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, 4H-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.
To date, more than 8000 natural and synthetic flavonoids are described. 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.

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)triazolylmethylene 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 chrome 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 recylization 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-
dicarboxylates 8 or their mixtures (Scheme 1). 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 isoflavanone 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 (R1 = H, Me; R2 = H), alkyl isocyanides (R3 = Bu, cyclo-C6H11), and methyl acetylenedicarboxylate in polyethylene glycol 400 (PEG-400) at room temperature gave selectively furan isoflavanone analogs 7 in 75—90% yields.

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

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 isoflavanone derivatives 12 (Scheme 2). 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. 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). 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.

Four-component condensation of 3-formylchromones 1, Meldrum’s acid, alkyl isocyanide, and alcohol resulted in succinimide derivatives 15 (Scheme 4). The reaction 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 R2 and R3, while the use of methanol promoted the pyrrolidone ring opening to give amido diesters 16 (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). The authors suppose that
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). 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. 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 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, the results obtained and the mechanisms of the reactions of 3-formylchromone 1a with amino acid derivatives proposed by Suschitzky and coworkers were revised. The reaction of compound 1a with methyl glycinate hydrochloride (22) in the presence of K₂CO₃ at a ratio 1a : 22 : K₂CO₃ 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). No product 23 is formed in this reaction performed with excesses of hydrochloride 22 and K₂CO₃ (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). The reaction in refluxing toluene with N-phenylmaleimide as a dipolarophile gave a mixture of cis/trans diastereomers 25 and pyrrole 21. Under similar conditions, the three-component condensation of 3-formylchromone 1a, N-methylglycine, and fullerene C₆₀ resulted in unique fullerene—chromone dyad 26. 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...
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Scheme 6

\[ R = \text{COOEt (18a, 19a), CN (18b)} \]

Scheme 7

Reagents and conditions: \( i \): \( \text{K}_2\text{CO}_3 \), 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 chromopyrrole 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 heteraryl methaneamines with 3-formylchromone 1a in the presence of TMSCl strongly depends on the reagent ratio. 5-Hetaryl-3-(2-hydroxybenzoyl)-1H-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 heteraryl methaneamines is independent of the reagent molar ratio and gives \( N \)-substituted salicyloylpyrroles 34 in 61—99\% yields (Scheme 12).\(^{50}\)
Ryabukhin and coworkers postulated two possible mechanisms of the TMSCl-activated reaction.\textsuperscript{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 \(\alpha,\beta\)-unsaturated moiety with either di-
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starting compounds 40 were synthesized by the SnCl2-catalyzed reaction of 3-formylchromones 1 with bromonitromethane followed by acetylation and β-elimination reactions.

Compound 41 bearing the pyrocatechol moiety (R1 = R2 = H, R3 = R4 = 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.

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.

Scheme 15 exemplifies the synthesis of imidazolyl chromones 42.

The role of 1,2-dicarbonyl compound could be played by o-quinones (1,2-naphthoquinone, 9,10-phenanthroquinone, and substituted isatines) (Scheme 16).

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]phenanthroline derivatives 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).

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.

Reagents and conditions: i. Me3SiCl (4 equiv.), DMF, 100 °C, 6—15 h.

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azomethane or hydrazine (Scheme 13). Thus, Shanker et al. reported 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. The reaction of ketone 35 with hydrazine hydrate in DMF and the reaction of α,β-dihalo carbonyl derivatives of chromone 38 with hydrazine 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). The treatment of nitrovinylchromones 40 with the generated in situ aromatic aldehyde N-methylhydrazones gave pyrazole isoflavone analogs 41 (Scheme 14). The starting compounds 40 were synthesized by the SnCl2-catalyzed reaction of 3-formylchromones 1 with bromonitromethane followed by acetylation and β-elimination reactions.

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**Scheme 13**

1 + \( \text{EtOH, pyridine, reflux, 7—7.5 h or microwave irradiation;} \)

\[ R^1 = \text{Ph, 4-ClC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4, 4-\text{OMeC}_6\text{H}_4, 2,4-\text{Cl}_2\text{C}_6\text{H}_3, \text{etc.}; R^2 = H, Me; R^3 = H, OH } \]

**Scheme 14**

1 + \( \text{BrCH}_2\text{NO}_2, \text{SnCl}_2, \text{THF, } \approx 20^\circ \text{C, 4 h; } ii. \text{Ac}_2\text{O, pyridine, CHCl}_3, \approx 20^\circ \text{C, 10 h; } iii. \text{TFA, MeOH, } \approx 20^\circ \text{C, 24 h. } \)

**Scheme 15**

\[ R^1 = R^2 = H, \text{Me, Ph, 2-ClC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4, 4-\text{OMeC}_6\text{H}_4, 2,4-\text{Cl}_2\text{C}_6\text{H}_3, \text{etc.}; R^1 = \text{Ph, R}^2 = H, 4-\text{OMeC}_6\text{H}_4 \]

**Reagents and conditions:**

1. EtOH, pyridine, reflux, 7—7.5 h or microwave irradiation; 2. N\(_2\)H\(_4\) \cdot \text{H}_2\text{O} (1 equiv.), AcOH, reflux, 8 h; 3. N\(_2\)H\(_4\) \cdot \text{H}_2\text{O} (2 equiv.), EtOH, reflux, 30 min; 4. AcOH, reflux, 6 h; 5. N\(_2\)H\(_4\) \cdot \text{H}_2\text{O} (1 equiv.), DMF, reflux, 18 h; 6. Br\(_2\), CHCl\(_3\), \( \approx 20^\circ \text{C; } 7. \text{N}_2\text{H}_4 \cdot \text{H}_2\text{O} (1 \text{ equiv.}, \text{pyridine, } \approx 20^\circ \text{C, 20 h or microwave irradiation.} \)

