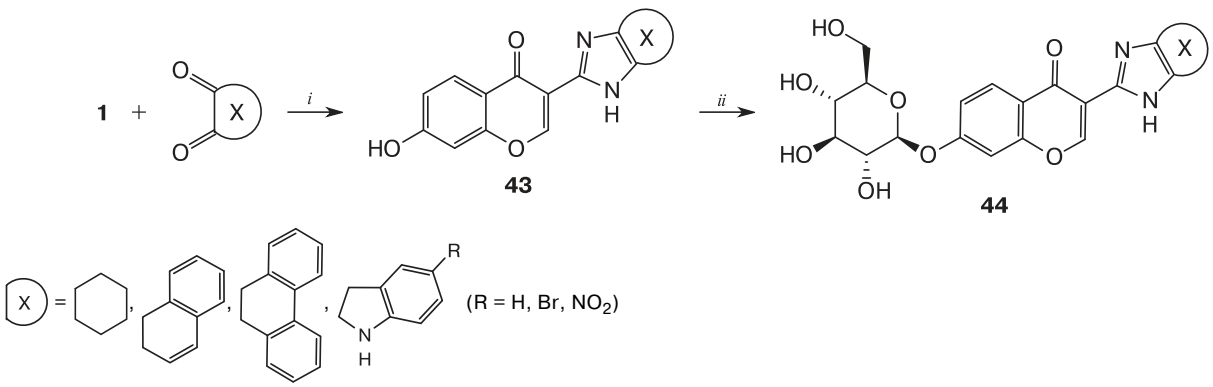
Scheme 15



R^1 = R^2 = H, Me, Ph, 2-ClC_6H_4, 4-ClC_6H_4, $NMe_2C_6H_4$, 4-MeC_6H_4; R^1 = Ph, R^2 = H, 4-$OMeC_6H_4$

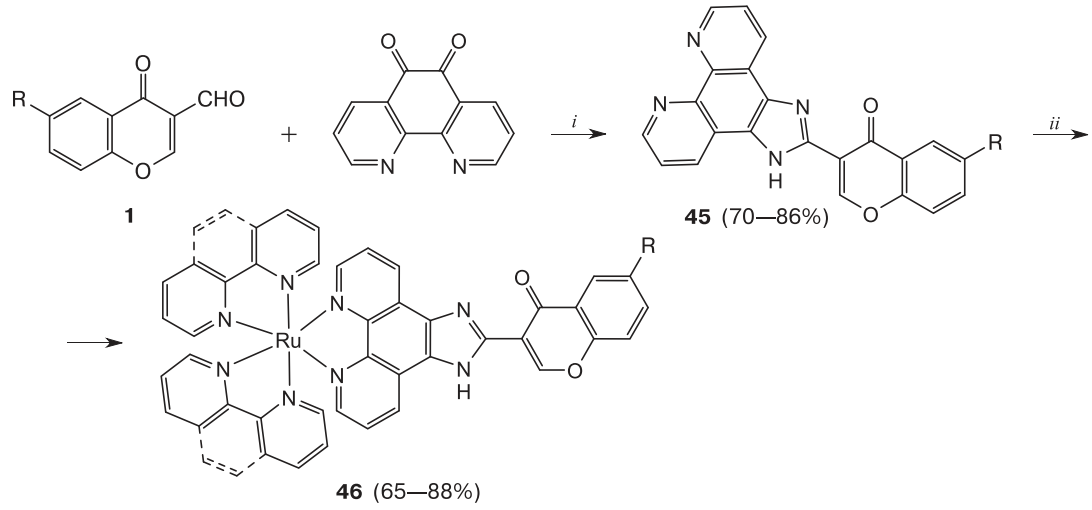
α-Hydroxyiminoketones **47** reacted with 3-formylchromone **1a** to give 3-(1-hydroxyimidazol-2-yl)chromones **48** (Scheme 18).[66] X-Ray diffraction studies indicated that in solid state compounds **48** existed as *N*-oxide tautomers **48′**. Compounds **48** were reduced to the corresponding imidazolyl chromones **49** by treatment of PPh_3 in glacial AcOH. The three-component reaction of compounds **1a**, **47**, and benzylamine gave *N*-benzyl(chromenyl)-imidazole *N*-oxide **50** (see Scheme 18).[66] The reaction of compound **1a** with dimedone monoxime gave rise to the fused derivative **51**.

Scheme 16



Reagents and conditions: *i*. NH_4OAc, AcOH; *ii*. 1) K_2CO_3, MeCN, Ar, 2) 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, 18-crown-6, 3) $Zn(OAc)_2$, MeOH.

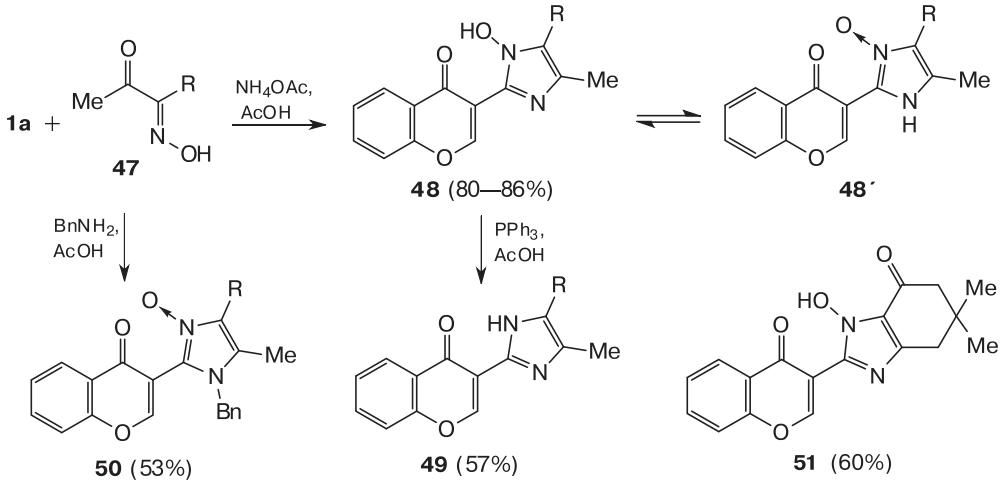
Scheme 17



R = H, Me, F, Cl, Br

Reagents and conditions: *i*. NH_4OAc, AcOH; *ii*. *cis*-$[Ru(bpy)_2Cl_2]\cdot 2H_2O$ or *cis*-$[Ru(phen)_2Cl_2]\cdot 2H_2O$, $(CH_2OH)_2$, Ar, 120 °C, 6 h.

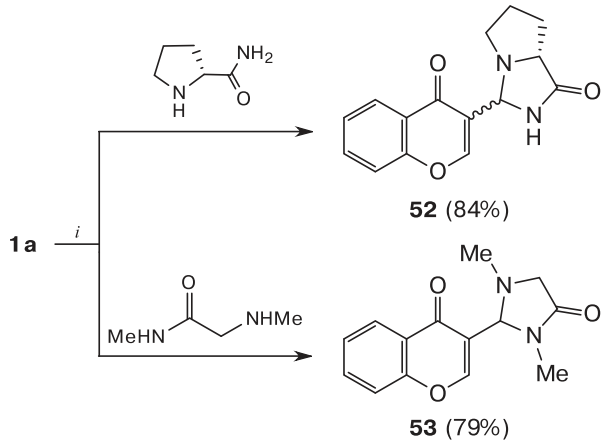
Scheme 18



R = Me, COMe, COOEt (**47**, **48**, **48′**)

The TMSCl-promoted addition of the amino acid derivatives to 3-formylchromone **1a** could result in either the products of [3+3] cyclocondensation involving the pyrone ring opening or [4+1] recyclization products, 2-chromonylpyrazolidin-5-ones **52** and **53** (Scheme 19).[50]

Scheme 19



Reagents and conditions: *i*. TMSCl (4 equiv.), DMF, 100 °C, 15 h.

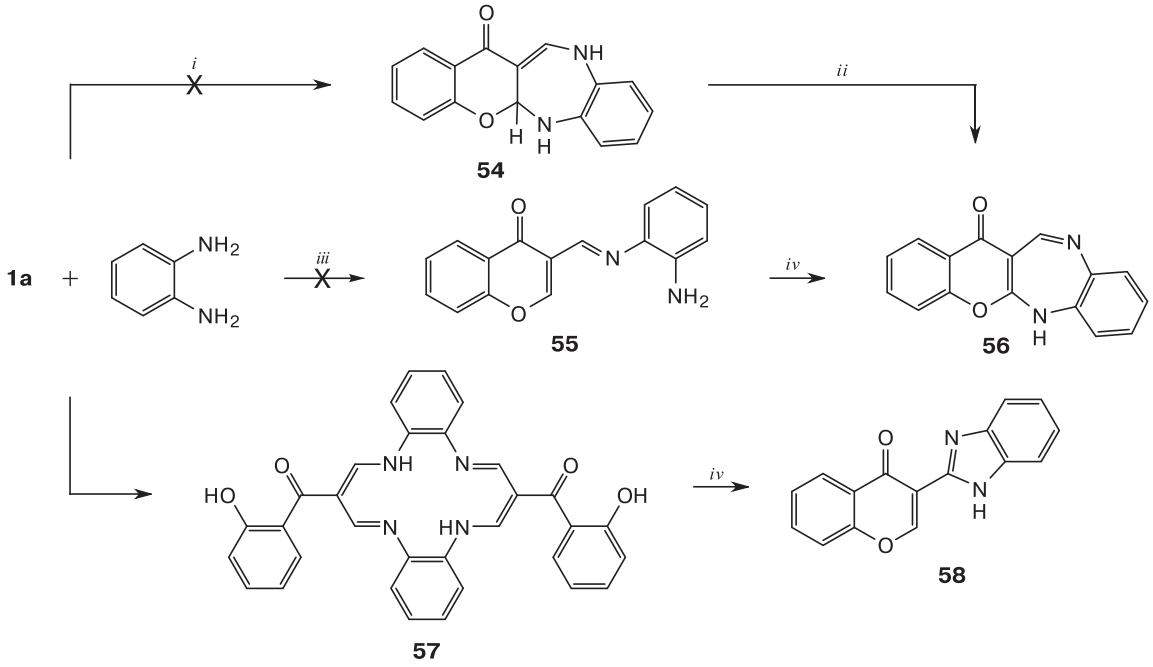
The structure of the product of the reaction of 3-formylchromone **1a** with *o*-phenylenediamine was controversial for several years (Scheme 20). Thus, Fitton and coworkers[67] suggested that the reaction of compound **1a** with *o*-phenylenediamine in chloroform at room temperature afforded benzodiazepinone **54**, while Ghosh and Khan[68] assigned the Schiff base structure **55** to the product of this reaction in refluxing EtOH. To the products obtained by oxidation of compound **54** with chloranil in refluxing xylene[67] and heterocyclization of compound **55** in refluxing AcOH,[68] the structure of benzo[*b*]chromeno-[2,3-*e*][1,4]diazepin-13(6*H*)-one (**56**) was attributed. Later, Winkler and coworkers suggested[69] that the reaction of **1a** with *o*-phenylenediamine gives dihydrotetraaza[14]-annulene **57** and unambiguously confirmed[70] this structure by X-ray diffraction analysis. A product of oxidation of compound **57** in refluxing AcOH was found to be 3-(benzimidazol-2-yl)chromone **58** (see Scheme 20).[69]

In order to shorten the reaction time and increase the yields of 3-(benzimidazol-2-yl)chromones **58**, the reaction of compound **1** with *o*-phenylenediamine was performed in the presence of the following catalysts: 3 mol.% of vanadyl sulfate (yield 78% for 8 h)[71], 1 equiv. of (bromodimethyl)-sulfonium bromide (yield 82% for 4 h),[72] and propanesulfonic acid-functionalized silica (yield 84% for 1 h).[73]

It is of note that the synthesis of the fused benzodiazepine compounds of type **56** from 2-methyl(phenyl)amino-3-formylchromone was described by Ishar and coworkers.[74]

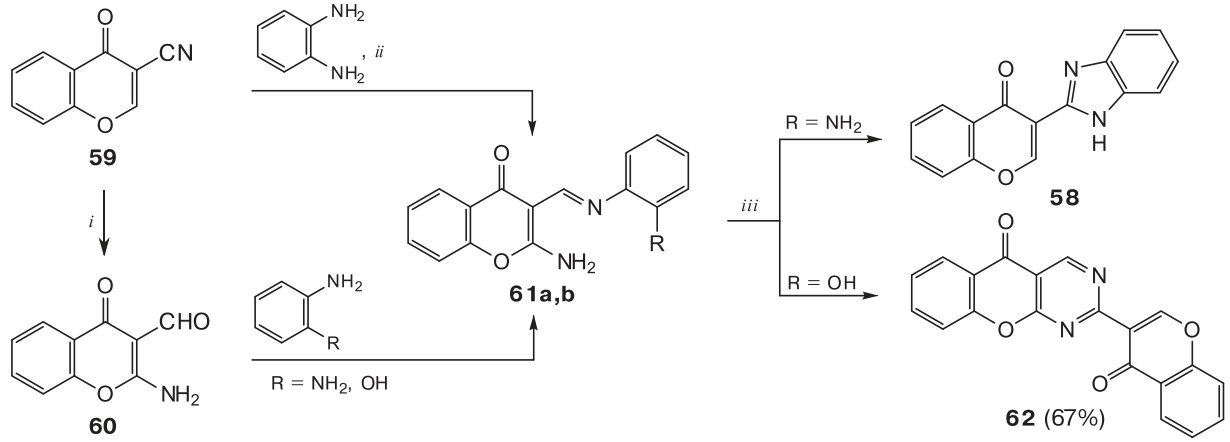
Sosnovskikh and coworkers[75] showed that the reaction of *o*-phenylenediamine with both 3-cyanochromone **59** and 2-amino-3-formylchromone **60** selectively gives (iminomethyl)chromone **61a** (Scheme 21). Refluxing of imine **61a** in AcOH for 3 h afforded 3-(benzimidazol-2-

Scheme 20



Reagents and conditions: *i*. $CHCl_3$, ~20 °C; *ii*. chloranil, xylene, reflux, 15 h; *iii*. EtOH, reflux, 1 h; *iv*. AcOH, reflux, 4 h.

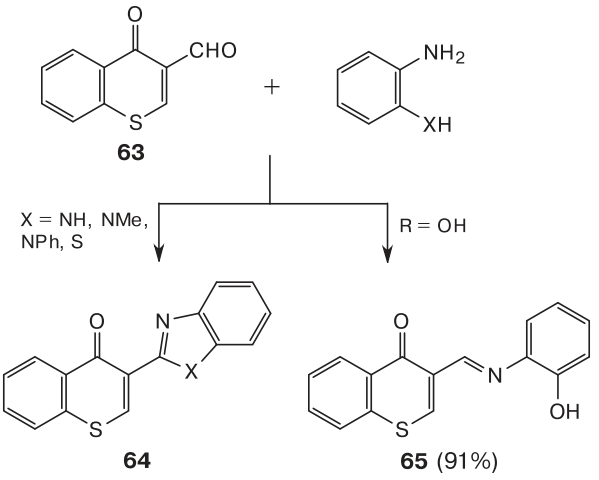
Scheme 21



61: R = NH_2 (**a**), OH (**b**)

Reagents and conditions: *i*. NaOH, H_2O; *ii*. EtOH or benzene, reflux; *iii*. AcOH, reflux.

