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3-PHENOXYCHROMONES: NATURAL DISTRIBUTION, SYNTHETIC AND MODIFICATION METHODS, BIOLOGICAL PROPERTIES

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The literature on the natural distribution, synthetic and chemical transformation methods, and pharmacological properties of 3-phenoxychromones were reviewed.

Key words: flavonoids, 3-phenoxychromones, Fabaceae, synthesis, modification.

Flavonoids are one of the most widely distributed groups of phenolic compounds that have C_6-C_3-C_6 structural fragment in common. The flavonoid molecule consists of two phenyl rings joined by a three-carbon aliphatic chain. Most flavonoids can be viewed as chromone or chromane derivatives that contain aryl radicals in the 2-, 3-, or 4-position.

Compounds in which the aryl substituent is bonded to the chromone nucleus through an O atom and that are called phenoxychromones are sometimes encountered among the natural flavonoids. The phenoxyl substituent can be located in the 2- or 3-position of the chromone system. Derivatives of 3-aryloxychromone with structures close to those of isoflavones are interesting because they have a variety of pharmacological properties.

Although such compounds are certainly interesting, reviews of synthetic methods and chemical and pharmacological properties have not appeared.

1. NATURAL DISTRIBUTION

Compounds based on both 2- and 3-phenoxychromone have been isolated from natural sources. Such unusual flavonoids have been isolated from plants of various families. Thus, 2-phenoxychromones are produced by plants of the Compositae [1, 2], Rosaceae [3, 4], Berberidaceae [5], Caesalpiniaceae [6], and Fabaceae [7] families. Reports of 3-aryloxychromones isolated from natural sources are much less common. In contrast with 2-phenoxychromones, derivatives of 3-phenoxychromone are rarely encountered secondary metabolites and are synthesized only by plants of the Fabaceae family. At present only five comopunds based on the 3-phenoxychromone skeleton have been isolated from natural sources.

Glyasperin E (**1**) was the first natural 3-phenoxychromone to be isolated and was a minor component from *Glycyrrhiza aspera* (Fabaceae) roots. It is widely used in Chinese folk medicine [8, 9]. Extracts of *Erythrina variegata* (Fabaceae) roots contained two derivatives of 3-phenoxychromone, eryvarins F (**2**) and G (**3**) [10].

The 3-phenoxychromone skeleton provides the basis for (-)-13-*homo*-13-oxa-6a,12a-dehydrorotenone (**4**) and 13-*homo*-13-oxa-6a,12a-dehydrodeguelin (**5**), which were isolated from *Lonchocarpus utilis* and *L. urucu* (Fabaceae) root resin that has insecticidal activity and have structures similar to rotenoids [11].

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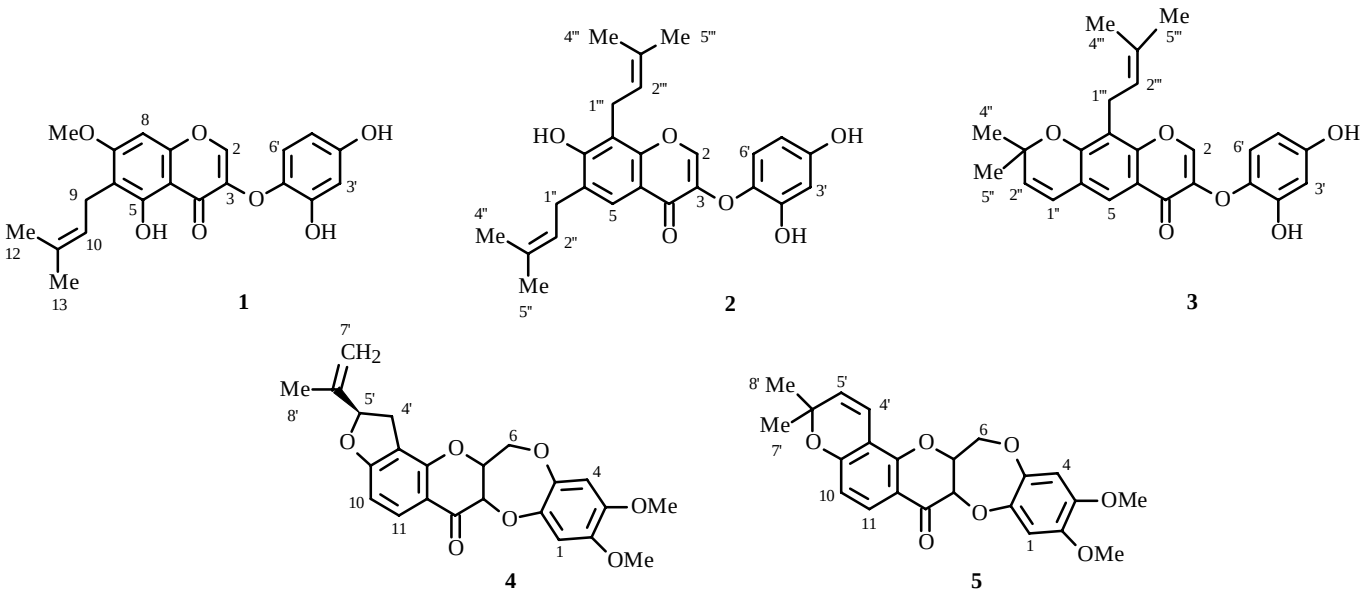