**α-Hydroxyiminoketones** 47 reacted with 3-formylchromone 1a to give 3-(1-hydroxyimidazol-2-yl)chromones 48 (Scheme 18). 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). The reaction of compound 1a with dimedone monoxime gave rise to the fused derivative 51.
Scheme 16

Reagents and conditions: i. NH₄OAc, AcOH; ii. 1) K₂CO₃, MeCN, Ar, 2) 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide, 18-crown-6, 3) Zn(OAc)₂, MeOH.

Scheme 17

Reagents and conditions: i. NH₄OAc, AcOH; ii. cis-[Ru(bpy)₂Cl₂]·2H₂O or cis-[Ru(phen)₂Cl₂]·2H₂O, (CH₂OH)₂, Ar, 120 °C, 6 h.

Scheme 18

Reagents and conditions: 1. NH₄OAc, AcOH; 2. BnNH₂, AcOH

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 \([4+1]\) recyclosion 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 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 \(58\) (Scheme 20).

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-functionalyzed 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.
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Scheme 21

\[ \text{59} \]

\[ \text{60} \]

\[ \text{61a, b} \]

\[ \text{62} \] (67%)

\[ \text{63} \]

\[ \text{64}, \text{65} \] (91%)

\[ \text{66} \]

\[ \text{67} \]

Reagents and conditions: \( i \). NaOH, H\(_2\)O; \( ii \). EtOH or benzene, reflux; \( iii \). AcOH, reflux.

Scheme 22

\[ \text{63} \]

\[ \text{64} \]

\[ \text{65} \] (91%)

The reaction of 3-formylthiochromone \( 63 \) reacted with \( o \)-phenylenediamines and 2-aminothiophenols to give 3-(benzimidazol-2-yl)thiochromones \( 64 \). In the case of 2-aminothiophenol, the reaction yielded the Schiff base \( 65 \) (Scheme 22).

Condensation of compound \( 1a \) with 2-aminothiophenol afforded 3-(benzothiazol-2-yl)chromone \( 66 \) (Scheme 23). 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 to afford \( N \)-phenyl-3-(chromon-3-yl)isoxazolidines \( 69-71 \) (Scheme 24). The reaction of formylchromones \( 1 \) with \( N \)-phenylhydroxylamine gave rise to nitrones \( 68 \) that readily reacted with different dipolarophiles to afford \( N \)-phenyl-3-(chromon-3-yl)isoxazolidines \( 69-71 \) (Scheme 24).

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). Thus, the alkyl substituents at the nitrogen atom favor the [3+2] cycloaddition of nitrone \( 68 \) to dimethyl acetylenedicarboxylate.
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 PPh3 but additives of PPh3 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 AlCl3-catalyzed reaction of compounds 59 with sodium azide resulted in 3-(1H-tetrazol-5-yl)chromones 74 with antiallergic activity (Scheme 26).86–91

2-Substituted 3-(1H-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.
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(Ciprofloxacin and Fluconazole for bacterial and fungal strains, respectively). 92

Nohara and coworkers 93 synthesized oxadiazole derivatives 75 by refluxing 3-tetrazolyl chromones 74 in Ac2O 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)aryl 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).

2-(Chromon-3-yl)-4-thiazolidinone derivatives 78 (Scheme 28) and 79 were synthesized by successive treatment of compound 1 with aromatic or heterocyclic 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

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 thiobenamide in refluxing toluene to give 3-(5-phenyl-3H-[1,2,4]dithiazol-3-yl)chromones 82. 101 Under these

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**Scheme 26**

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

Reagents and conditions: i. NH2OH • HCl; ii. NaN3, AlCl3; iii. Ac2O, reflux, 1.5 h.

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**Scheme 27**

R1 = H, Cl, NO2; R2 = H, F, Cl, NO2

Reagents and conditions: i. (Het)ArC(O)NHNH2, ii. PhI(OAc)2, CH2Cl2 or Br2, NaOAc, NaOH.

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**Scheme 28**

R1 = H, Me, Cl; R2 = H, Alk, OAlk, Hal

Reagents and conditions: TsOH, benzene, reflux, 9 h or Na2SO4, TsOH, benzene, microwave irradiation (in a sealed tube), 140°C, 5 min.

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**Scheme 29**

79: R1 = H, Me, Cl; R2 = H, Me; R3 = H, Me;

80: R = Me, Ph, 4-MeC6H4, 2-HOC6H4, 4-MeOC6H4, 3-CIC6H4, 4-O2NC6H4, etc.

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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. 3-Aminothiazoles and 2-aminobenzothiazoles in this reaction produced derivatives of imidazo[2,1-b]thiazole and benzo[d]imidazo[2,1-b]thiazole, respectively (see Scheme 30).

The prolonged reflux of a mixture of 2-amino-3-formylchromone, isocyanide, and 2-aminopyridine, 2-aminopyrazine or 2-aminopyrimidine in MeOH in the presence of TsOH/ZnCl2 resulted in derivatives — (Scheme 31).