Scheme 22



yl)chromone **58**. It is interesting to note, that refluxing of anil **61b** synthesized by the reaction of compound **60** with 2-aminophenol gave no the expected 1,3-benzoxazole but only the self-condensation product, chromonopyrimidine **62** (see Scheme 21).[75,76]

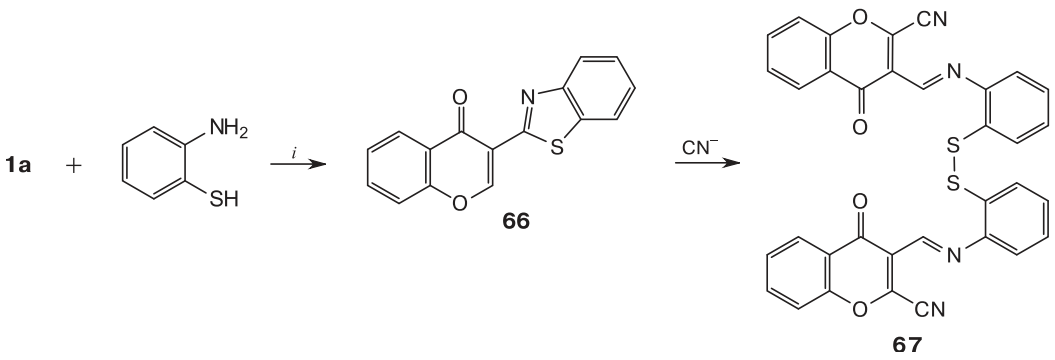
3-Formylthiochromone **63** reacted with *o*-phenylenediamines and 2-aminothiophenols to give 3-(benzimidazol-2-yl)thiochromones **64**. In the case of 2-aminophenol, the reaction yielded the Schiff base **65** (Scheme 22).[77]

Condensation of compound **1a** with 2-aminothiophenol afforded 3-(benzothiazol-2-yl)chromone **66** (Scheme 23).[78] Structure of product **66** was confirmed by X-ray analysis. Compound **66** was suggested as chemosensor for cyanide ions, it selectively reacted with the cyanide ions to give disulfide **67**.

The reaction of formylchromones **1** with *N*-phenylhydroxylamine gave rise to nitrones **68** that readily reacted with different dipolarophiles[79—84] to afford *N*-phenyl-3-(chromon-3-yl)isoxazolidines **69—71** (Scheme 24).[79,80,82]

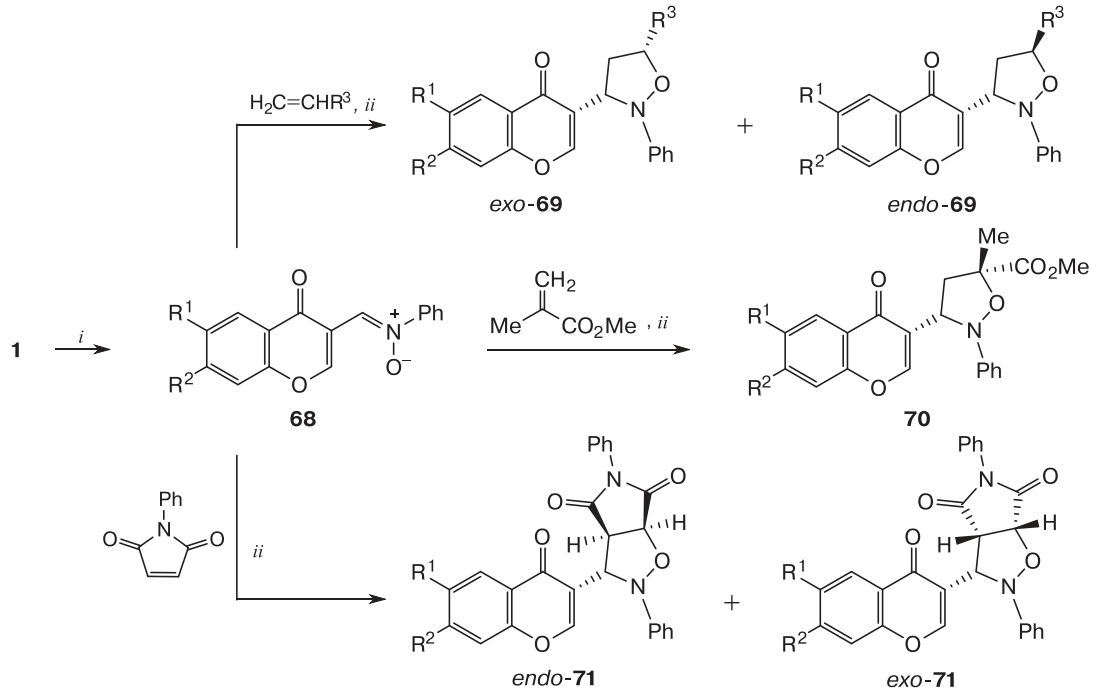
The reaction of nitrone **68** with 2 equiv. of dimethyl acetylenedicarboxylate is controlled by the nature of the substituent at the nitrogen atom (Scheme 25).[85] Thus, the alkyl substituents at the nitrogen atom favor the [3+2] cycloaddition of nitrone **68** to dimethyl acetylenedicarb-

Scheme 23



Conditions: *i*. EtOH (anhydr.), reflux, 6 h.

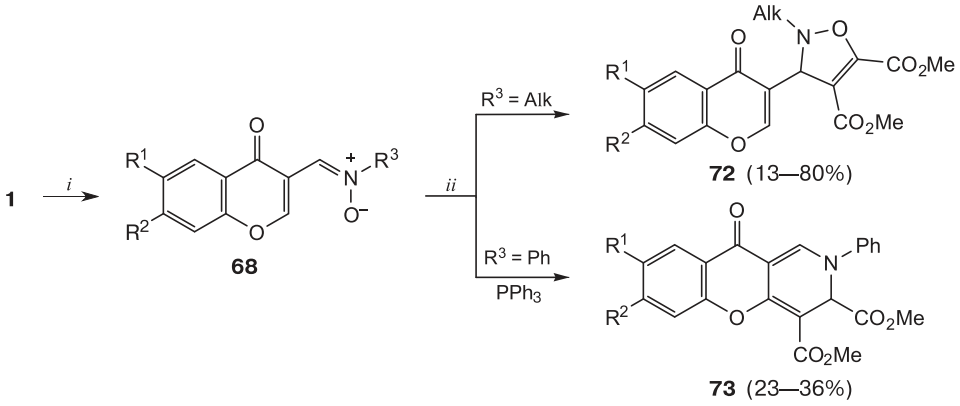
Scheme 24



R^1 = H, Me, F, Cl, Br; R^2 = H, Cl, R^3 = OEt, OBu^i, Ph, pyridin-4-yl, CN, CO_2Me, $CONH_2$

Reagents and conditions: *i*. PhNHOH, benzene; *ii*. CH_2Cl_2, ~20 °C.

Scheme 25



R^1 = H, Me, Cl; R^2 = H, Me; R^3 = Me, Bn, Ph

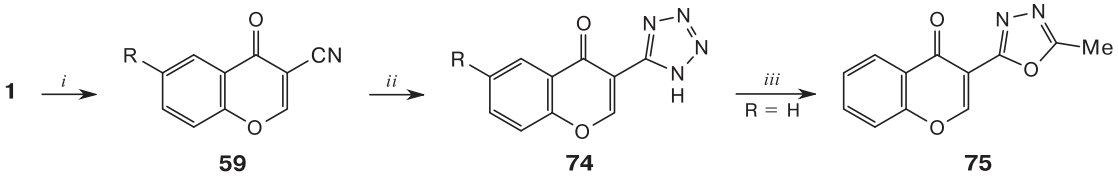
Reagents and conditions: *i*. $R^3NHOH \cdot HCl$, Et_3N, toluene; *ii*. MeOOCC≡CCOOMe, CH_2Cl_2.

oxylate to give dihydroisoxasole derivatives **72**, whereas *N*-phenyl derivatives selectively produce the fused compounds **73**. It is of note that the highest yields of compounds **73** were achieved in the presence of 1.2 equiv. of PPh_3 but additives of PPh_3 have no effect on the yield of compounds **72**.

Treatment of 3-formylchromones **1** with hydroxylamine in acidic media gave substituted 3-cyanochromones **59**. The $AlCl_3$-catalyzed reaction of compounds **59** with sodium azide resulted in 3-(1*H*-tetrazol-5-yl)chromones **74** with antiallergic activity (Scheme 26).[86—91]

2-Substituted 3-(1*H*-tetrazol-5-yl)chromones **76** show antimicrobial activity against *S. aureus, E. coli, B. subtilis*, *Pseudomonas aeruginosa* and antifungal activity against *C. albicans* and *A. niger* with minimal inhibitory concentrations comparable with that of the reference drugs

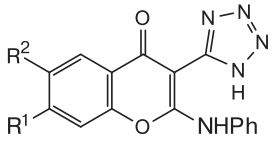
Scheme 26



R = H, Me, Et, OMe, Cl, *etc*.

Reagents and conditions: *i*. $NH_2OH \cdot HCl$; *ii*. NaN_3, $AlCl_3$; *iii*. Ac_2O, reflux, 1.5 h.

(Ciprofloxacin and Fluconazole for bacterial and fungal strains, respectively).[92]

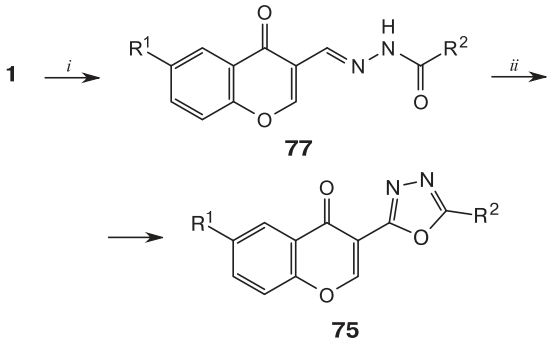


R^1 = H, Cl, NO_2; R^2 = H, F, Cl, NO_2

Nohara and coworkers[93] synthesized oxadiazole derivatives **75** by refluxing 3-tetrazolyl chromones **74** in Ac_2O for 1.5 h (see Scheme 26).

More convenient synthetic approach to compounds **75** that allows widely vary aryl and hetaryl substituents in the oxadiazole moiety is intramolecular cyclization of (3-formylchromone)aroyl hydrazides **77**. This reaction can be enabled by treatment of compounds **75** with either bromine and sodium acetate in basic medium[94,95] or diacetoxyiodobenzene in dichloromethane[96] (Scheme 27).

Scheme 27

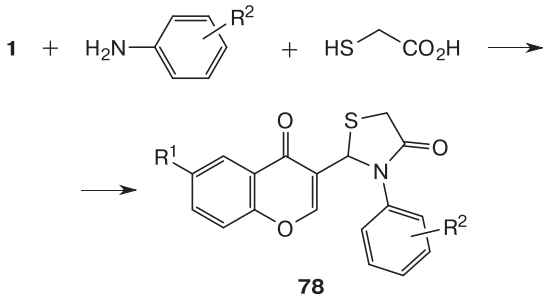


R^1 = H, OMe, R^2 = Ar, Het

Reagents and conditions: *i*. (Het)ArC(O)$NHNH_2$, *ii*. $PhI(OAc)_2$, CH_2Cl_2 or Br_2, NaOAc, NaOH.

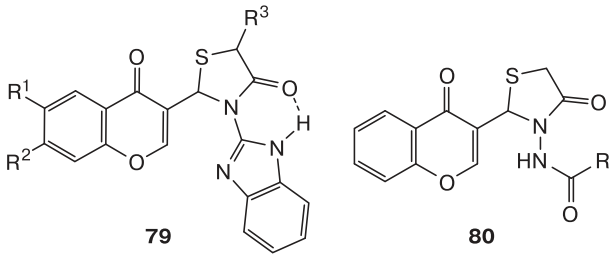
2-(Chromon-3-yl)-4-thiazolidinone derivatives **78** (Scheme 28) and **79** were synthesized by successive treatment of compound **1** with aromatic[97] or heterocyclic[98] amines and mercaptoacetic acid as well as by three-component microwave-assisted reaction of the above compounds. Microwave irradiation significantly shortened the reaction time and increased the yields and purity of the target products. Condensation of *N*-acylhydrazones of aldehydes **1** with mercaptoacetic acid gave *N*-carbonylamino-2-(chromon-3-yl)-4-thiazolidinones **80**.[99]

Scheme 28



R^1 = H, Me, Cl; R^2 = H, Alk, OAlk, Hal

Reagents and conditions: TsOH, benzene, reflux, 9 h or Na_2SO_4, TsOH, benzene, microwave irradiation (in a sealed tube), 140 °C, 5 min.

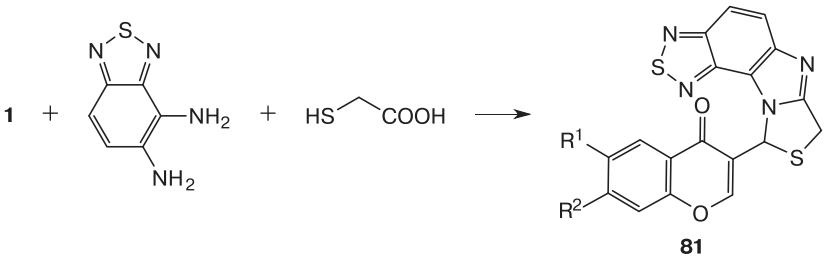


79: R^1 = H, Me, Cl; R^2 = H, Me; R^3 = H, Me;
80: R = Me, Ph, 4-MeC_6H_4, 2-HOC_6H_4, 4-$MeOC_6H_4$, 3-ClC_6H_4, 4-$O_2NC_6H_4$, *etc*.

The replacement of primary amine with aromatic 1,2-diamine led to the fused derivatives **81** with thiazolidine moiety (Scheme 29).[100] It was found that antimicrobial activity of compounds **81** is lower than that of the reference drugs Ciprofloxacin and Griseofulvin.

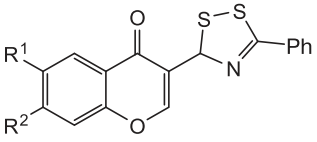
3-Formylchromones **1** reacted with 2 equiv. of thiobenzamide in refluxing toluene to give 3-(5-phenyl-3*H*-[1,2,4]dithiazol-3-yl)chromones **82**.[101] Under these

Scheme 29

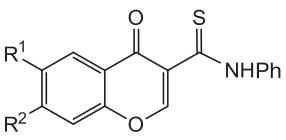


81: R^1 = H, R^2 = H, OH; R^1 = Br, R^2 = H, OH; R^1 = Cl, R^2 = OH

Conditions: benzene, reflux, 36—48 h or microwave irradiation, 12—20 min.



82a—g (70—74%)



83a—g (60—78%)

Compounds **82** and **83**	R^1	R^2	Compounds **82** and **83**	R^1	R^2
a	H	H	**e**	Cl	H
b	F	H	**f**	F	Cl
c	H	Cl	**g**	Me	H
d	Cl	Cl			

conditions, the reaction of 2-aminophenyl-3-formylchromone with thiobenzamide gave raise to chromone-3-carbothioic acid *N*-phenylamides **83**.[101] Compounds **82** and **83** displayed significant cytotoxicity against a number of human cancer cell lines. Thus, compounds **82a** (IC_{50} = = 10.5 μmol L^{-1}), **82b** (IC_{50} = 14.6 μmol L^{-1}), and **82e** (IC_{50} = 10 μmol L^{-1}) showed the highest cytotoxicity against neuroblastoma, and compound **82c** (IC_{50} = 10.5 μmol L^{-1}) was most cytotoxic against ovarian cancer cell line.