The physicochemical constants of 3-phenoxychromones isolated from plants are given below.

1. Glyasperin E

Glycyrrhiza aspera [8].

$C_{21}H_{20}O_7$, mp 166-167°C (hexane:acetone) [8].

UV spectrum (MeOH) [8]: 234 (4.54), 254 (4.64), 262 (4.62), 296 (4.29), 335 (3.82); (MeOH + $AlCl_3$) [8]: 273 (4.69), 318 (4.31), 381 (3.89); (MeOH + AcONa) [8]: 257 (4.68), 296 (4.34), 338 (3.82); (MeOH + MeONa) [8]: 374 (4.96), 382 (3.89).

Mass spectrum [8]: 385 (26), 384 (100) $[M]^+$, 369 (11), 341 (76), 330 (15), 329 (73), 328 (13), 311 (18), 297 (6), 275 (7), 260 (14), 259 (61), 245 (11), 233 (12), 232 (15), 217 (11), 203 (10), 179 (20), 150 (10), 110 (16), 97 (10), 69 (12). HRMS [8]: 384.1227.

PMR spectrum [400 MHz, $(CD_3)_2CO$, J/Hz) [8]: 1.63 (3H, s, CH_3-13), 1.76 (3H, s, CH_3-12), 3.33 (2H, br. d, CH_2-9), 3.98 (3H, s, OCH_3-7), 5.18 (1H, br. t, H-10), 6.29 (1H, dd, J = 2, 8, H-5′), 6.49 (1H, d, J = 2, H-3′), 6.68 (1H, s, H-8), 7.02 (1H, d, J = 8, H-6′), 8.32 (1H, br. s, OH-2′), 8.67 (1H, br. s, OH-4′), 8.39 (1H, s, H-2), 12.35 (1H, s, OH-5), NOESY [8].

^{13}C NMR spectrum [100 MHz, $(CD_3)_2CO$] [8]: 149.16 (C-2), 142.89 (C-3), 178.54 (C-4), 106.85 (C-4a), 158.77 (C-5), 113.43 (C-6), 164.77 (C-7), 91.15 (C-8), 157.31 (C-8a), 21.92 (C-9), 122.68 (C-10), 132.08 (C-11), 17.85 (C-12), 25.85 (C-13), 139.01 (C-1′), 150.70 (C-2′), 105.17 (C-3′), 156.29 (C-4′), 107.35 (C-5′), 121.43 (C-6′), 56.79 (OCH_3).

2. Eryvarin F

Erythrina variegata [10]

$C_{25}H_{26}O_6$

UV spectrum (MeOH) [10]: 203 (4.56), 246 (4.34), 288 (3.97), 309 (4.07).

IR spectrum (KBr) [10]: 3400, 1630, 1600.

EIMS [10]: 422 (100) $[M]^+$, 405 (9), 351 (8), 273 (15), 227 (9), 217 (13), 173 (10), 161 (18), 150 (11). HREIMS [10]: 422.1725.