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, structure of 1,4-dihydropyridine was ascribed to the product of the reaction of compound 1 with ethyl acetoacetate and liquid ammonia in methanol. However, later these acid under microwave irradiation conditions gave imidazo[1,2-α]pyridine isoflavone analogs (Scheme 30). 3-Aminothiazoles and 2-aminobenzothiazoles in this reaction produced derivatives of imidazo[2,1-b]thiazole and benzo[d]imidazo[2,1-b]thiazole, respectively (see Scheme 30).

The prolonged reflux of a mixture of 2-amino-3-formylchromone, isocyanide, and 2-aminopyridine, 2-aminopyrazine or 2-aminopyrimidine in MeOH in the presence of TsOH/ZnCl2 resulted in derivatives (Scheme 31).

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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, structure of 1,4-dihydropyridine was ascribed to the product of the reaction of compound 1 with ethyl acetoacetate and liquid ammonia in methanol. However, later these acid under microwave irradiation conditions gave imidazo[1,2-α]pyridine isoflavone analogs (Scheme 30). 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. 3-Aminothiazoles and 2-aminobenzothiazoles in this reaction produced derivatives of imidazo[2,1-b]thiazole and benzo[d]imidazo[2,1-b]thiazole, respectively (see Scheme 30).

The prolonged reflux of a mixture of 2-amino-3-formylchromone, isocyanide, and 2-aminopyridine, 2-aminopyrazine or 2-aminopyrimidine in MeOH in the presence of TsOH/ZnCl2 resulted in derivatives (Scheme 31).

1.2. Isoflavone hetero analogs with six-membered heterocycles

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results were revised. The structure of the reaction product is determined by the nature of the CH acidic component (Scheme 32). 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.

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 $\text{H}_6\text{P}_2\text{W}_{18}\text{O}_{62}\cdot24\text{H}_2\text{O}$ gave a mixture of the corresponding dihydropyridines 90 and 5-salicyloylpyridines 92.

However, under these conditions the main reaction products were salicyloylpyridines 92. The use of the $\text{Bi}_2\text{WO}_6$ nano particles to catalyze this reaction in aqueous media at room temperature gave rise to dihydropyridine 90 ($R^1 = \text{H}, R^2 = \text{Et}$) in 92% yield. Firuzi and coworkers described the similar reaction of 6(7)-hydroxy-3-formylchromones with $\beta$-ketoesters and ammonium acetate, which in the presence of $\text{Ba(NO}_3\text{)}_2$ as a catalyst in refluxing EtOH gave the corresponding hydroxy derivatives 93.
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 (R1= 7-OAc, R2 = Me, R 3 = Me) with 51.32% enzyme inhibition at 10 μmol L⁻¹.

Gorlitzer and Michels 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 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

\[ \text{Reagents and conditions: } i. \ H_{14}[NaP_{5}W_{29}MoO_{110}] (0.5 \text{ mol.%}), \ 80 ^\circ \text{C}, 30 \text{ min.} \]

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(4H)-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. Derivative 97 was synthesized by the reaction of 6-formylfurochromone 1b, malononitrile, and ammonium acetate.

Unsymmetrical 1,4-dihydropyridines can be obtained by the Hantzsch synthesis using two different dicarbonyl compounds. 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_{5}W_{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

\[ \text{Reagents and conditions: } i. \ H_{14}[NaP_{5}W_{29}MoO_{110}] (0.5 \text{ mol.%}), \ 80 ^\circ \text{C}, 30 \text{ min.} \]

Unsymmetrical 1,4-dihydropyridines can be obtained by the Hantzsch synthesis using two different dicarbonyl compounds. Thus, Arumugam and Perumal successfully synthesized tetrahydroquinoline derivative 98 (in 93% yield) by four-component condensation of 3-formylchromone 1a, dimedone, methyl acetoacetate, and ammonium acetate.
Condensation of 3-formylchromones 1, 2-amino-
chromone as an amine, and dimedone or 1,3-cyclohex-
anedione as a C-nucleophile gave the fused systems, 11-(chromon-3-yl)-8,9-dihydro-6H-chromeno[2,3-b]-
quinolin-10,12(7H,11H)-diones 99 (Scheme 35). 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 that a plausible 
mechanism leading to compounds 99 involved the condensation 
of formylchromones 1 with CH acid (dimedone or 1,3-cyclo-
hexanedione), 1,4-addition of enamine (2-aminochromone) 
to the Knoevenagel adduct, and subsequent cyclization.

Successive treatment of compounds 1 with malono-
itrile and cyanoacetic acid hydrazide gave compounds 100a-c whatever reaction sequence was used (Scheme 36). Diaminodihydropyridines 100 were the starting comp-
ounds 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-formylchro-
mine \( (1, R = 6-\text{Cl}) \), and chromone-3-carboxylic acid 
yielded \( [1,2,4] \)triazolo[1,5-\text{a}]pyridine derivatives 101—103 
(Scheme 37). Synthetic approaches to pyrido[1,2-b][1,2,4]-
triazine derivatives 104—107 are shown in Scheme 38.