The Groebke—Blackburn—Bienaymé three component reaction between 3-formylchromones **1**, 2-aminoazine (2-aminopyridine), and isocyanide in methanol in the presence of catalytic amounts of $InCl_3$ and chloroacetic acid under microwave irradiation conditions gave imidazo[1,2-*a*]pyridine isoflavone analogs **84** (Scheme 30).[102] Instead of microwave activation, this reaction can be performed in an eutectic mixture of choline chloride and urea (1 : 2) that also plays the role of an organocatalyst.[103] 3-Aminothiazoles and 2-aminobenzothiazoles in this reaction produced derivatives of imidazo[2,1-*b*]thiazole **85** and benzo[*d*]imidazo[2,1-*b*]thiazole **86**, respectively (see Scheme 30).[104]

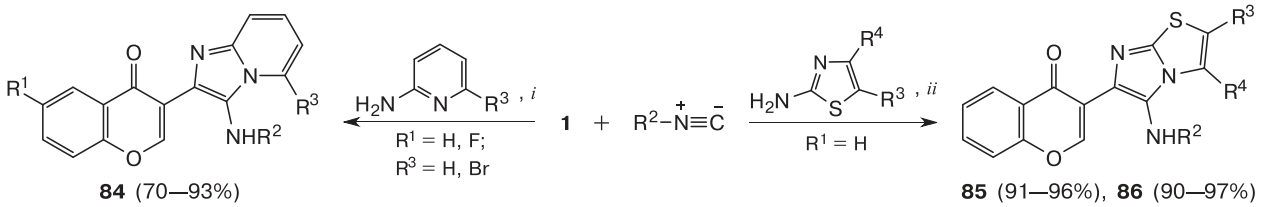
The prolonged reflux of a mixture of 2-amino-3-formylchromone **60**, isocyanide, and 2-aminopyridine, 2-aminopyrazine or 2-aminopyrimidine in MeOH in the presence of $TsOH/ZnCl_2$ resulted in derivatives **87**—**89** (Scheme 31).[105]

1.2. Isoflavone hetero analogs with six-membered heterocycles

Synthetic approaches to pyridine isoflavone analogs were briefly outlined in previous Section (see Schemes 6 and 7).

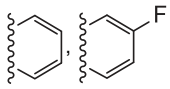
The Hantzsch reaction involving 3-formylchromones **1** proceeded ambiguously. In the early works,[106] structure of 1,4-dihydropyridine **90** was ascribed to the product of the reaction of compound **1** with ethyl acetoacetate and liquid ammonia in methanol. However, later[107] these

Scheme 30



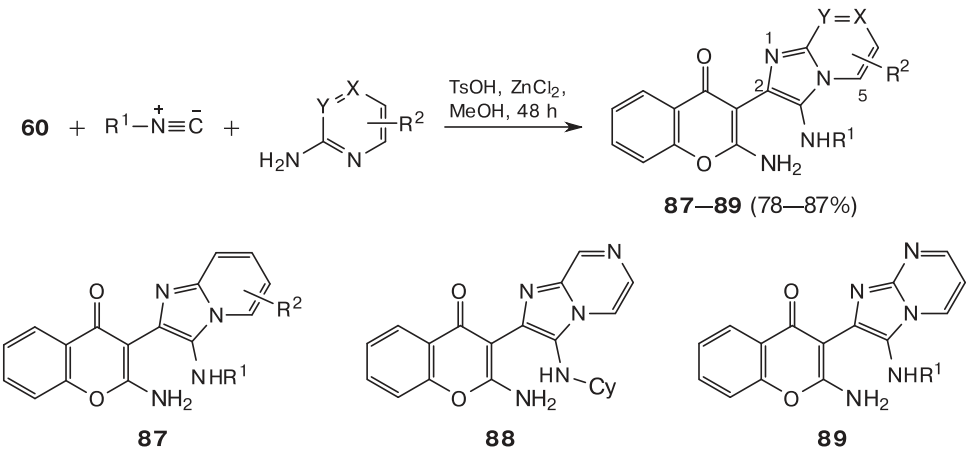
84 (70—93%) **85** (91—96%), **86** (90—97%)

84—86: R^2 = Bu^t, *cyclo*-C_6H_{11}, Bn, 4-$MeOCH_2C_6H_4$, 3,4-$(MeO)_2C_6H_3CH_2CH_2$
85: R^3 = H, R^4 = H

86: $R^3 + R^4$ = 

Reagents and conditions: *i*. $InCl_3$, $ClCH_2COOH$, MeOH, microwave irradiation, 1 h; *ii*. toluene, microwave irradiation, 100 °C, 10 min.

Scheme 31



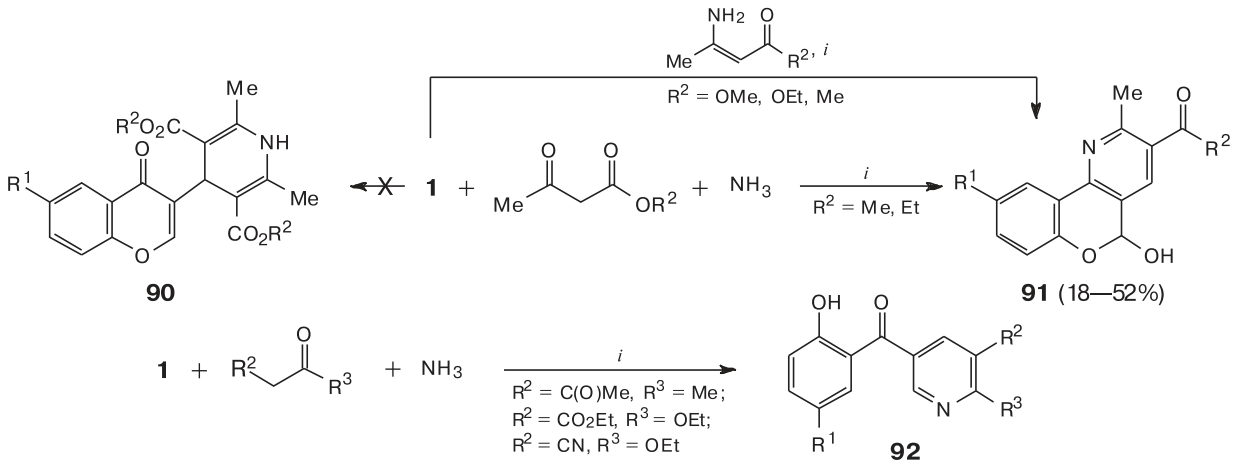
Cy is *cyclo*-C_6H_{11}.

87: R^1 = *cyclo*-C_6H_{11}, R^2 = 6-Br, 5-Me, 8-Me; R^1 = Bu^t, R^2 = 6-Br; R^1 = 1,1,3,3-tetramethylbutyl, R^2 = 6-Br; R^1 = Bn, R^2 = 6-Br, H
89: R^1 = 1,1,3,3-tetramethylbutyl; *cyclo*-C_6H_{11}

results were revised. The structure of the reaction product is determined by the nature of the CH acidic component (Scheme 32).[107] Thus, under the Hantzsch reaction conditions 3-formylchromones **1** reacted with acetoacetic acid esters and ammonia to give benzopyranopyridines **91**. These products were also obtained by the reaction of compounds **1** with enamines derived by treatment of the corresponding dicarbonyl compounds with liquid ammonia in refluxing alcohol. The reaction of 3-formylchromone **1** with acetylacetone, diethyl malonate, ethyl cyanoacetate and ammonia (or ammonium acetate) afforded salicyloylpyridines **92**.[107]

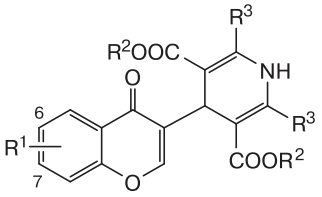
Recently, several attempts have been made to develop the synthesis procedures to access 1,4-dihydropyridine isoflavone analogs. The solvent-free reaction of 3-formylchromone **1**, ethyl acetoacetate, and ammonium acetate catalyzed with Wells—Dawson heteropolyacids $H_6P_2W_{18}O_{62} \cdot 24H_2O$ gave a mixture of the corresponding dihydropyridines **90** and 5-salicyloylpyridines **92**.[108] However, under these conditions the main reaction products were salicyloylpyridines **92**. The use of the Bi_2WO_6 nano particles to catalyze this reaction in aqueous media at room temperature gave rise to dihydropyridine **90** (R^1 = H, R^2 = Et) in 92% yield.[109] Firuzi and coworkers[110] described the similar reaction of 6(7)-hydroxy-3-formylchromones with β-ketoesters and ammonium acetate, which in the presence of $Ba(NO_3)_2$ as a catalyst in refluxing EtOH gave the corresponding hydroxy derivatives **93**

Scheme 32



R^1 = H, Me, Cl

Conditions: *i*. EtOH (or MeOH for methyl esters), reflux.



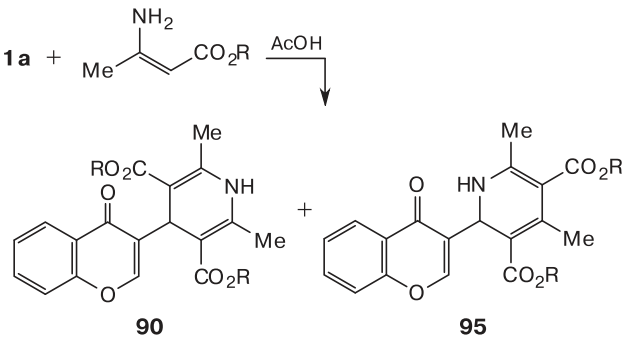
93, **94**

93: R^1= 6-OH, 7-OH; R^2 = Me, Et; R^3 = Me, Pr
94: R^1= 6-OAc, 7-OAc, 6-OC(O)C_5H_{11}, 7-OC(O)C_5H_{11}; R^2 = Me, Et; R^3 = Me, Pr

in 62—66% yields. Acylation of hydroxy derivatives **93** with acetic and hexanoic anhydrides furnished compounds **94**. It was found that derivatives **94** inhibit β-secretase (BACE-1), an aspartyl protease responsible for amyloid-β production and one of the promising targets in the treatment of Alzheimer's disease. The derivatives bearing the substituents at the position 7 of the chromone ring system were found more active than 6-substituted analogs. Moreover, the 7-acetyl-substituted derivatives were more active than 7-hexanoyloxy analogs. The most potent BACE-1 inhibitor was 7-acetoxy derivative **94** (R^1= 7-OAc, R^2 = Et, R^3 = Me) with 51.32% enzyme inhibition at 10 μmol L^{-1}.

Gorlitzer and Michels[111] reported that 3-formylchromone **1a** reacted with aminocrotonates to give mixtures of isomeric dihydropyridines **90** and **95** (Scheme 33), however more recent publications contradict this result. Thus, Ryabukhin and coworkers[112] obtained only product **90** (R = Et) in 76% yield by performing this reaction in DMF in the presence of the four-fold excess of TMSCl under ultrasound activation conditions.

Scheme 33

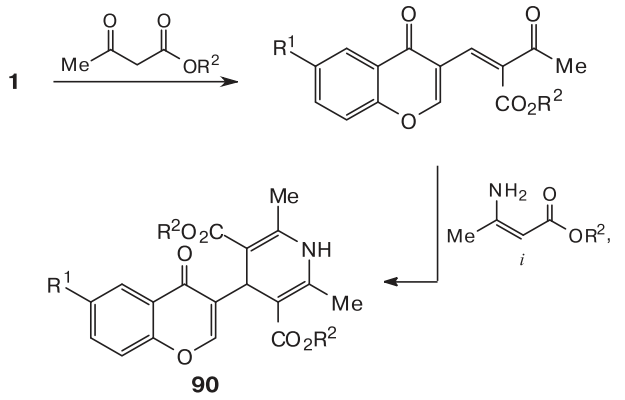


90 **95**

R = Me, Et

The amount of the side salicyloylpyridines **92** could be reduced by step-by-step synthesis of 1,4-dihydropyridine derivatives.[113] Solvent-free condensation of 2-acetyl-3-(chromon-3-yl)acrylates with 3-aminocrotonates catalyzed by 0.5 mol.% of Preyssler heteropolyacid $H_{14}[NaP_5W_{29}MoO_{110}]$ produced the corresponding 1,4-dihydropyridines **90** in high yields (up to 87%) (Scheme 34). The starting 2-acetyl-3-(chromon-3-yl)acrylates were prepared by the Knoevenagel condensation between 3-formylchromones **1** and 1,3-dicarbonyl compounds.

Scheme 34

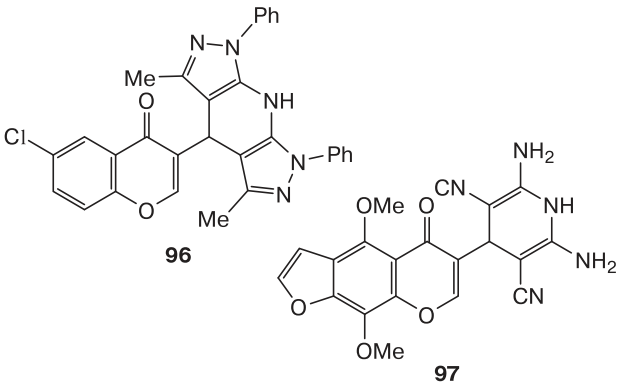


90

R^1 = H, Me, Cl; R^2 = Me, Et

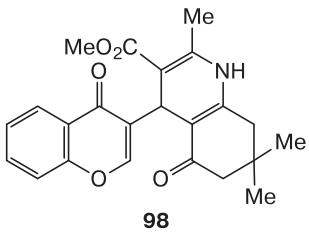
Reagents and conditions: *i*. $H_{14}[NaP_5W_{29}MoO_{110}]$ (0.5 mol.%), 80 °C, 30 min.

Variation of the CH-acidic components in the Hantzsch synthesis provided a wide structural variety of 1,4-dihydropyridine isoflavone analogs. For instance, the microwave-assisted condensation of 3-formylchromone **1a** with 3-methyl-1-phenylpyrazol-5(4*H*)-one (2 equiv.) and ammonium acetate in PEG-400 resulted in the fused system **96**. Compound **96** showed antimicrobial activity comparable to that of the reference drug Penicillin and moderate antifungal activity.[114] Derivative **97** was synthesized by the reaction of 6-formylfurochromone **1b**, malononitrile, and ammonium acetate.[115]



96 **97**

Unsymmetrical 1,4-dihydropyridines can be obtained by the Hantzsch synthesis using two different dicarbonyl compounds. Thus, Arumugam and Perumal[116] successfully synthesized tetrahydroquinoline derivative **98** (in 93% yield) by four-component condensation of 3-formylchromone **1a**, dimedone, methyl acetoacetate, and ammonium acetate.



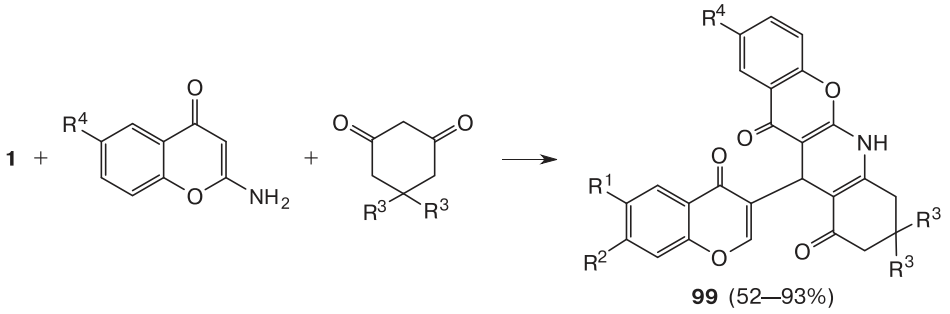
98

Condensation of 3-formylchromones **1**, 2-aminochromone as an amine, and dimedone or 1,3-cyclohexanedione as a *C*-nucleophile gave the fused systems, 11-(chromon-3-yl)-8,9-dihydro-6*H*-chromeno[2,3-*b*]-quinolin-10,12(7*H*,11*H*)-diones **99** (Scheme 35).[117] The highest yields of the target products were achieved by carrying out the reactions in 0.5 *M* aqueous sodium dodecyl sulfate (SDS). The authors suggested[117] that a plausible mechanism leading to compounds **99** involved the condensation of formylchromones **1** with CH acid (dimedone or 1,3-cyclohexanedione), 1,4-addition of enamine (2-aminochromone) to the Knoevenagel adduct, and subsequent cyclization.