PMR spectrum (600 MHz, $CDCl_3$, J/Hz) [10]: 1.75 (3H, s, CH_3-5‴), 1.77 (3H, s, CH_3-4″), 1.79 (3H, s, CH_3-5″), 1.85 (3H, s, CH_3-4‴), 3.41 (2H, d, J = 7.3, CH_2-1″), 3.59 (2H, d, J = 7.3, CH_2-1‴), 5.08 (1H, br. s, OH), 5.21 (1H, t, J = 7.3, H-2‴), 5.29 (1H, t, J = 7.3, H-2″), 6.28 (1H, dd, J = 2.9, 8.8, H-8′), 6.29 (1H, br. s, OH), 6.51 (1H, d, J = 2.9, H-3′), 6.96 (1H, d, J = 8.8, H-6′), 7.90 (1H, s, H-5), 8.27 (1H, s, H-2), 9.48 (1H, br. s, OH).

HMBC, NOESY [10].

^{13}C NMR spectrum (150 MHz, $CDCl_3$) [10]: 148.5 (C-2), 144.0 (C-3), 175.4 (C-4), 123.9 (C-5), 127.2 (C-6), 158.5 (C-7), 114.8 (C-8), 154.2 (C-9), 117.3 (C-10), 140.2 (C-1′), 150.3 (C-2′), 105.5 (C-3′), 154.0 (C-4′), 106.7 (C-5′), 121.7 (C-6′), 29.5 (C-1″), 120.2* (C-2″), 136.2 (C-3″), 17.9** (C-4″), 25.8 (C-5″), 22.3 (C-1‴), 120.4* (C-2‴), 135.6 (C-3‴), 18.0** (C-4‴), 25.8 (C-5‴).

3. Eryvarin G

Erythrina variegata [10]

$C_{25}H_{24}O_6$

UV spectrum (MeOH) [10]: 204 (4.55), 268 (4.46), 331 (3.88), 346 (3.83).

IR spectrum (KBr) [10]: 3500, 1630, 1600.

EIMS [10]: 420 (81) $[M]^+$, 405 (100), 349 (12), 281 (15), 255 (20), 187 (10). HREIMS [10]: 420.1567.

PMR spectrum (600 MHz, $CDCl_3$, J/Hz) [10]: 1.47 (6H, s, CH_3-4‴, CH_3-5″), 1.68 (3H, s, CH_3-5‴), 1.82 (3H, s, CH_3-4‴), 3.49 (2H, d, J = 7.3, CH_2-1‴), 4.99 (1H, br. s, OH), 5.15 (1H, t, J = 7.3, H-2‴), 5.77 (1H, d, J = 9.5, H-2″), 6.29 (1H, dd, J = 2.9, 8.8, H-8′), 6.41 (1H, d, J = 9.5, H-1″), 6.50 (1H, d, J = 2.9, H-3′), 6.97 (1H, d, J = 8.8, H-6′), 7.73 (1H, s, H-5), 8.26 (1H, s, H-2), 9.52 (1H, br. s, OH). HMBC, NOESY [10].

^{13}C NMR spectrum (150 MHz, $CDCl_3$) [10]: 148.5 (C-2), 144.0 (C-3), 175.3 (C-4), 120.4 (C-5), 120.0 (C-6), 156.1 (C-7), 117.2 (C-8), 155.5 (C-9), 117.6 (C-10), 140.3 (C-1′), 150.4 (C-2′), 105.5 (C-3′), 154.0 (C-4′), 106.6 (C-5′), 121.8 (C-6′), 121.5 (C-1″), 132.2 (C-2″), 78.1 (C-3″), 28.4 (C-4″), 28.4 (C-5″), 21.9 (C-1‴), 120.8 (C-2‴), 132.6 (C-3‴), 18.0 (C-4‴), 25.7 (C-5‴).

4. (-)-13-*Homo*-13-oxa-6a,12a-dehydrorotenone

Lonchocarpus utilis and *L. urucu* [11]

$C_{23}H_{20}O_7$, mp 159-160°C (hexane:ethylacetate) [11]

$[\alpha]_D$ -38.1° (*c* 1.33, $CHCl_3$) [11]

UV spectrum (MeOH) [11]: 256, 300.