Scheme 35

\[
\begin{align*}
1 + \text{CH}_2(\text{CN})_2, \text{H}_2\text{O} & \rightarrow \text{R}^4 \quad \text{O} \\
1 + \text{NCCH}_2(\text{O})\text{NHNH}_2, \text{EtOH} & \rightarrow \text{R}^4 \quad \text{O} \\
\end{align*}
\]

99: \( R^1 = \text{H, Me, Cl, OH}; R^2 = \text{H, Me}; R^3 = \text{Me, H}; R^4 = \text{H, Me, Cl, Br} \)

Scheme 36

\[
\begin{align*}
\text{100a-c (61—77%)} & \\
\end{align*}
\]

100: \( R = \text{H (a), Me (b), Cl (c)} \)

Scheme 37

101: \( R = \text{H (a), Me (b)} \)

Reagents and conditions: \( i \) (for 101a). HCOOEt, pyridine; \( ii \) (for 101b). Ac\(_2\)O; \( iii \) (for 101c). \( R = 6-\text{Cl} \), piperidine; \( iv \). POCl\(_3\); \( v \). FeCl\(_3\), DMSO.
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).

Ali and Ibrahim 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).

Condensation of 2-amino-3-formylchromone 60 with 5-hydroxydopamine gave tetrahydroquinoline isoflavone analog 114. The iodine-catalyzed reaction of compound 1a with tryptamine (the Pictet—Spengler reaction...
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1,2,3,4-tetrahydrocarboline isoflavone analog 115 furnished by the Biginelli reaction. Thus, the three-component condensation of 3-formylchromones 1, urea, and \( \beta \)-ketoesters was used to synthesize a series of (chromonyl)-tetrahydropyrimidines 116-118. To catalyze the Biginelli reaction the following catalysts were used: TsOH, sulfonic acid-functionalized mesoporous silica (MCM-41-SO\(_3\)H), and ionic liquid (triethylammonium hydrosulfate).

Hydrazides 117 were synthesized by heating the corresponding ethyl esters 116 with hydrazine hydrate in the presence of triethylammonium hydrosulfate under solvent-free conditions. 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 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.

Tetrahydropyrimidine isoflavone analogs can be synthesized by the solvent-free Biginelli-type reaction catalyzed by either sulfated silica tungstic acid or TsOH. 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-Formylfurochrome 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.

Reagents and conditions: i. CAN (5 mol. %), MeCN (aqueous), \(-20^\circ\text{C}\); ii. CAN (2.5 equiv.), MeCN, N\(_2\), 0 \({}^\circ\text{C}\), 20 min.

Scheme 40

Scheme 41
1,3-Benzoxazine isoflavone analogs 121 were synthesized in high yields by the reaction of 3-formylchromone 1a and 2-aminobenzyl alcohol in the presence of monochloroacetic acid.\textsuperscript{130,131} The reaction of 3-formylchromone 1a with 1-[2-amino-1-(4-methoxyphenyl)ethyl]cyclohexanol gave spiro derivative 122.\textsuperscript{130}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{121-122}
\caption{121: R = H, Me, Cl}
\end{figure}

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 hydroxysulfate. 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.\textsuperscript{132}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{123a,123b}
\caption{123a,b}
\end{figure}

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\textsuperscript{133} or 2-amino-4,5,6,7-tetrahydrobenzothiophene-3-carboxamide in DMF for 3 h\textsuperscript{134} under aerobic conditions, the initially formed dihydroquinolines are oxidized to give quinazolinones 124 and 125.

The solvent-free Lewis acid-catalyzed reaction of compound 1a, primary aromatic amine, and isatoic anhydride afforded 1H-phenyl-2,3-dihydroquinazolinones 126. Siddiqui and coworkers demonstrated that LaCl\textsubscript{3} supported on nano sized silica (nano-SiO\textsubscript{2}) most efficiently catalyzed this reaction (Scheme 42).\textsuperscript{135}

Four-component condensation between 3-formylchromone 1a, isatoic anhydride, hydrazine, and 2-sulfobenzimidazole that is used as a source of the sulfonamide moiety gave rise to (chromonyl)quinazolinones 127.
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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). The same reaction under basic catalysis conditions gave rise to pyridin-2-one derivatives 130 (Scheme 44).

Acid-catalyzed condensation of 3-formylchromones 1 with 2-aminophenylpyrrole resulted in 4,5-dihydropyrrolo[1,2-a]quinoxaline isoflavone analogs 131 (Scheme 45). Using AcOH as a catalyst, pyrrolo[1,2-a]quinoxaline 131a was obtained in 86% yield. Rashidi et al. 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 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-dihydropyrindolo[1,2-a]quinoxaline 132 in 86% yield (see Scheme 45).

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

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

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

The functionalized pyran isoflavone analogs and were synthesized by three-component reaction involving 3-formylchromone 1a, malononitrile and either di-
medone or β-naphthol in the presence of bismuth tungstate as a catalyst (Scheme 50). Panja et al.\textsuperscript{145} reported the synthesis of 1-(cyclohexyl-imino)pyrano[3,4-\textit{b}]chromones 141. The pyrano[3,4-\textit{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-\textit{b}]chromenediones.\textsuperscript{145}

Scheme 50

\[
\begin{align*}
\text{Reagents and conditions:} & \quad i. \text{Bi}_2\text{WO}_6 (5 \text{ equiv.}), \text{H}_2\text{O}, \sim 20 ^\circ \text{C}, 10 \text{ min.}
\end{align*}
\]