Successive treatment of compounds **1** with malononitrile and cyanoacetic acid hydrazide gave compounds **100a—c** whatever reaction sequence was used (Scheme 36).[118—120]

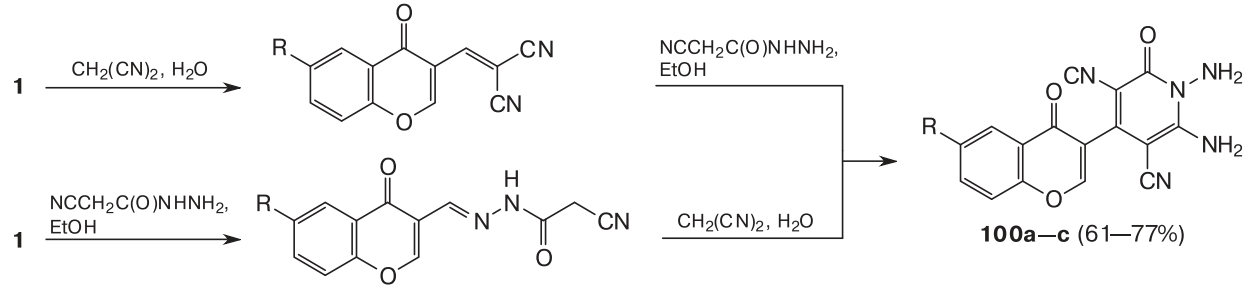
Diaminodihydropyridines **100** were the starting compounds for the synthesis of a large series of isoflavone hetero analogs. Thus, the reaction of compound **100c** with acetic anhydride, ethyl formate, 6-chloro-3-formylchromone (**1**, R = 6-Cl), and chromone-3-carboxylic acid yielded [1,2,4]triazolo[1,5-*a*]pyridine derivatives **101—103** (Scheme 37).[120] Synthetic approaches to pyrido[1,2-*b*][1,2,4]-triazine derivatives **104—107** are shown in Scheme 38.[120]

Scheme 35



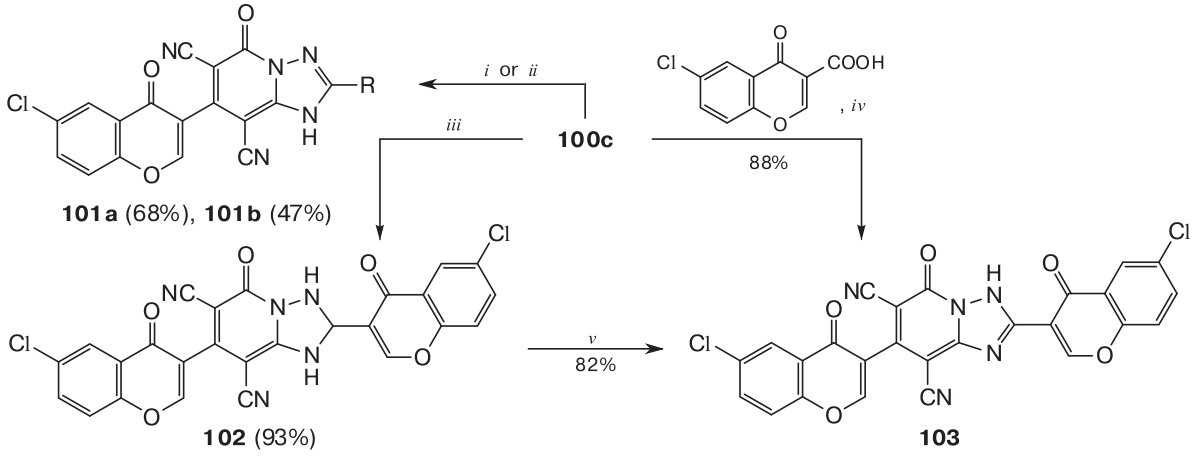
99: R^1 = H, Me, Cl, OH; R^2 = H, Me; R^3 = Me, H; R^4 = H, Me, Cl, Br

Scheme 36



100: R = H (**a**), Me (**b**), Cl (**c**)

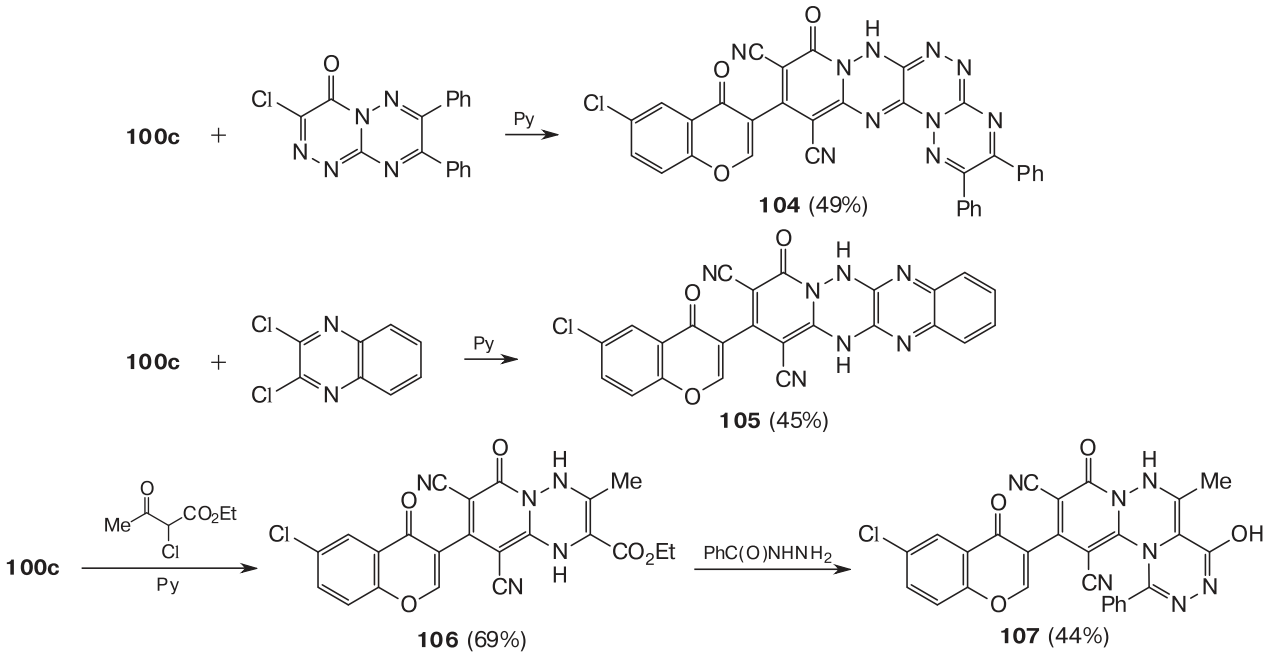
Scheme 37



101: R = H (**a**), Me (**b**)

Reagents and conditions: *i* (for **101a**). HCOOEt, pyridine; *ii* (for **101b**). Ac_2O; *iii*. **1** (R = 6-Cl), piperidine; *iv*. $POCl_3$; *v*. $FeCl_3$, DMSO.

Scheme 38

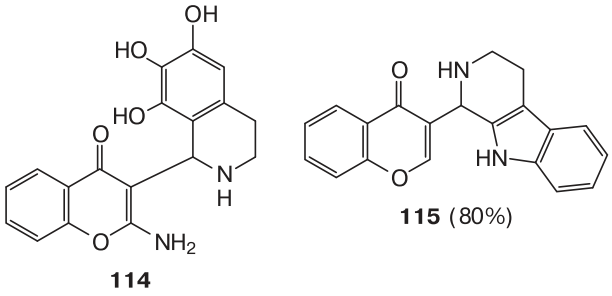


Condensation of compound **100c** with acetylacetone, 4-(dimethylamino)but-3-en-2-one, 2-cyano-3-methylsulfanyl-*N*-phenyl-3-(phenylamino)prop-2-enamide, and 4-chlorobenzylidenemalononitrile gave pyrido[1,2-*b*]-[1,2,4]triazepin-7-one derivatives **108—111** (Scheme 39).[120]

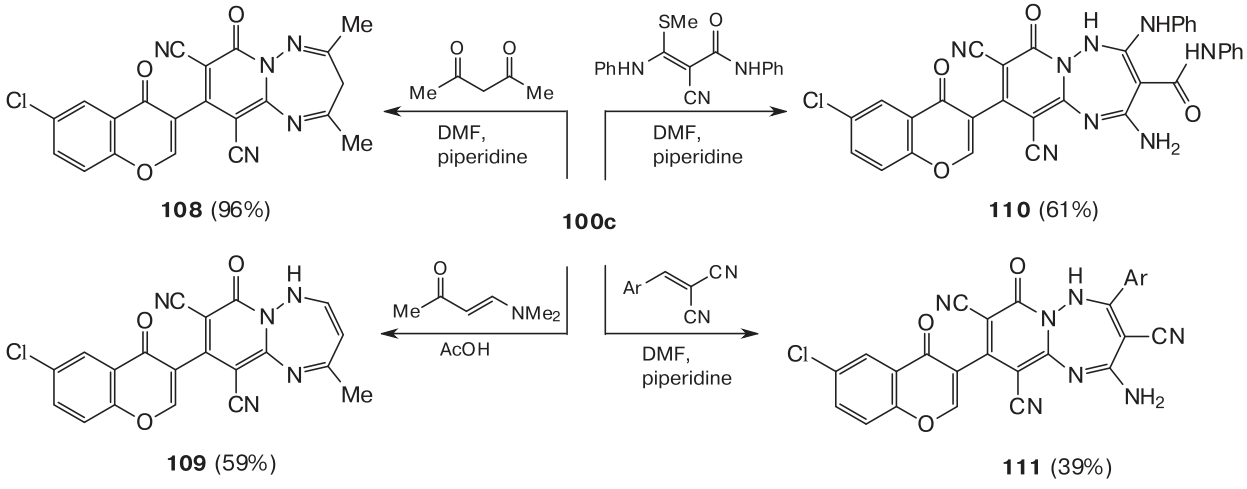
Ali and Ibrahim[120] examined antimicrobial activity of the synthesized compounds and found that the highest activity is exhibited by compounds **102—104**.

The reaction of 3-formylchromone **1a**, aromatic amine, and 1-vinylpyrrolidin-2-one in aqueous MeCN catalyzed by 5 mol.% of ceric ammonium nitrate (CAN) afforded tetrahydroquinolines **112**. Quinolines **113** were synthesized by oxidation of compounds **112** (R = H, Me) with the excess of CAN (Scheme 40).[121]

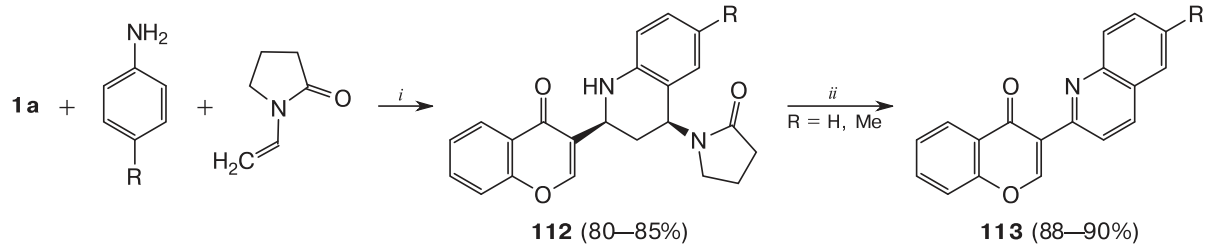
Condensation of 2-amino-3-formylchromone **60** with 5-hydroxydopamine gave tetrahydroquinoline isoflavone analog **114**.[122] The iodine-catalyzed reaction of compound **1a** with tryptamine (the Pictet—Spengler reac-



Scheme 39



Scheme 40

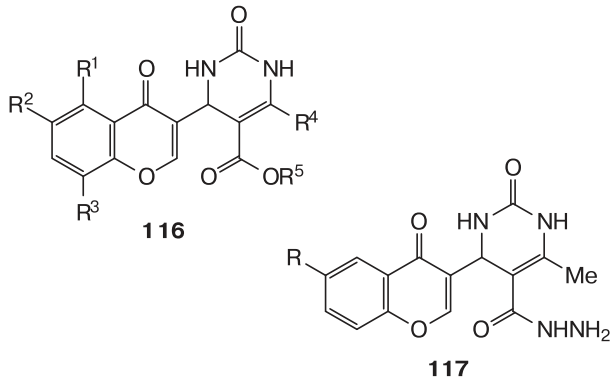


112: R = H, Me, OMe

Reagents and conditions: *i*. CAN (5 mol.%), MeCN (aqueous), ~20 °C; *ii*. CAN (2.5 equiv.), MeCN, N_2, 0 °C, 20 min.

tion) furnished 1,2,3,4-tetrahydrocarboline isoflavone analog **115**.[123]

Tetrahydropyrimidine isoflavone analogs can be synthesized by the Biginelli reaction. Thus, the three-component condensation of 3-formylchromones **1**, urea, and β-ketoesters was used to synthesize a series of (chromonyl)-tetrahydropyrimidines **116**.[124—126] To catalyze the Biginelli reaction the following catalysts were used: TsOH,[124] sulfonic acid-functionalized mesoporous silica (MCM-41-SO_3H),[125] and ionic liquid (triethylammonium hydrosulfate).[126] Hydrazides **117** were synthesized by heating the corresponding ethyl esters **116** with hydrazine hydrate in the presence of triethylammonium hydrosulfate under solvent-free conditions.[126] Compounds **116** and **117** were screened for their antituberculosis and antitumor activities. Raju *et al*. demonstrated that activity of compound **116** (R^1 = Ph, R^2 = R^3 = H, R^4 = CF_3, R^5 = Et) against *M. tuberculosis* H37Rv is comparable to that of the standard drugs Ethambutol and Ciprofloxacin and cytotoxicity of derivative **116** (R^1 = R^2 = H, R^3 = NO_2, R^4 = Me, R^5 = Et) against human neuroblastoma cell line SK-N-SH is similar to that of the reference drug Doxorubicin. Nikalje and coworkers[126] showed that antibacterial activity of compounds **117** against *E. coli* 1411 is comparable to that of the reference drug Cycloserine and its antifungal activity is equal to that of the standard drug Miconazole.