EIMS [11]: 408 (100) $[M]^+$, 393 (7) $[M - 15]^+$, 365 (25) $[M - 43]^+$, 206 (12), 161 (21), 187 (29), 178 (19).

PMR spectrum (300 MHz, $CDCl_3$, J/Hz) [11]: 1.79 (3H, s, CH_3-8′), 3.15 (1H, dd, J = 7.9, 15.8, CH_2-4′α), 3.49 (1H, dd, J = 9.9, 15.8, CH_2-4′β), 3.84 (6H, s, OCH_3-2, OCH_3-3), 4.97 (1H, s, CH_2-7′α), 5.08 (2H, s, CH_2-6), 5.12 (1H, s, CH_2-7′β), 5.39 (1H, dd, J = 7.9, 9.9, H-5′), 6.63 (1H, s, H-4), 6.88 (1H, d, J = 8.6, H-10), 6.93 (1H, s, H-1), 8.12 (1H, d, J = 8.6, H-11).

XSA [11]

^{13}C NMR spectrum (75 MHz, $CDCl_3$) [11]: 117.9 (C-1), 150.3 (C-1a), 145.4 (C-2), 145.8 (C-3), 104.7 (C-4), 142.0 (C-4a), 69.5 (C-6), 142.4 (C-6a), 152.1 (C-7a), 112.6 (C-8), 165.0 (C-9), 108.5 (C-10), 127.9 (C-11), 105.4 (C-11a), 171.7 (C-12), 140.5 (C-12a), 31.4 (C-4′), 87.8 (C-5′), 142.7 (C-6′), 112.9 (C-7′), 17.0 (C-8′), 56.3 (OCH_3-2), 56.3 (OCH_3-3).

5. 13-*Homo*-13-oxa-6a,12a-dehydrodeguelin

Lonchocarpus utilis and *L. urucu* [11]

$C_{23}H_{20}O_7$, mp 216-217°C ($CHCl_3$:acetone) [11]

UV spectrum (MeOH) [11]: 264, 295, 322.

EIMS [11]: 408 (100) $[M]^+$, 393 (17) $[M - 15]^+$, 365 (12) $[M - 43]^+$, 206 (6), 191 (6), 187 (36), 178 (3).

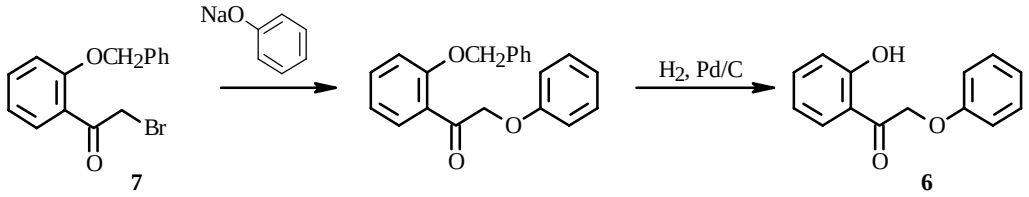
PMR spectrum (300 MHz, $CDCl_3$, J/Hz) [11]: 1.43 (6H, s, CH_3-7′, CH_3-8′), 3.85 (6H, s, OCH_3-2, OCH_3-3), 5.11 (2H, s, CH_2-6), 5.71 (1H, d, J = 10.1, H-5′), 6.64 (1H, s, H-4), 6.72 (1H, d, J = 10.1, H-4′), 6.84 (1H, d, J = 9.8, H-10), 6.94 (1H, s, H-1), 8.04 (1H, d, J = 9.8, H-11).

^{13}C NMR spectrum (75 MHz, $CDCl_3$) [11]: 117.4 (C-1), 150.4 (C-1a), 145.5 (C-2), 145.8 (C-3), 104.7 (C-4), 142.0 (C-4a), 69.5 (C-6), 142.4 (C-6a), 150.8 (C-7a), 108.8 (C-8), 157.4 (C-9), 114.5 (C-10), 126.4 (C-11), 105.4 (C-11a), 171.7 (C-12), 140.5 (C-12a), 115.1 (C-4′), 130.3 (C-5′), 77.8 (C-6′), 28.1 (C-7′), 28.1 (C-8′), 56.3 (OCH_3-2), 56.3 (OCH_3-3).