Scheme 51

\[
\begin{align*}
\text{Cy is cyclohexyl.} \\
R^1 = \text{H, Me, Cl}; R^2 = \text{H, OH}
\end{align*}
\]

\[
\text{Reagents and conditions:} & \quad i. \text{cyclo-C}_6\text{H}_{11}\text{NC}, \text{MeCN}, \text{reflux, 30 min}; ii. \text{HCl (cat.)}, \text{EtOH}, \text{heating, 2 h.}
\]

Scheme 52

\[
\begin{align*}
\text{Reagents and conditions:} & \quad i. \text{THF, } \sim 20 ^\circ \text{C}; ii. \text{CuBr}_2, \text{DMSO, microwave irradiation}; iii. \text{SeO}_2, 3\text{-methylbutan-1-ol, reflux, 48 h.}
\end{align*}
\]

145: R^1 = Me, Cl; R^2 = H, Cl, Br, NO\textsubscript{2}; R^3 = H, Me, Cl, Br, NH\textsubscript{2}
146: R^1, R^2 = H, Me; R^3 = H, Me, OMe
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 CuBr₂ 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 isooamyl alcohol (Scheme 52).148

Gabr and coworkers149 demonstrated that the product of condensation of 6-chloro-3-formylchromone with 4-acetyl-5,6-diphenylpyridazin-3(2H)-one in the presence of piperidine underwent similar cyclization to give compound 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-1H-benzo[b][1,4]diazepin-2-yl)-4H-chromen-4-ones 150151,152 and 3-(4-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-2-yl)-4H-chromen-4-ones 150152,153 (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-4H-chromen-3-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl]-2H-chromen-2-ones 151.154 The use of dimerone as a CH acidic component gave rise to the fused 3,3-dimethyl-11-(4-oxo-4H-chromen-3-yl)-2,3,4,5,10,11-hexahydro-1H-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.

![Scheme 53](image-url)
chloride 154 (synthesized by the reaction of SOCl₂ with DMF in anhydrous benzene) with methanesulfonic acid and triethylamine in anhydrous CH₂Cl₂ reacted with nitrone 68 to give 3-(2,2-dioxido-4,5-dihydro-3H-benzo-[f][1,2,5]oxathiazepin-4-yl)-4H-chromen-4-one 153 (Scheme 54).

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 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]-4H-chromen-4-ones is the reaction of nucleophilic (π-rich) heterocycles (indoles, pyrroles) with 3-formylchromones.

Thus, Sosnovskikh and coworkers described the synthesis of 3-[di(1H-indol-3-yl)methyl]-4H-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%).

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 156a was synthesized in butanol in the presence of perchloric acid as a catalyst. Product 156j was prepared by heating the corresponding reagents in aqueous medium. Compounds 156 were synthesized but in lower yields using 1 equiv. of indoles.

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 or in MeCN in the presence of the catalysts (10 mol.% of the complex of 3-(diphenylphosphino)benzenesulfonic acid sodium salt (TPPMS) with CBr₄, [CuCl₂(py)₂], and 5 mol.% of Yb(OTf)₃).

The reaction of 6,8-dibromo-3-formylchromone (1c) even with excess (3 equiv.) of indole gave only 3-[(1H-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).

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

Catalyst- and solvent-free reaction of N-methylpyrrolo with 3-formylchromones 1 proceeded exclusively as nucleophilic 1,4-addition (1,4-AN) to afford 2-hydroxy-3-[1-methyl-1H-pyrrolo-2-yl]methylenechroman-4-ones 160. Note that plausible 1,2-addition (1,2-AN) does not


Scheme 57

3-Formylchromones 1 reacted with pyrrole in the presence of trifluoroacetic acid as a catalyst to give 3-[di-(1H-pyrrol-2-yl)methyl]-4H-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-1H-indol-3-yl)(6-fluoro-4-oxo-4H-chromen-3-yl)methyl]-4-hydroxy-2H-chromen-2-one (162).162 Microwave-assisted indium triflate-catalyzed reaction of 3-formylchromone 1a, substituted indoles, and anilines gave rise to 3-[(1H-indol-3-yl)(arylamino)methyl]-4H-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 Pratap and coworkers167 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.

The four-component condensation of 3-formylchromones 1, anilines, isocyanides, and azidotrimethylsilane...
(the azido-Ugi reaction) gave 3-[(arylamino)(1H-tetrazol-5-yl)methyl]-4H-chromen-4-ones 164 (Scheme 58).\textsuperscript{168,169}

Compounds 164 show antiprotozoal activity against *Entamoeba histolytica*, *Giardia lamblia*, and *Trichomonas 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.\textsuperscript{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.\textsuperscript{169}

Mehrparvar *et al.*\textsuperscript{170} demonstrated the possibility to introduce the carbonyl group into the (chromonyl)hetaryl-methane 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

\[
\begin{align*}
\text{R}^1 &= \text{H, F; R}^2 = \text{H, Br, I, NO}_2; \text{R}^3 = \text{H, OMe; R}^4 = \text{H, Cl, I, OMe, NO}_2; \text{R}^5 = \text{H, OMe; R}^6 = \text{Bu', cyclo-C}_6\text{H}_{11}, 2,6-\text{Me}_2\text{C}_6\text{H}_3 \\
\text{Reagents and conditions: } &\text{InCl}_3 (5 \text{ mol.\%}), \text{propan-2-ol (anhydrous), } \sim 20 \text{ °C, 2 h.}
\end{align*}
\]