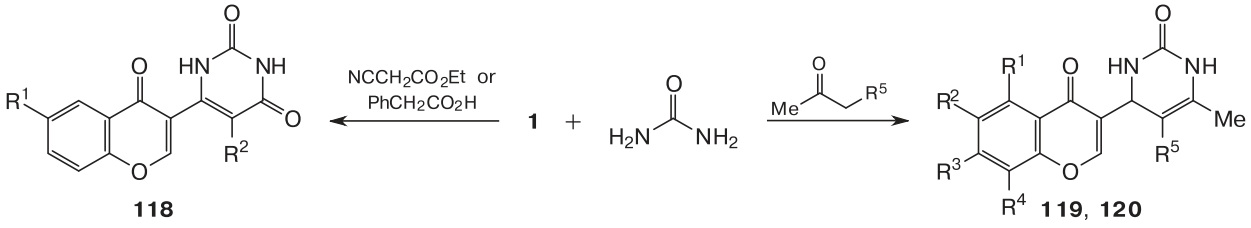


116: R^1 = H, Me, Ph; R^2 = H, Me, OMe, Br, NO_2, *etc*.; R^3 = H, NO_2; R^4 = Me, Et, Ph, *etc*.; R^5 = Me, Et, C_2H_4OMe

117: R = Me, OMe, F

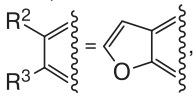
Tetrahydropyrimidine isoflavone analogs can be synthesized by the solvent-free Biginelli-type reaction catalyzed by either sulfated silica tungstic acid[127] or TsOH[128] (Scheme 41). The reaction of 3-formylchromones **1**, urea, and ethyl cyanoacetate or phenylacetic acid afforded compounds **118**. The use of ethyl acetoacetate gave rise to product **119**. 6-Formylfurochromone **1b** similarly reacted with acetoacetic esters and acetylacetone to give the corresponding products **120** (see Scheme 41). The yields and purity of the target products could be enhanced by performing the reaction under microwave irradiation conditions.[128,129]

Scheme 41

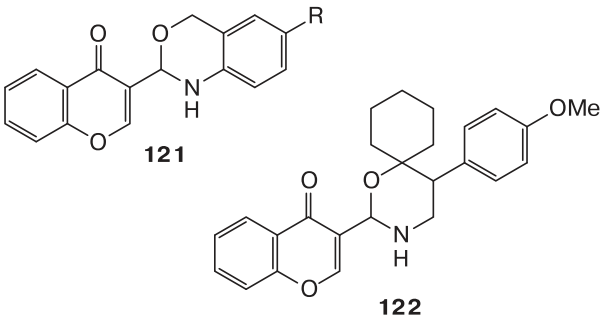


118: R^1 = H, Me, Cl; R^2 = CN, Ph

119: R^1= R^2 = R^3 = R^4 = H, R^5 = COOEt

120: R^1 = R^4 = OMe,  , R^5 = C(O)Me, COOEt, $COOBu^t$

1,3-Benzoxazine isoflavone analogs **121** were synthesized in high yields by the reaction of 3-formylchromone **1a** and 2-aminobenzylic alcohol in the presence of monochloroacetic acid.[130,131] The reaction of 3-formylchromone **1a** with 1-[2-amino-1-(4-methoxyphenyl)ethyl]cyclohexanol gave spiro derivative **122**.[130]

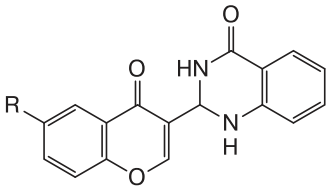


121

122

121: R = H, Me, Cl

2,3-Dihydroquinazolin-4-one moiety at the position 3 of the chromone core (compounds **123a,b**) was constructed by condensation of 3-formylchromones **1** with 2-aminobenzamide in EtOH catalyzed by 10 mol.% 3-methyl-1-ethylimidazolium hydrosulfate. Compound **123a** was found to be more cytotoxic against MDA-MB-231 cell line (a highly aggressive, invasive, and poorly differentiated triple-negative breast cancer) than the reference drug 5-Fluorouracil.[132]



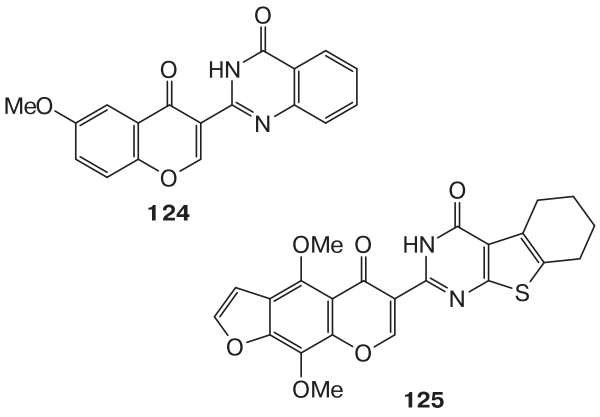
123a,b

R = Me (**a**), Cl (**b**)

The reaction of formylchromones **1** with aromatic acid amino amides can be employed for the synthesis of quinazoline derivatives. Thus, upon heating of formylchromones **1** with either 2-aminobenzamide in DMSO for 20 h[133] or 2-amino-4,5,6,7-tetrahydrobenzothiophene-3-carboxamide in DMF for 3 h[134] under aerobic conditions, the initially formed dihydroquinolines are oxidized to give quinazolinones **124**[133] and **125**.[134]

The solvent-free Lewis acid-catalyzed reaction of compound **1a**, primary aromatic amine, and isatoic anhydride afforded *N*-phenyl-2,3-dihydroquinazolinones **126**. Siddiqui and coworkers demonstrated that $LaCl_3$ supported on nano sized silica (nano-SiO_2) most efficiently catalyzed this reaction (Scheme 42).[135]

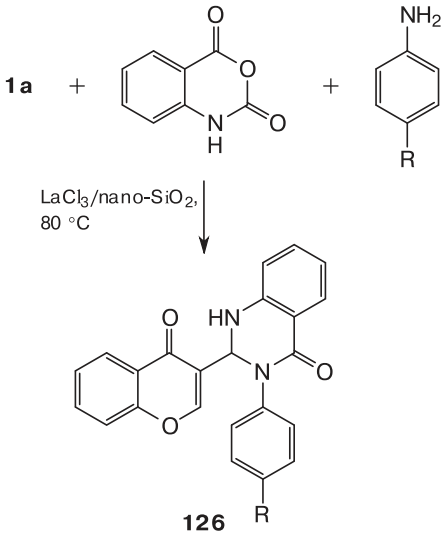
Four-component condensation between 3-formylchromone **1a**, isatoic anhydride, hydrazine, and 2-sulfobenzimide that is used as a source of the sulfonamide moiety gave rise to (chromonyl)quinazolinones **127**



124

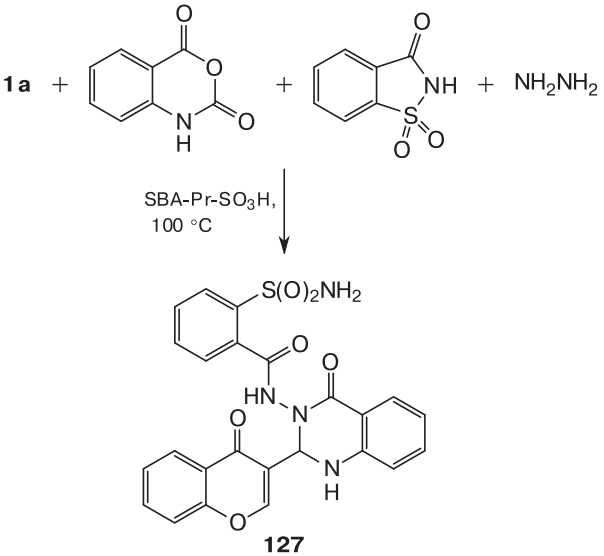
125

Scheme 42

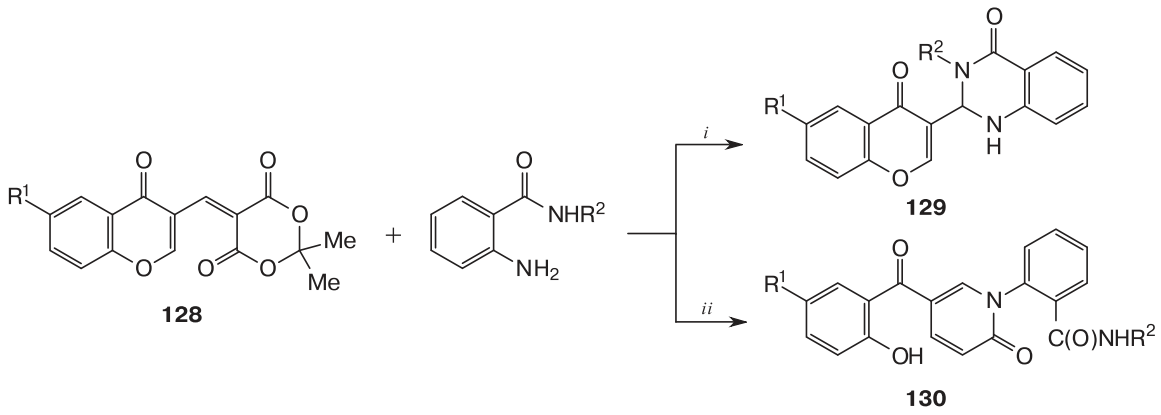


R = H, Me, OMe, Cl, NO_2

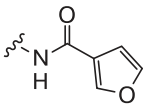
Scheme 43



Scheme 44



R^1 = H, Br

R^2 = CH_2=$CHCH_2$, Bn, $PhCH_2CH_2$, PhNH, 4-$MeOC_6H_4NH$, PhC(O)NH, 

Reagents and conditions: *i*. Me_3SO_3H (20 mol.%), EtOH, 70 °C; *ii*. K_2CO_3 (30 mol.%), EtOH, 70 °C.

(Scheme 43).[136] The reaction was performed under solvent-free conditions using propylsulfonic acid-functionalized mesoporous silica (SBA-Pr-SO_3H) as a catalyst.

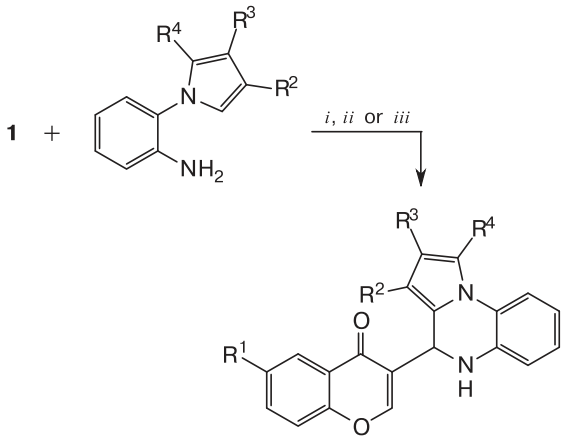
Compounds **128**, the adducts of 3-formylchromones **1** with Meldrum's acid, reacted with substituted amides and anthranilic acid hydrazides under acid catalysis conditions to produce *N*-substituted 2,3-dihydroquinazolinones **129** in 48—84% yields (Scheme 44).[137] The same reaction under basic catalysis conditions gave rise to pyridin-2-one derivatives **130** (Scheme 44).[137]

Acid-catalyzed condensation of 3-formylchromones **1** with 2-aminophenylpyrrole resulted in 4,5-dihydropyrrolo[1,2-*a*]quinoxaline isoflavone analogs **131** (Scheme 45).[138,139] Using AcOH as a catalyst, pyrrolo[1,2-*a*]quinoxaline **131a** was obtained in 86% yield.[138] Rashidi *et al.*[139] reported the synthesis of compound **131b** in aqueous media under catalysis with ionic liquid [PPy]HSO_4 supported on nano-sized silica ([PPy]HSO_4 • nano-SiO_2). Under these conditions, 98% yield of the target product **131b** was achieved. Tang and coworkers[140] expanded the substrate scope of this reaction and used 1-(2-aminophenyl)-3-methylindole as a substrate and *N*-oxoammonium salt $[TEMPO]^+PF_6^-$ as a catalyst. Under these conditions, the reaction produced 5,6-dihydroindolo[1,2-*a*]quinoxaline **132** in 86% yield (see Scheme 45).[140]

Dihydropyrazinones **134** were synthesized by the reaction of 3-formylchromone **1a**, isocyanides, substituted anilines, and 2-azidoacetic acid (Scheme 46).[141] Bazgir and coworkers[141] believe that the four-component Ugi reaction initially produced intermediates **133** that further underwent PPh_3-catalyzed intramolecular aza-Wittig cyclization.

Dihydroquinoxaline isoflavone analogs **135** were synthesized by three-component TsOH-catalyzed condensation of compound **1b**, *o*-phenylenediamine, and isocyanates (Scheme 47).[142]

Scheme 45



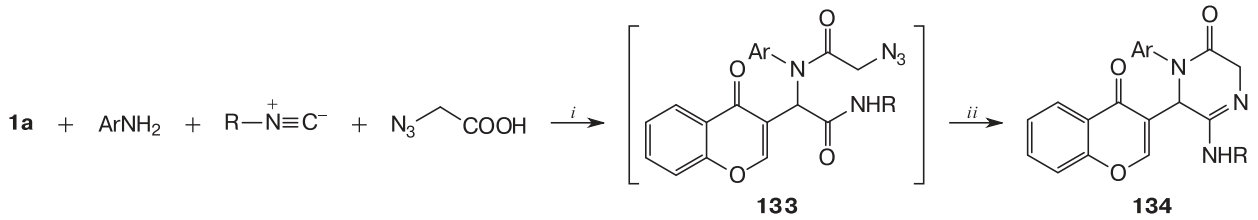
R^1 = H (**131a**, **132**), Cl (**131b**); R^2 = R^3 = R^4 = H (**131a,b**);

R^2 = Me, R^3 = R^4 =  (**132**)

Reagents, conditions, and yields: *i* (for **131a**). AcOH (cat.), EtOH, 50 °C, 5—10 min, 86%; *ii* (for **131b**). [PPy]HSO_4 • nano-SiO_2 (0.8 mol.%), H_2O, 70 °C, 40 min, 98%; *iii* (for **132**). $[TEMPO]^+PF_6^-$ (1.0 mol.%), MeCN, ~20 °C, 86%.

The reaction of 3-formylchromone **1a** with 2 equiv. of dimedone **136a** in pyridine at room temperature followed by treatment with concentrated HCl and recrystallization from EtOH acidified with HCl gave 3-(3,3,6,6-tetra-

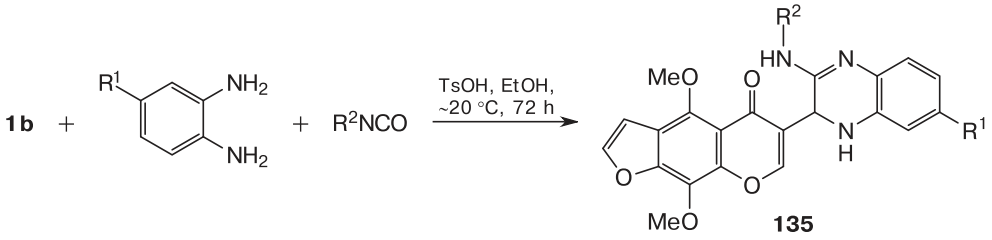
Scheme 46



Ar = 4-MeC_6H_4, 3,4-$Me_2C_6H_3$, 4-$MeOC_6H_4$; R = *cyclo*-C_6H_{11}, Bu^t, 2,6-$Me_2C_6H_3$, $C(Me)_2CH_2Bu^t$

Reagents and conditions: *i*. THF, ~20 °C, 24 h; *ii*. PPh_3, toluene (anhydrous), Ar, ~20 °C, 24 h.

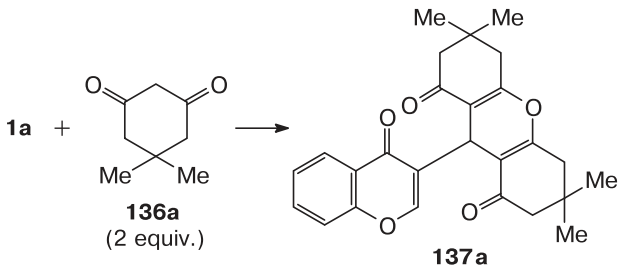
Scheme 47



R^1 = H, NO_2, COOH; R^2 = Me, *cyclo*-C_6H_{11}, Ph

methyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthen-9-yl)chromone (**137a**) (Scheme 48).[143]

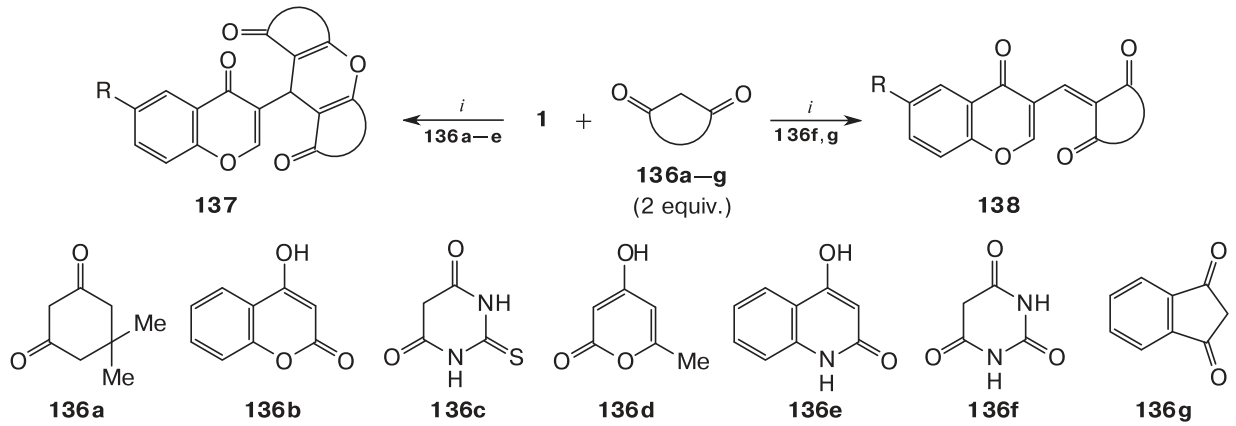
Scheme 48



Deshmukh and coworkers[144] studied the reaction of 3-formylchromones **1** with (hetero)cyclic 1,3-dicarbonyl compounds **136a—g** (Scheme 49). The reaction was carried out at a ratio **1** : **136** of 1 : 2 in 50% aqueous EtOH in the presence of (±)-camphorsulfonic acid as a catalyst. The reaction of 3-formylchromones **1** with active methylene compounds **136a—e** gave pyrone isoflavone analogs **137**, while the reaction of compounds **1** with barbituric acid (**136f**) and 1,3-indanedione (**136g**) gave rise to only the corresponding Knoevenagel adducts **138** that do not react with the second molecule of active methylene compound.