2. METHODS FOR SYNTHESIZING 3-PHENOXYCHROMONES

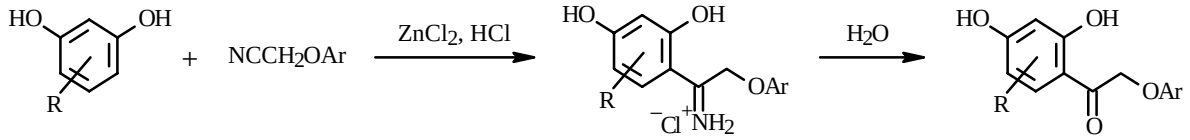
The classical method for synthesizing 3-phenoxychromones is based on C-formylation or C-acylation at the methylene group of precursors, substituted 2′-hydroxy-2-phenoxyacetophenones, with subsequent cyclization. Many syntheses of 3-phenoxychromones are based on this principle and use various formylating and acylating agents. On the one hand, this is due to the availability of the starting aryloxyacetophenones; on the other, to the simplicity of converting these synthons to the desired 3-phenoxychromones.

Thus, it is advisable first to examine the principal preparative methods for synthesizing 2-hydroxy-α-aryloxyacetophenones, key intermediates in the synthesis of 3-phenoxychromones. The most simple 2′-hydroxy-2-phenoxyacetophenone (**6**) was prepared by alkylating sodium phenoxide with the appropriate phenacylbromide **7** with subsequent removal of the protecting benzyl group using hydrogen [12].



7 **6**

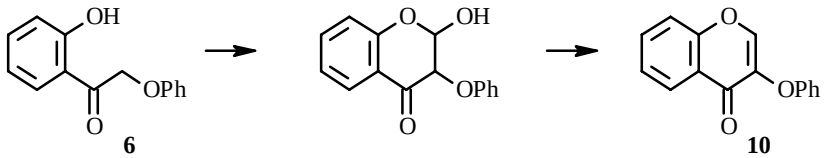
The most convenient method for synthesizing α-phenoxy-2-hydroxyacetophenone derivatives is based on the Houben—Hoesch reaction [13]. 2′-Hydroxy-2-phenoxyacetophenones **9** were prepared by condensation of the corresponding aryloxyacetonitriles with polyphenols (resorcinol, 2-methylresorcinol, 4-ethylresorcinol, phloroglucinol, etc.) in benzene:ether in the presence of anhydrous $ZnCl_2$ and dry HCl with subsequent acidolysis of the resulting ketimine hydrochloride **8** [8, 14-19]. Using this approach, various α-phenoxy-2-hydroxyacetophenones containing substituents in both the phenol and aryloxy fragments were prepared.



8 **9**

3-Aryloxychromones were formed from the corresponding 2-hydroxy-α-aryloxyacetophenones via formylation or other methods and subsequent heterocyclization of the intermediate. The methods known today for preparing 3-phenoxychromones from α-phenoxy-2-hydroxyacetophenones can be divided into two main groups. The first is based on cyclization of 2-hydroxyacetophenones using derivatives of carboxylic acids in the presence of bases; the second, on heterocyclization of ketones under acid-catalysis conditions.

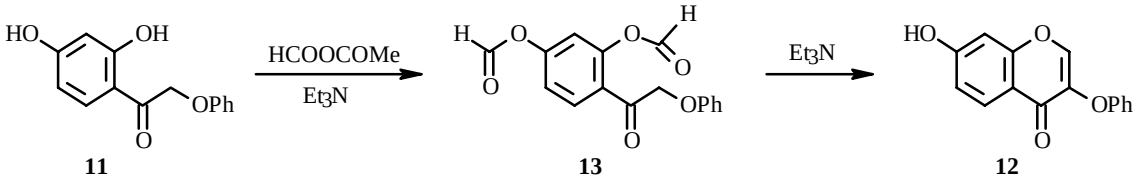
Szabo and Kiss [12] developed a method for preparing 3-phenoxychromones that consisted of Claisen condensation of 2-hydroxyacetophenones with methylformate in the presence of sodium *t*-butoxide with subsequent treatment of the intermediate 2-hydroxychromanone with HCl in ethanol. 3-Phenoxychromone (**10**) was prepared starting with 2′-hydroxy-2-phenoxyacetophenone (**6**).