### Scheme 59

\[
\begin{align*}
\text{R}^1 &= \text{H, Cl, Br; R}^2 = \text{Me, Et, Pr} \\
\text{Z} &= (10), (11) \\
\text{Reagents and conditions: } &\text{i. Et}_3\text{N (50 mol.\%), R}^2\text{OH—H}_2\text{O (1 : 1), } 60 \text{ °C, 6 h; ii. Et}_3\text{N (50 mol.\%), propan-2-ol—H}_2\text{O (1 : 1), } 60 \text{ °C, 6 h.}
\end{align*}
\]
This difference in the structure of the products Mehrparvar et al.\textsuperscript{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 Knoevenagel 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.\textsuperscript{170}

3-[(2-Oxo-5-arylfuran-3(2H)-ylidene)methyl]-4H-chromen-4-ones 167a—d were synthesized by the reaction of 3-formylchromones 1 with β-aroylpropionic acids, and (chlorosulfonyloxy)-N,N-dimethylmethaniminium chloride (154) (Scheme 60).\textsuperscript{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 was obtained. The reaction of compound 167d with phenylhydrazine afforded chromylidene pyridazinone derivative 171 (see Scheme 60).\textsuperscript{172}

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

Venkateswararao et al.\textsuperscript{173} used enones 148 as the starting material for the synthesis of 3,3’-methylenebis(4H-chromen-4-ones) 174 and 3-[(4-oxochroman-3-yl)methyl]-4H-chromen-4-one 175 (Scheme 61). Enones 148 were prepared by the reaction of 3-formylchromones 1 with 1-[2-(benzilxy)phenyl]-2-(triphenylphosphoranyliden)eethanones. 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 (R1 = R2 = H) are the main products of the reaction of 3-formylchromone 1a with iron pentacarbonyl (2 equiv.) and hexamethapal (4 equiv.).\textsuperscript{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.\textsuperscript{173} It was found that the most active compounds contain cyclohexylmethylx 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

\begin{center}
\includegraphics[width=\textwidth]{Scheme60.png}
\end{center}

\textbf{Reagents and conditions:} \textit{i.} 1) CH2Cl2, 0 °C, 2) Et3N, ~20 °C, 5 h; \textit{ii.} AcONH4 (4 equiv.), EtOH (anhydrous), reflux, 2 h; \textit{iii.} NH2NH2·H2O, benzene, reflux, 2 h; \textit{iv.} NH2NH2·H2O (2 equiv.), EtOH (anhydrous), ~20 °C, 4 h or reflux, 1 h; \textit{v.} PhNH2NH2, EtOH (anhydrous), reflux, 30 min.
double bond in one of the chromone moieties decreased the activity.\textsuperscript{173}

\[ 2\text{-aryl- and alkylamino-substituted 3,3\textquotesingle-methylenebis[2-aryl(alkyl)amino-4H-chromen-4-ones]} \]

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).\textsuperscript{175} Condensation of 3-formylchromones 1 (R = H, Br) and 2-amino-3-formylchromones (60) with chromanone in EtOH in the presence of piperidine or diethylamine.\textsuperscript{175} Compounds (and especially 2-amino derivatives) binds with calf thymus DNA presumably by intercalation. Amino derivative (R\textsuperscript{1} = H, R\textsuperscript{2} = NH\textsubscript{2}) also efficiently inhibit acetylcholinesterase being only slightly inferior to reference drug Tacrine.\textsuperscript{176}

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

Condensation of 3-formylchromones 1 with benzoferan-2-ones, benzoferan-3-ones, naphthofuran-2-ones, and naphthofuran-3-ones produced the corresponding derivatives 180—183 that can be regarded as chromone-based aurone analogs.\textsuperscript{178} Anticancer activity of compounds 180—183 was tested \textit{in vitro} against the murine L1210 leukemia cell line. Compound 183 (R = H) was found to be most active with IC\textsubscript{50} = 1.6 µmol L\textsuperscript{-1}.\textsuperscript{178} Among the synthetic aurone analogs evaluated against K562 chronic myeloid leukemia cells, derivative 181 (R\textsuperscript{1} = 6-Me, R\textsuperscript{2} = Me) was found the most active. Compound 181 at a concentration of 50 µmol L\textsuperscript{-1} blocked
the K562 cell cycle in G1 phase and induced about 24% apoptosis. The replacement of the chromone moiety with coumarin core afforded compounds capable of blocking the cell cycle in G2 phase.

The (Z)-3-[(4-oxo-4H-chromen-3-yl)methylene]indolin-2-one derivatives were synthesized by condensation of 3-formylchromones 1 with indolinones. Compound showed pronounced anticancer activity inhibiting growth of 60 human cancer cell lines with the average GI50 values of 3.2 μmol L−1. Compounds were found to be selective inhibitors of cyclooxygenase-2 (IC50 of 29—20 μmol L−1, selectivity indices of 46 and 337, respectively). Compound exhibited an analgesic potential higher than Diclofenac.

Condensation of 3-formylchromone 1a with hydantoin, thiohydantoin, and thiazolidin-2,4-diones gave derivatives 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. Dundar and coworkers 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 and alkylated at the N(3) nitrogen atom and thioxo group were also synthesized.
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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\(H\)-azolidine-2,4-diones 188 and chromanones 189 as the by-products.\(^{184}\)

Compounds 188 are the agonists of PPAR-\(\gamma\) 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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The authors declare no competing interests.