The functionalized pyran isoflavone analogs **139** and **140** were synthesized by three-component reaction involving 3-formylchromone **1a**, malononitrile and either di-

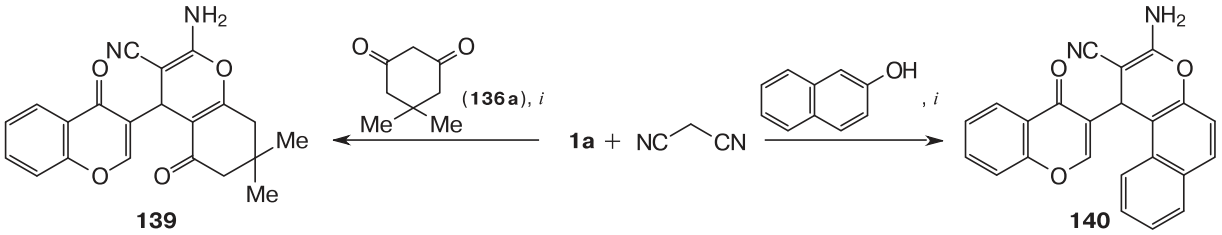
Scheme 49



R = H, F

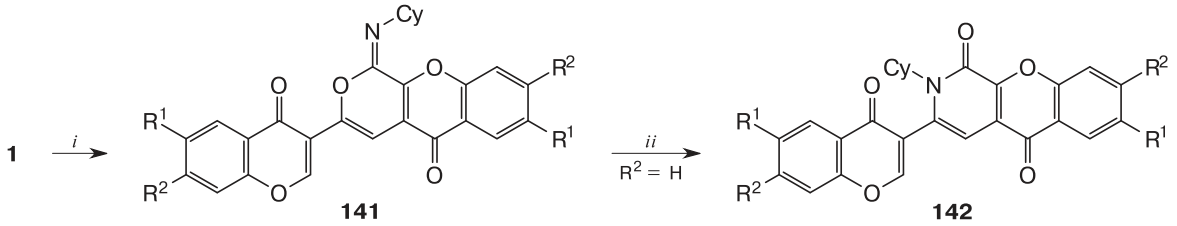
Reagents and conditions: *i*. (±)-10-camphorsulfonic acid (20 mol.%), EtOH—H_2O (1 : 1), reflux, 30—60 min.

Scheme 50



Reagents and conditions: *i.* Bi_2WO_6 (5 equiv.), H_2O, ~20 °C, 10 min.

Scheme 51



Cy is cyclohexyl.

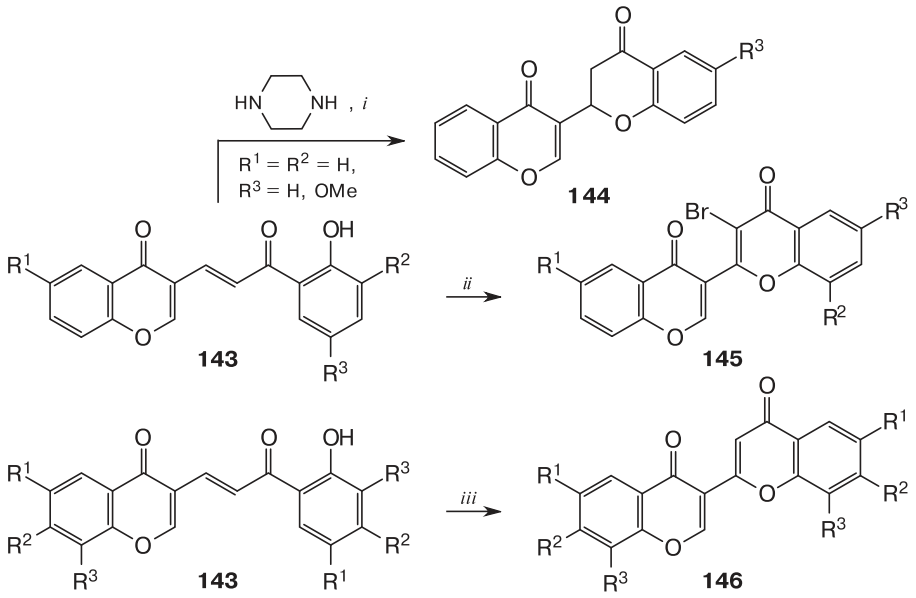
R^1 = H, Me, Cl; R^2 = H, OH

Reagents and conditions: *i. cyclo*-$C_6H_{11}NC$, MeCN, reflux, 30 min; *ii.* HCl (cat.), EtOH, heating, 2 h.

medone or β-naphthol in the presence of bismuth tungstate as a catalyst (Scheme 50).[109]

Panja *et al.*[145] reported the synthesis of 1-(cyclohexylimino)pyrano[3,4-*b*]chromones **141**. The pyrano[3,4-*b*]chromone core is the central constitutive part of rotenone, the natural compound with a wide spectrum of biological activity. Compounds **141** were obtained by the reaction of 2 equiv. of formylchromones **1** with cyclohexyl isocyanide. On heating in EtOH in the presence of HCl, imine **141** underwent rearrangement to lactam **142** (Scheme 51). The authors failed to hydrolyze imines **141** and to isolate the corresponding pyrano[3,4-*b*]chromenediones.[145]

Scheme 52



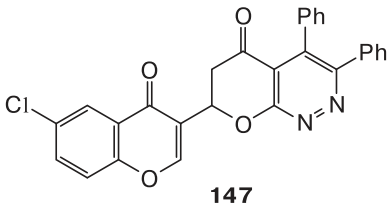
145: R^1 = Me, Cl; R^2 = H, Cl, Br, NO_2; R^3 = H, Me, Cl, Br, NH_2

146: R^1, R^2 = H, Me; R^3 = H, Me, OMe

Reagents and conditions: *i.* THF, ~20 °C; *ii.* $CuBr_2$, DMSO, microwave irradiation; *iii.* SeO_2, 3-methylbutan-1-ol, reflux, 48 h.

Similarly to 2′-hydroxychalcones, compounds **143** that were synthesized by condensation of 3-formylchromones **1** with substituted 2-hydroxyacetophenones underwent cyclization to give chromenochromone derivatives **144**.[146] Intramolecular cyclization of derivatives **143** resulting in 2,3′-bischromones is also known.[147,148] Thus, microwave-assisted reaction of compounds **143** with $CuBr_2$ gave rise to 3-bromo-substituted 2,3′-bischromones **145**.[147] 2,3′-Bischromones **146** were synthesized by prolonged reflux of compounds **143** with selenium dioxide in isoamyl alcohol (Scheme 52).[148]

Gabr and coworkers[149] demonstrated that the product of condensation of 6-chloro-3-formylchromone with 4-acetyl-5,6-diphenylpyridazin-3(2*H*)-one in the presence of piperidine underwent similar cyclization to give compound **147**.



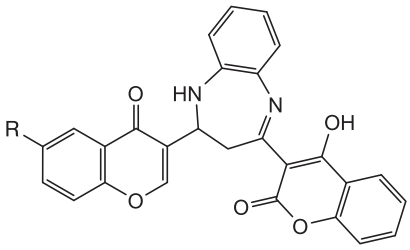
147

1.3. Isoflavone hetero analogs with seven-membered heterocycles

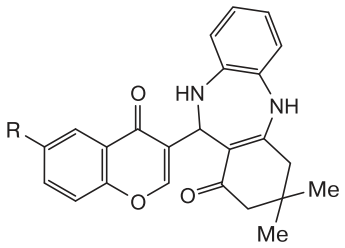
Isoflavone analogs with seven-membered heterocycles can be synthesized by the reaction of the chromone derivatives **148** bearing enone moiety with binucleophiles.[150—153] The reaction of enones **148** with *o*-phenylenediamine and 2-aminothiophenol gave, respectively, 3-(4-phenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-yl)-4*H*-chromen-4-ones **149**[150,151] and 3-(4-phenyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-2-yl)-4*H*-chromen-4-ones **150**[152,153] (Scheme 53).

Albanese *et al.*[152] demonstrated that the use of perfluorinated solvents, *e.g.*, hexafluoropropan-2-ol, allows increasing the product yields. The authors believe that due to its high acidity hexafluoropropan-2-ol can activate both the carbonyl and thiol groups *via* hydrogen bonding and behave as a proton shuttle.

Three-component condensation of 3-formylchromones **1**, *o*-phenylenediamine, and 3-acetyl-4-hydroxycoumarin catalyzed by nano silica-supported *N*-propylsulfamic acid resulted in 4-hydroxy-3-[2-(4-oxo-4*H*-chromen-3-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-4-yl]-2*H*-chromen-2-ones **151**.[154] The use of dimedone as a CH acidic component gave rise to the fused 3,3-dimethyl-11-(4-oxo-4*H*-chromen-3-yl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-ones **152**.[155] The reaction requires no solvent and can be also catalyzed by silica-supported $Fe(OTs)_3$.



151 (88—90%)

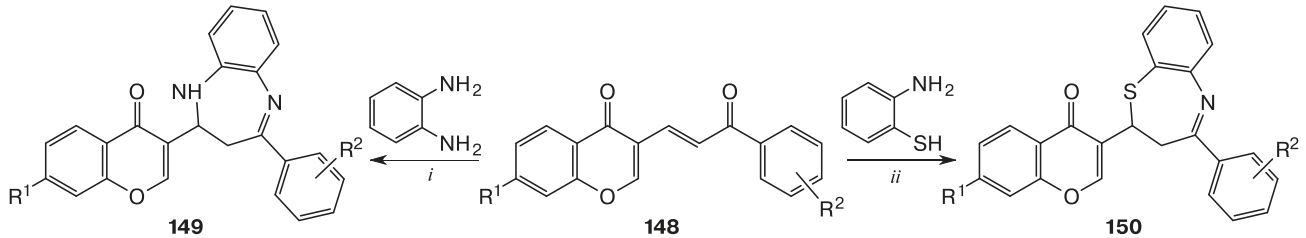


152 (92—93%)

151: R = H, Me;
152: R = H, Me, Cl

Sulfene **155** generated *in situ* by successive treatment of (chlorosulfinyloxy)-*N*,*N*-dimethylmethaneiminium

Scheme 53

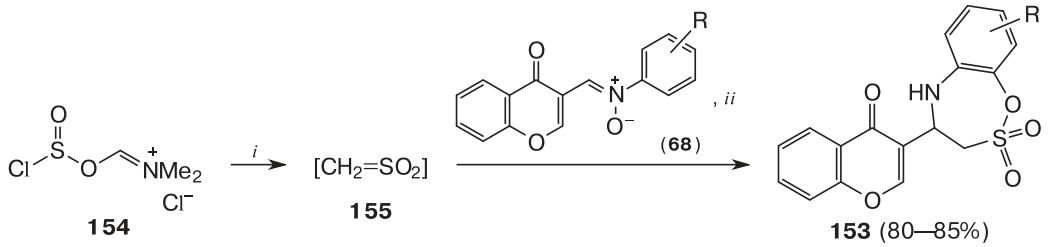


149 **148** **150**

149: R^1 = H, OH; R^2 = H, 4-Cl, 4-F
150: R^1 = H; R^2 = H, 4-Cl, 4-Me, 4-OMe

Reagents and conditions: *i*. AcOH (cat.), DMF, microwave irradiation, 15 min; *ii*. 1,1,1,3,3,3-hexafluoropropan-2-ol, 28 °C, 6 h or MeOH, AcOH (cat.), reflux, 2 h.

Scheme 54



R = H, 6-Me, 8-Me, 8-OMe, 8-Cl

Reagents and conditions: *i*. $MeSO_3H$, CH_2Cl_2 (anhydrous), 0 °C, 10 min; *ii*. Et_3N, ~20 °C, 3 h.

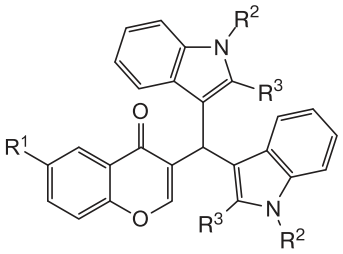
chloride **154** (synthesized by the reaction of $SOCl_2$ with DMF in anhydrous benzene) with methanesulfonic acid and triethylamine in anhydrous CH_2Cl_2 reacted with nitrone **68** to give 3-(2,2-dioxido-4,5-dihydro-3*H*-benzo[*f*][1,2,5]oxathiazepin-4-yl)-4*H*-chromen-4-one **153** (Scheme 54).[156]

2. Synthesis of heterocyclic analogs of homoisoflavonoids

Homoisoflavonoids are the homologs of isoflavonoids and constitute a small family of natural oxygen heterocycles, the derivatives of 3-benzylchromone (chromanone) or 3-benzylidenechromanone. These compounds show antioxidant, anti-inflammatory, antimutagen, antimicrobial, and antiviral activities. Some natural homoisoflavonoids show the cytostatic effects against different cancer cell lines and inhibit angiogenesis. It was also found[157] that these compounds are capable of inhibiting phosphodiesterases type IV and V. Despite the extensive studies over the last decades in chemistry of benz-γ-pyrone derivatives, homoisoflavones are far less explored.