References

1. The Handbook of Medicinal Chemistry: Principles and Practice, Eds A. Davis, S. E. Ward, Royal Society of Chemistry, Cambridge, 2015, 753 pp.
2. R. Barret, Medicinal Chemistry. Fundamentals, Elsevier, London, 2018, 172 pp.
3. T. K. Bagavieva, S. E. Yagunov, S. V. Kholshin, A. E. Prosenko, Russ. Chem. Bull., 2019, 68, 194; DOI: 10.1007/s11172-019-2438-y.
4. T. K. Bagavieva, S. E. Yagunov, S. V. Kholshin, I. A. Emelyanova, O. I. Prosenko, A. E. Prosenko, Russ. Chem. Bull., 2019, 68, 2283; DOI: 10.1007/s11172-019-2701-2.
5. S. Alseekh, L. Perez de Souza, M. Benina, A. R. Fernie, Phytochemistry, 2020, 174, 112347; DOI: 10.1016/j.phytochem.2020.112347.
6. A. Ahmad, M. Kaleem, Z. Ahmed, H. Shafiq, Food Res. Int., 2015, 77, 221; DOI: 10.1016/j.foodres.2015.06.021.
7. D. Raffa, B. Maggio, M. V. Raimondi, F. Plescia, G. Daidone, Eur. J. Med. Chem., 2017, 142, 213; DOI: 10.1016/j.ejmech.2017.07.034.
8. F. Perez-Vizcaíno, C. G. Fraga, Arch. Biochem. Biophys., 2018, 646, 107; DOI: 10.1016/j.abb.2018.03.022.
9. A. Lichota, L. Gwozdzinski, K. Gwozdzinski, Eur. J. Med. Chem., 2019, 176, 68; DOI: 10.1016/j.ejmech.2019.04.075.
10. F. F. de Araújo, D. de Paulo Farias, I. A. Neri-Numa, Eur. J. Med. Chem., 2020, 127535; DOI: 10.1016/j.ejmech.2020.127535.
11. Y. C. Loh, S. Y. Chan, W. Y. Tew, C. W. Oo, M. F. Yam, Life Sci., 2020, 249, 117512; DOI: 10.1016/j.lfs.2020.117512.
12. M. Russo, S. Mocci, C. Spagnuolo, I. Tedesco, G. L. Russo, Chem. Biol. Interact., 2020, 109211; DOI: 10.1016/j.cbi.2020.109211.
13. A. D. S. Antonio, L. M. S. Wiedemann, V. F. Veiga-Junior, RSC Adv., 2020, 10, 23379; DOI: 10.1039/D0RA03774E.
14. P. Sestili, V. Stocchi, Front. Pharmacol., 2020, 11, 1; DOI: 10.3389/fphar.2020.00854.
15. M. S. Frasinyuk, V. P. Khilya, Chem. Heterocycl. Compd., 1999, 35, 3; DOI: 10.1007/BF02251655.
16. A. L. Kazakov, V. P. Khilya, V. V. Mezerhistskii, in Prirodnye i modifitsirovannye isoflavonoidy [Natural and Chemically Modified Isoflavonoids], Izd-vo Rostov Univ., Rostov-on-Don, 1985, p. 184 (in Russian).
17. Spravochnik lekarstvennykh sredstv Vidal [Vidal Drug Information System]; https://www.vidal.ru/drugs/menoril (date of access 10.04.2021) (in Russian).
18. Regist lekarstvennykh sredstv Rossii [Register of Medicines of Russia]; https://www.tslnet.ru/mmm_index_id_2581.htm (date of access 10.04.2021) (in Russian).
19. P. Sophors, Y. M. Kim, G. Y. Seo, J.-S. Huh, Y. Lim, D. S. Koh, M. Cho, Biochem. Biophys. Res. Commun., 2016, 472, 332; DOI: 10.1016/j.bbr.2016.02.106.
20. A. Singh, D. Bimal, R. Kumar, V. K. Maikhuri, M. Thirumal, N. N. Senapati, A. K. Prasad, Synth. Commun., 2018, 48, 2339; DOI: 10.1080/00397911.2018.1480041.
21. V. Nalla, A. Shaikh, P. R. Vyas, M. Karthikeyan, P. Yogeeswari, D. Siriam, M. Muthukrishnan, R. Soc. Open Sci., 2018, 5, 171750; DOI: 10.1098/rsos.171750.
22. S. Sepúlveda-Boza, G. H. Walizei, M. C. Rezende, Y. Vasquez, C. Mascayano, L. Mejías, Sci., 2018, 5, 2018, DOI: 10.1016/j.bbrc.2016.02.106.
23. V. P. Khilya, V. V. Ishchenko, in Izbrannye metody sintesa i modificatsii geterocyclov [Selected Methods of Synthesis and Modification of Heterocycles], Ed. V. G. Kartsev, IBS PRESS, Moscow, 2003, Vol. 2, p. 503 (in Russian).
24. M. Selepe, F. Van Heerden, Molecules, 2013, 18, 4739; DOI: 10.3390/molecules18044739.
25. Q. Yang, Z. Zhang, B. Liang, Molecules, 2020, 25, 1564; DOI: 10.3390/molecules25071564.
26. A. Kumar, G. Tripathi, M. L. N. Rao, in Access to Flavonoids through Cross-Coupling Reactions, LAP LAMBERT Acad. Publ., 2016, 228 pp.
27. J. Wan, Z. Tu, Y. Wang, Chem. — Eur. J., 2019, 25, 6907; DOI: 10.1002/chem.201901025.
28. C. K. Ghosh, J. Heterocycl. Chem., 1983, 20, 1437; DOI: 10.1002/jhet.5570200601.
29. C. K. Ghosh, A. Patra, J. Heterocycl. Chem., 2008, 45, 1529; DOI: 10.1002/jhet.5570450601.
30. C. K. Ghosh, A. Chakraborty, Arkivoc, 2015, Part vi, 288; DOI: 10.3998/ark.5550190.p009.020.
31. G. Sabitha, Aldrichimica Acta, 1996, 29, 15.
32. G. M. Ziarani, P. Mohatehnia, F. Mohajer, R. Moradi, Heterocycles, 2020, 100, 993; DOI: 10.3987/REV-20-926.
33. A. S. Plaskon, O. O. Grygorenko, S. V. Ryabukhin, Tetrahedron, 2012, 68, 2743; DOI: 10.1016/j.tet.2012.01.077.
34. C. K. Ghosh, S. K. Karak, J. Heterocycl. Chem., 2005, 42, 1035; DOI: 10.1002/jhet.5570420601.
35. C. K. Ghosh, A. Chakraborty, Arkivoc, 2015, Part vi, 417; DOI: 10.3998/ark.5550190.p009.273.
36. C. K. Ghosh, A. Chakraborty, Arkivoc, 2016, Part i, 375; DOI: 10.3998/ark.5550190.p009.712.
37. M. A. Terzidis, J. Stephanidou-Stephanatou, C. A. Tsoleridis, J. Org. Chem., 2010, 75, 1948; DOI: 10.1021/jo902072j.
38. B. V. S. Reddy, D. Somashekar, A. M. Reddy, J. S. Yadav, B. Sridhar, Synthesis, 2010, 2069; DOI: 10.1055/s-0030-1218762.
39. M. B. Teimouri, F. Mashayekhi, E. Alishaie, J. Iran. Chem. Soc., 2016, 13, 583; DOI: 10.1007/s13738-015-0769-7.
40. A. Meydani, S. Yousef, R. Gharibi, S. Kazemi, M. B. Teimouri, ChemistrySelect, 2019, 4, 3315; DOI: 10.1002/slct.201900009.
41. N. M. Fawzy, A. M. Nasef, A. M. Soliman, M. S. Aly, Chem. Res., 2017, 2, 293; http://chemjr.org/download/vol-2-iss-5-2017/chemjr-2017-02-05-293-308.pdf.
42. M. Teimouri, B. Asnaashari, M. Moayedi, S. Naderi, Synlett, 2014, 26, 101; DOI: 10.1055/s-0034-1378926.
Heterocyclic analogs of isoflavonoids

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167. D. Prajapati, S. Gadhwal, R. Sarma, Lett. Org. Chem., 2008, 5, 365; DOI: 10.2174/157017808784872133.
168. P. A. Cano, A. Islas-Jacome, J. Gonzalez-Marrero, L. Ypez-Mulia, F. Calzada, R. Gmez-Monta, Bioorg. Med. Chem., 2014, 22, 1370; DOI: 10.1016/j.bmc.2013.12.069.
169. P. A. Cano, A. Islas-Jacome, A. Rangel-Serrano, F. Anaya-Velazquez, F. Padilla-Vaca, E. Trujillo-Esquivel, P. Ponce-Noyola, A. Martnez-Richa, R. Gmez-Monta, Molecules, 2015, 20, 12436; DOI: 10.3390/molecules200712436.
170. S. Mehrparvar, S. Balalaie, M. Rabbanzadeh, F. Rominger, E. Ghabraie, Org. Biomol. Chem., 2014, 12, 5757; DOI: 10.1039/c4ob00618f.
171. A. K. El-Ziaty, W. S. I. Abou-Elmagd, S. K. Ramadan, A. I. Hashem, Egypt. J. Chem., 2016, 59, 637; DOI: 10.21608/ ejchem.2016.1440.
172. A. K. El-Ziaty, W. S. I. Abou-Elmagd, S. K. Ramadan, A. I. Hashem, Synth. Commun., 2017, 47, 471; DOI: 10.1080/ 00397911.2016.1271896.
173. E. Venkateswarao, V. K. Sharma, M. Manickam, J. Yun, S.-H. Jung, Bioorg. Med. Chem. Lett., 2014, 24, 5256; DOI: 10.1016/j.bmcl.2014.09.057.
174. A. A. Ambartsumyan, T. T. Vasil’eva, O. V. Chakhovskaya, N. E. Mysova, V. A. Tuskaev, V. N. Khustalev, K. A. Kochetkov, Russ. J. Org. Chem., 2012, 48, 451; DOI: 10.1134/ S1070428012030207.
175. S. Maiti, S. K. Panja, C. Bandyopadhyay, Tetrahedron Lett., 2009, 50, 3966; DOI: 10.1016/j.tetlet.2009.04.087.
176. M. Parveen, A. M. Malla, Z. Yaseen, A. Ali, M. Alam, J. Photochem. Photobiol., B, 2014, 130, 179; DOI: 10.1016/j.jphotobiol.2013.11.019.
177. M. A. Ibrahim, H. M. Hassanin, Y. A.-A. Gabr, Y. A.-S. Alnamer, Eur. J. Chem., 2010, 1, 195; DOI: 10.5155/ eurjchem.1.3.195-199.91.