The simplest synthetic approach to 3-[di(hetaryl)methyl]-4*H*-chromen-4-ones is the reaction of nucleophilic (π-rich) heterocycles (indoles, pyrroles) with 3-formylchromones **1**.[158—164]

Thus, Sosnovskikh and coworkers[158,163] described the synthesis of 3-[di(1*H*-indol-3-yl)methyl]-4*H*-chromen-4-ones **156a—h**. Solvent- and catalyst-free reaction of 3-formylchromones **1** with excess (3 equiv.) of indole, 1-methylindole, or 2-methylindole gave the target products **156a—h** in the yields from moderate to high (51—79%).[158] The authors emphasized that the poorly separable mixtures were obtained when the reactions were carried out in solvent or under both acidic and basic catalytic conditions; while, the presence of electron-withdrawing substituents in the chromone ring system facilitated polymerization of the reaction mixture. Compound **156i** was synthesized in butanol in the presence of perchloric acid as a catalyst.[158] Product **156j** was prepared by heating the corresponding reagents in aqueous medium.[158] Compounds **156** were synthesized but in lower yields using 1 equiv. of indoles.[163]



156a—j

$R^1 = R^2 = R^3 = H$ (**a**); $R^1 = R^3 = H$, $R^2 = Me$ (**b**); $R^1 = R^2 = H$, $R^3 = Me$ (**c**);
$R^1 = Me$, $R^2 = R^3 = H$ (**d**); $R^1 = R^2 = Me$, $R^3 = H$ (**e**);
$R^1 = R^3 = Me$, $R^2 = H$ (**f**); $R^1 = OMe$, $R^2 = R^3 = H$ (**g**);
$R^1 = OMe$, $R^2 = H$, $R^3 = Me$ (**h**); $R^1 = Cl$, $R^2 = R^3 = H$ (**i**);
$R^1 = NO_2$, $R^2 = R^3 = H$ (**j**)

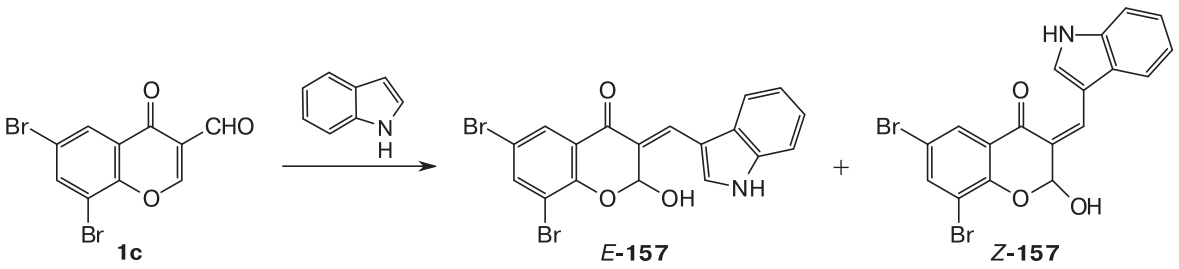
The higher yields (up to 70—90%) of bis-adducts **156** were achieved and the negative effects of electron-withdrawing substituents in the chromone core were reduced by reacting 3-formylchromones **1** with indoles either in eutectic mixture of oxalic acid and proline at room temperature[159] or in MeCN in the presence of the catalysts (10 mol.% of the complex of 3-(diphenylphosphino)benzenesulfonic acid sodium salt (TPPMS) with CBr_4,[160] $[CuCl_2(py)_2]$,[161] and 5 mol.% of $Yb(OTf)_3$[162]).

The reaction of 6,8-dibromo-3-formylchromone (**1c**) even with excess (3 equiv.) of indole gave only 3-[(1*H*-indol-3-yl)methylene]-6,8-dibromo-2-hydroxychroman-4-one (**157**) in 30% yield. Product **157** exists as a 91 : 9 mixture of (*E*)- and (*Z*)-diastereomers (Scheme 55).[158,163]

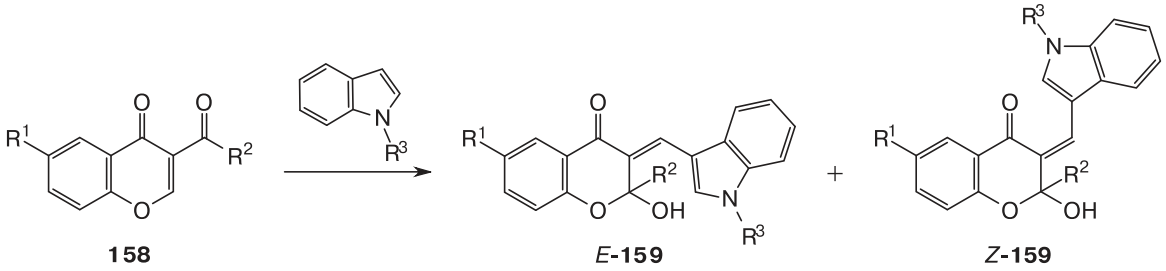
3-(Polyfluoroacetyl)chromones **158** reacted with indole and *N*-methylindole in anhydrous pyridine to give compounds **159** as a mixtures of *E*- and *Z*-isomers (Scheme 56).[165,166]

Catalyst- and solvent-free reaction of *N*-methylpyrrol with 3-formylchromones **1** proceeded exclusively as nucleophilic 1,4-addition (1,4-A_N) to afford *E*-2-hydroxy-3-[(1-methyl-1*H*-pyrrol-2-yl)methylene]chroman-4-ones **160**. Note that plausible 1,2-addition (1,2-A_N) does not

Scheme 55



Scheme 56

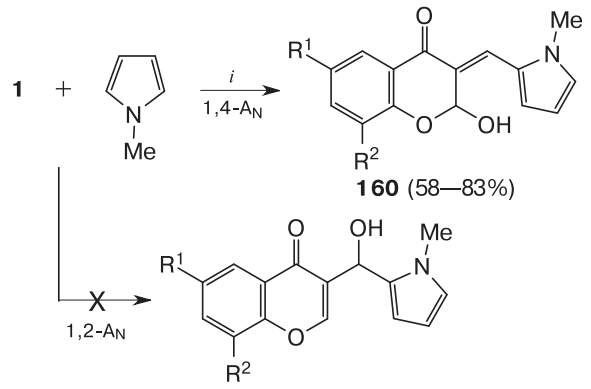


R^1 = H, Me, Cl; R^2 = CF_3, CF_2H, $(CF_2)_2H$; R^3 = H, Me

Conditions: pyridine (anhydrous), reflux, 3 h.

occur (Scheme 57).[158,163] *N*-Methylpyrrole similarly reacted with polyfluoroacetylchromones **158**.[165]

Scheme 57

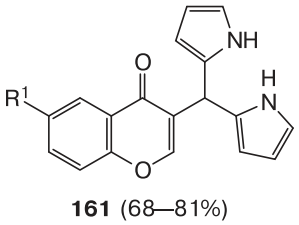


R^1 = H, Cl, Br, NO_2; R^2 = H, Br

Conditions: *i*. 85—90 °C, 45 min.

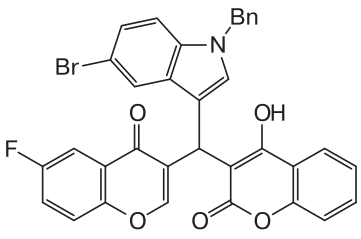
3-Formylchromones **1** reacted with pyrrole in the presence of trifluoroacetic acid as a catalyst to give 3-[di(1*H*-pyrrol-2-yl)methyl]-4*H*-chromen-4-ones **161**.[164]

The reactions involving 3-formylchromones **1**, π-rich heterocycle, and the third component open up the prospects for the synthesis of the functionalized 3-[di(hetaryl)methyl]chromone derivatives. The three-component condensation of equimolar amounts of indole, 4-hydroxycoumarin, and 6-fluoro-3-formylchromone **1** (R = 6-F) resulted in unsymmetrical 3-[(1-benzyl-5-bromo-1*H*-indol-3-yl)(6-fluoro-4-oxo-4*H*-chromen-3-yl)methyl]-4-hydroxy-2*H*-chromen-2-one (**162**).[162] Microwave-assisted indium triflate-catalyzed reaction of 3-formylchromone **1a**, substituted indoles, and anilines gave rise to 3-[(1*H*-indol-3-yl)(arylamino)methyl]-4*H*-chromen-4-ones **163** in 70—83% yields and the corresponding (chromon-3-yl)bis(indol-3-yl)methanes **156** as the side products.[167] Prajapati and coworkers[167] believe that imines generated by the reaction of 3-formylchromone **1a** and anilines underwent the nucleophilic attack with indole to give the target products **163** but competitive elimination of amine followed by the condensation of intermediates with the second indole molecule led to the minor products **156**.

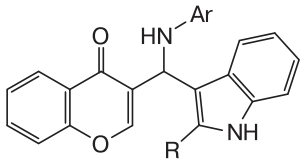


R^1 = H, Me, Pr^i

The four-component condensation of 3-formylchromones **1**, anilines, isocyanides, and azidotrimethylsilane



162 (57%)



163 (70—83%)

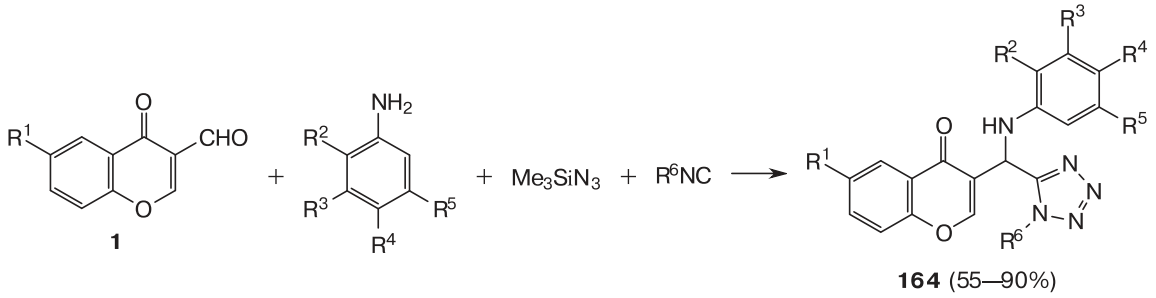
163: R = H, Me; Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-$O_2NC_6H_4$

(the azido-Ugi reaction) gave 3-[(arylamino)(1*H*-tetrazol-5-yl)methyl]-4*H*-chromen-4-ones **164** (Scheme 58).[168,169]

Compounds **164** show antiprotozoal activity against *Entamoeba histolytica, Giardia lamblia*, and *Trichomona vaginalis*. Despite the fact that activity of compounds **164** was lower than that of the reference drug Metronidazole, they are regarded as suitable alternatives for the antiparasitic treatment of metronidazole-resistant strains.[168] Fluoro- and iodo-substituted derivatives **164** exhibited the highest antimicrobial (*P. aeruginosa* and *S. aureus*), antiprotozoal (*E. histolytica*), and antifungal (*Sporothrix schenckii, C. albicans*, and *Candida tropicalis*) activities.[169]

Mehrparvar *et al.*[170] demonstrated the possibility to introduce the carbonyl group into the (chromonyl)hetarylmethane core. The successive treatment of 3-formylchromones **1** with Meldrum's acid, 4-hydroxycoumarin (**10**) or 4-hydroxy-6-methylpyran-2-one (**11**) in aqueous primary alcohol gave esters **165**. The use of propan-2-ol instead of primary alcohols resulted in lactones **166** (Scheme 59).

Scheme 58

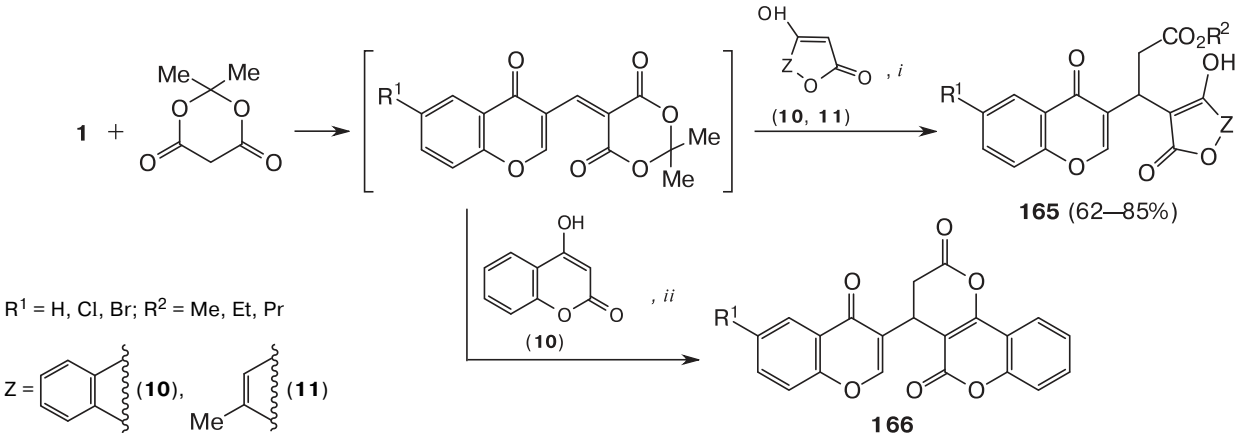


164 (55—90%)

R^1 = H, F; R^2 = H, Br, I, NO_2; R^3 = H, OMe; R^4 = H, Cl, I, OMe, NO_2; R^5 = H, OMe; R^6 = Bu^t, *cyclo*-C_6H_{11}, 2,6-$Me_2C_6H_3$

Reagents and conditions: $InCl_3$ (5 mol.%), propan-2-ol (anhydrous), ~20 °C, 2 h.

Scheme 59



165 (62—85%)

166

R^1 = H, Cl, Br; R^2 = Me, Et, Pr

Z = (**10**), (**11**)

Reagents and conditions: *i*. Et_3N (50 mol.%), R^2OH—H_2O (1 : 1), 60 °C, 6 h; *ii*. Et_3N (50 mol.%), propan-2-ol—H_2O (1 : 1), 60 °C, 6 h.

This difference in the structure of the products Mehrparvar *et al.*[170] rationalized by the relative ease of addition of primary alcohols to the ketene moiety of the intermediates formed by the Michael addition of deprotonated form of 4-hydroxycoumarin **10** and 4-hydroxy-6-methylpyran-2-one **11** to the Knoevenagel intermediates and subsequent elimination of acetone. The Knoevenalgel adducts are resulted from the reaction of 3-formylchromone and Meldrum´s acid. When the reaction was carried out in propan-2-ol no addition of alcohol to ketene occurred. As the authors suggested, the hydroxy group of 4-hydroxycoumarin played a role of nucleophile. Its addition to ketene and subsequent decarboxylation gave rise to lactone **166**.[170]

3-[(2-Oxo-5-arylfuran-3(2*H*)-ylidene)methyl]-4*H*-chromen-4-ones **167a—d** were synthesized by the reaction of 3-formylchromones **1** with β-aroylpropionic acids, and (chlorosulfinyloxy)-*N,N*-dimethylmethaneiminium chloride (**154**) (Scheme 60).[171,172] The treatment of (furanylidene)-methylchromenone **167d** with ammonium acetate in EtOH gave pyrrolone **168**. The structure of the product formed in the reaction of compound **167d** with hydrazine is determined by the solvent nature. In benzene, [(phenylpyridazin-4-yl)methyl]chromenone **169** is formed, while in ethanol [(phenylpyridazin-4-yl)methyl]quinolinone **170** was obtained. The reaction of compound **167d** with phenylhydrazine afforded chromylidene pyridazinone derivative **171** (see Scheme 60).[172]

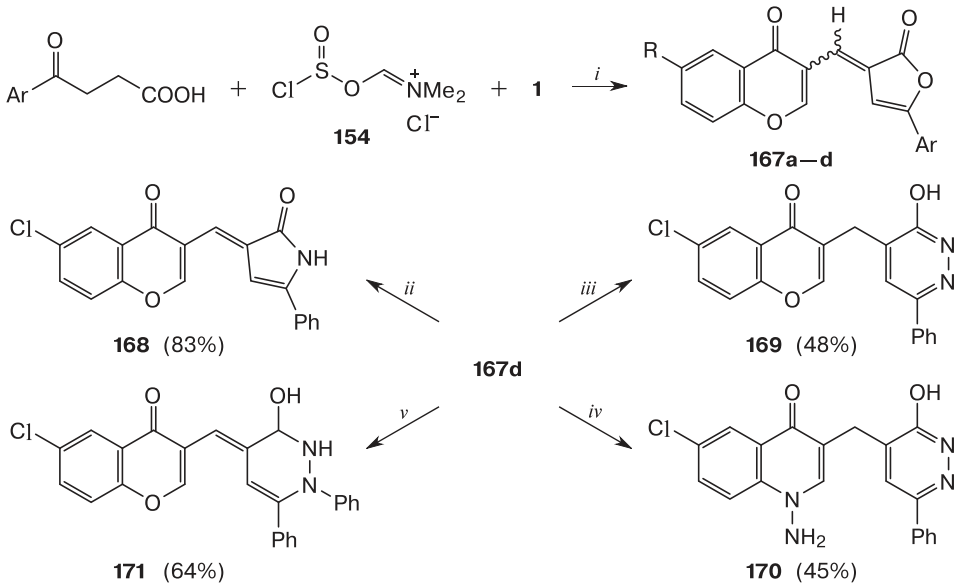
Derivatives **167d** and **168—171** showed moderate antimicrobial activity. The most promising compound **167d** inhibited the growth of *E. coli* and *S. aureus*, however its activity was lower than that of amoxicillin. Compound **167d** also exhibited antifungal activity against *C. albicans*.[172]

Venkateswararao *et al.*[173] used enones **148** as the starting material for the synthesis of 3,3´-methylenebis(4*H*-chromen-4-ones) **174** and 3-[(4-oxochroman-3-yl)methyl]-4*H*-chromen-4-one **175** (Scheme 61). Enones **148** were prepared by the reaction of 3-formylchromones **1** with 1-[2-(benzyloxy)phenyl]-2-(triphenylphosphoranylidene)ethanones. Reduction of compounds **148** with cyclohexene (2 equiv.) in the presence of 20% Pd/C afforded ketones **172** and **173**. The degree of reduction depended on the reaction time. Further cyclization of ketones **172** and **173** gave the target compounds **174** and **175**.

It is of note that derivatives of type **175** ($R^1 = R^2 = H$) are the main products of the reaction of 3-formylchromone **1a** with iron pentacarbonyl (2 equiv.) and hexamethapol (4 equiv.).[174]

Compounds **174** and **175** were evaluated for their ability to inhibit the growth of the following cancer cell lines: prostate cancer PC-3, lung adenocarcinoma NCI-H23, breast cancer MDA-MB-231, colorectal adenocarcinoma HCT-15, gastric cancer NUGC-3, and renal adenocarcinoma ACHN.[173] It was found that the most active compounds contain cyclohexylmethoxy group at the position 5 of one of the chromone cores and electron-releasing substituents (Me, OMe) or hydrogen-bonding groups (OH) at the position 7 of another. Reduction of the

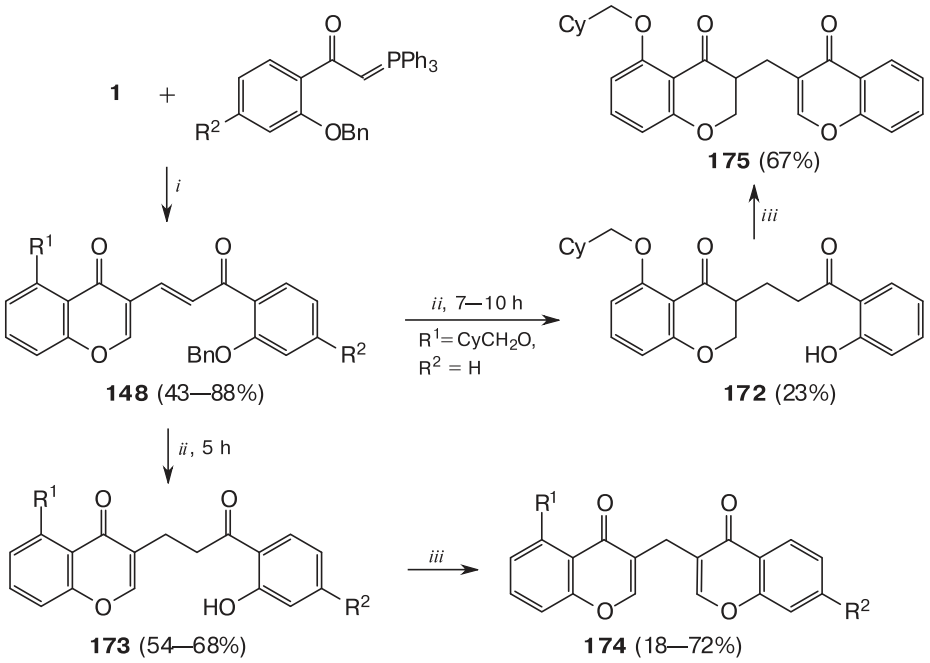
Scheme 60



R = H; Ar = Ph (**a**), 4-Me-C_6H_4 (**b**), 4-Cl-C_6H_4 (**c**); R = Cl, Ar = Ph (**d**)

Reagents and conditions: *i*. 1) CH_2Cl_2, 0 °C, 2) Et_3N, ~20 °C, 5 h; *ii*. $AcONH_4$ (4 equiv.), EtOH (anhydrous), reflux, 2 h; *iii*. $NH_2NH_2 \cdot H_2O$, benzene, reflux, 2 h; *iv*. $NH_2NH_2 \cdot H_2O$ (2 equiv.), EtOH (anhydrous), ~20 °C, 4 h or reflux, 1 h; *v*. $PhNH_2NH_2$, EtOH (anhydrous), reflux, 30 min.

Scheme 61

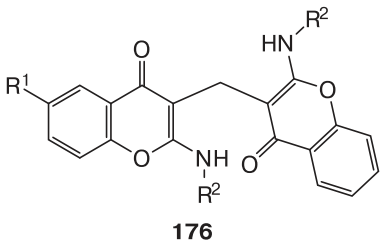


R^1 = H, OH, OMe, OBn, OBu^i, OPe^i, $CyCH_2O$ (Cy is cyclohexyl)
R^2 = H, Me, OMe, OH, Cl, OBn

Reagents and conditions: *i*. CH_2Cl_2, ~20 °C, ~16 h; *ii*. cyclohexene (2 equiv.), THF, MeOH (1 : 1), 20% Pd/C, reflux; *iii*. $BF_3 \cdot Et_2O$ (6.5 equiv.), N_2, MsCl (4.2 equiv.), DMF, 50 °C, 8 h.

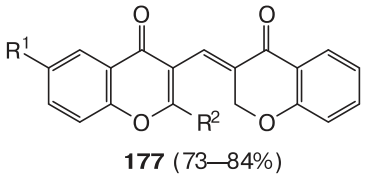
double bond in one of the chromone moieties decreased the activity.[173]

2-Aryl- and alkylamino-substituted 3,3′-methylenebis[2-aryl(alkyl)amino-4*H*-chromen-4-ones] **176** were synthesized by heating 3-formylchromones bearing 2-positioned secondary amino group with the formaldehyde excess in DMF in the presence of secondary amine (piperidine or diethylamine).[175] Condensation of 3-formylchromones **1** (R = H, Br) and 2-amino-3-formylchromones (**60**) with chromanone in EtOH in the presence of piperidine gave the corresponding (*E*)-3-[(4-oxochroman-3-ylidene)-methyl]-4*H*-chromen-4-ones **177**.[176] Compounds **177** (and especially 2-amino derivatives) binds with calf thymus DNA presumably by intercalation. Amino derivative **177** (R^1 = H, R^2 = NH_2) also efficiently inhibit acetylcholinesterase being only slightly inferior to reference drug Tacrine.[176]



176

176: R^1 = H, Me; R^2 = Me, Et, Ph, 4-MeC_6H_4



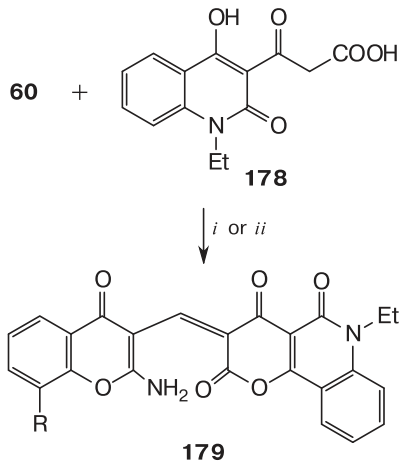
177 (73—84%)

177: R^1 = H, Br; R^2 = H, NH_2

2-Amino-3-formylchromone (**60**) reacted with β-ketoacid **178** to give (*E*)-3-[(2-amino-4-oxo-4*H*-chromen-3-yl)methylidene]-6-ethyl-2*H*-pyrano[3,2-*c*]quinoline-2,4,5(3*H*,6*H*)-triones **179** (Scheme 62).[177] It is of note that compounds **179** were also synthesized by the piperidine-catalyzed reaction of β-ketoacid **178** with the corresponding 3-cyanochromones.[177]

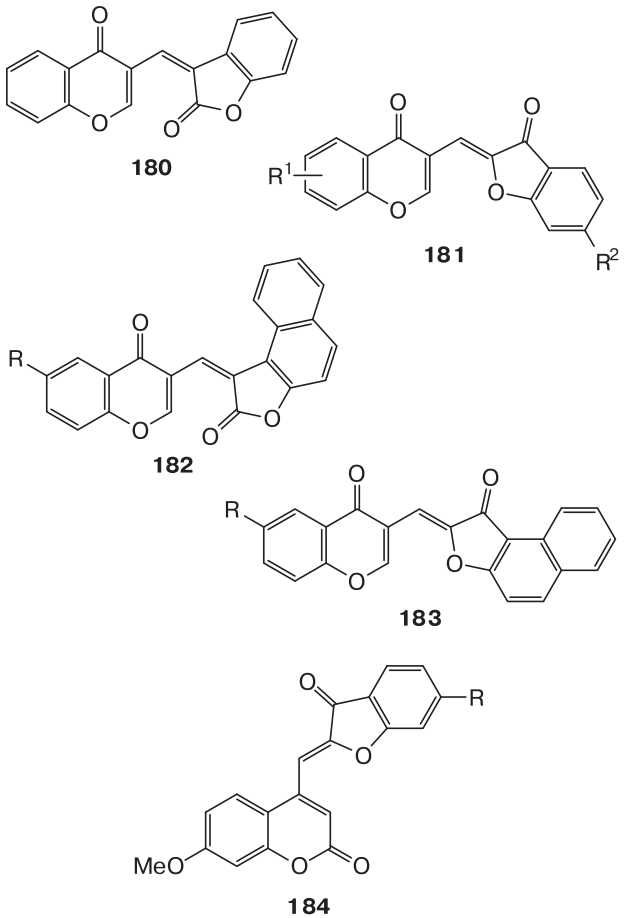
Condensation of 3-formylchromones **1** with benzofuran-2-ones, benzofuran-3-ones, naphthofuran-2-ones, and naphthofuran-3-ones produced the corresponding derivatives **180—183** that can be regarded as chromone-based aurone analogs.[178,179] Anticancer activity of compounds **180—183** was tested *in vitro* against the murine L1210 leukemia cell line. Compound **183** (R = H) was found to be most active with IC_{50} = 1.6 μmol L^{-1}.[178] Among the synthetic aurone analogs evaluated against K562 chronic myeloid leukemia cells, derivative **181** (R^1 = 6-Me, R^2 = Me) was found the most active. Compound **181** at a concentration of 50 μmol L^{-1} blocked

Scheme 62



R = H, $CH_2CH{=}CH_2$

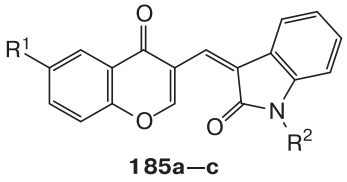
Reagents and conditions: *i*. DMF, piperidine (cat.), reflux, 2 h; *ii*. AcONa, AcOH (glacial), reflux, 2 h.



181: R^1 = H, 6-Me, 7-Me, 6-Cl, 7-Cl, 6-F, 7-F, 5-OMe, 7-OMe; R^2 = H, Me
182, **183:** R = H, Me, Cl, NO_2
184: R = H, Me

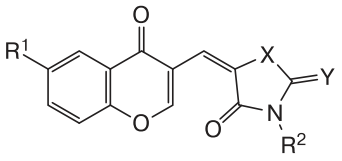
the K562 cell cycle in G1 phase and induced about 24% apoptosis.[179] The replacement of the chromone moiety with coumarin core afforded compounds **184** capable of blocking the cell cycle in G2 phase.[179]

The (*Z*)-3-[(4-oxo-4*H*-chromen-3-yl)methylene]indolin-2-one derivatives **185** were synthesized by condensation of 3-formylchromones **1** with indolinones.[180,181] Compound **185a** showed pronounced anticancer activity inhibiting growth of 60 human cancer cell lines with the average GI_{50} values of 3.2 μmol L^{-1}.[180] Compounds **185b,c** were found to be selective inhibitors of cyclooxygenase-2 (IC_{50} of 29—20 μmol L^{-1}, selectivity indices of 46 and 337, respectively). Compound **185b** exhibited an analgesic potential higher than Diclofenac.[181]

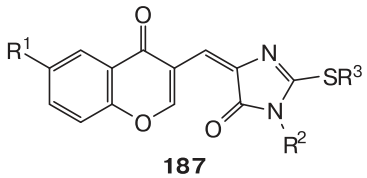


185: R^1 = H, R^2 = 2,6-$Cl_2C_6H_3$ (**a**); R^1 = R^2 = H (**b**); R^1 = Br, R^2 = H (**c**)

Condensation of 3-formylchromone **1a** with hydantoin, thiohydantoin, and thiazolidin-2,4-diones gave derivatives **186a—c** showing insulinotropic activity. At concentration of 1 μg mL^{-1} in the presence of 5.6 μmol L^{-1} glucose, these compounds are able to increase insulin release; however, their activity is lower than that of glibenclamide.[182] Dundar and coworkers[183] synthesized a large series of adducts of 6-methyl-3-formylchromone **1** (R = 6-Me) with hydantoin, thiohydantoin, and thiazolidin-2,4-dione, for example, compounds **186d—f**. As promising insulinotropic agents, derivatives **186g—j** and **187** alkylated at the N(3) nitrogen atom and thioxo group were also synthesized.[182,183]



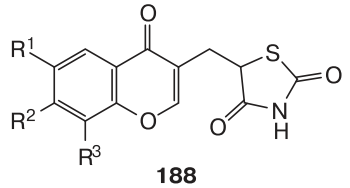
Compounds **186**	R_1	R^2	X	Y
a	H	H	NH	O
b	H	H	NH	S
c	H	H	S	O
d	Me	H	NH	O
e	H	Me	S	O
f	H	Me	NMe	O
g	H	Et	S	O
h	H	Et	NH	O
i	Me	Me	S	O
j	Me	Me	NMe	O
k	Me	Et	S	O
l	Me	Et	NH	O



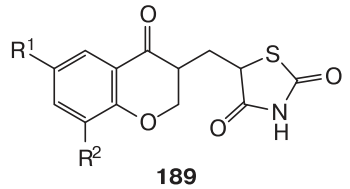
187

R^1 = H, Me; R^2 = Me, Et; R^3 = Me, Et

Reduction of chromonyl-1,3-thiazolidine-2,4-diones **186** (X = S, Y = O, R^2 = H) with H_2 over Pd/C gave rise to the target 5-[(4-oxo-4*H*-chromen-3-yl)methyl]thiazolidine-2,4-diones **188** and chromanones **189** as the by-products.[184]



188



189

188: R^1 = H, Me, OMe, Br, Cl, F; R^2 = H, F, OMe, Me; R^3 = H, Cl
189: R^1 = H, Me, OMe, Br, Cl, F; R^2 = H, Cl

Compounds **188** are the agonists of PPAR-γ receptors activation of which lowers the glucose level in blood at type 2 diabetes. Compounds **188** were as effective in lowering the blood glucose level as the standard drug Pioglitazone. The authors noted that derivatives **188** exhibit no hepatotoxicity, which is the major drawback encountered for such commercial thiazolidinone antidiabetic drugs as Pioglitazone and Rosiglitazone. Compounds **189** with the reduced double bond at the chromone core were found inactive.[184]

Conclusions

From the data summarized in the present review, one can conclude the high promise of the development of chemistry of heterocyclic analogs of natural compounds, isoflavone and homoisoflavone, based on readily available and highly reactive 3-formylchromone. The developed synthetic approaches are not limited only to the construction of heterocyclic cores based on the formyl group. The reactions are often accompanied by different recyclizations involving the C(2) nucleophilic center. This forms the basis for multicomponent reactions and allows the library synthesis of heterocyclic isoflavonoid analogs and thus accelerated the search for the most promising compounds in terms of biological activity. Additional synthetic possibilities are offered by the use of the simplest 3-formylchromone derivatives, namely, 3-cyanochromone, 2-amino-3-formylchromone, and the products of its condensation with C- and N-nucleophiles, as the starting materials. The considered synthetic approaches allow environmentally friendly synthesis of low-toxic compounds showing a wide spectrum of pharmacological activity.

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This work does not involve human participants and animal subjects.

The authors declare no competing interests.

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