6 **10**

7-Methoxy- and 5,7-dimethoxy-3-phenoxychromones were prepared analogously. This method has limited preparative value because it is necessary to protect all hydroxyls in the starting ketone except for the 2-hydroxyl, which is involved in forming the pyrone ring. Therefore, many chemists have directed their efforts to a search for a general method of preparing 3-phenoxychromones that does not require introducing protecting groups and their subsequent removal.

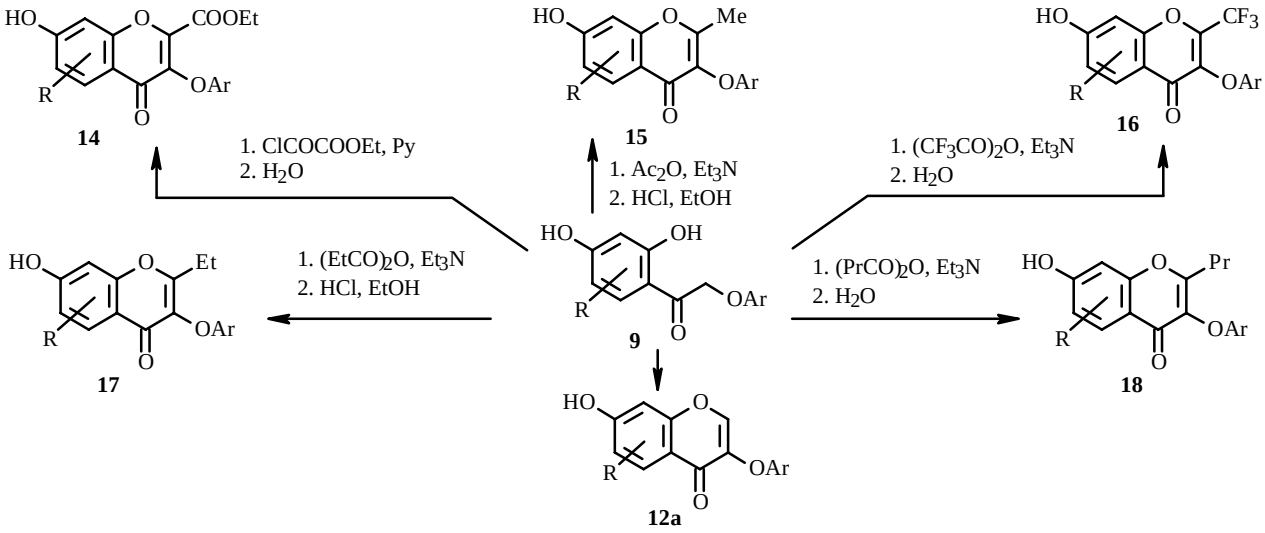
It is known from the literature that one of the most suitable methods for preparing isoflavones and their heterocyclic analogs is cyclization of 2-hydroxyacetophenones by acetic—formic anhydride in the presence of bases [20]. However, this method is unsuitable for converting α-aryloxy-2,4-dihydroxyacetophenones into the corresponding 3-aryloxychromones. The hydroxy groups of α-phenyloxyacetophenone **11** are fully formylated in the presence of triethylamine by acetic—formic anhydride. However, only a small portion (20-30%) of it is converted to the desired chromone **12** [21, 22]. Therefore, formylated acetophenone **13** is preferentially deformylated in the second reaction step. Such a path for the heterocyclization is due to the introduction of an electronegative O atom betweeen the methylene and the phenyl. This decreases the electronic effect of the phenyl substituent on the methylene protons and deactivates it as a result.



11 **13** **12**

The Venkataraman orthoformate method for heterocyclization of 2-hydroxyacetophenones occurs with extensive polymerization of the reaction mixture [23]. Therefore, the desired chromone is formed in only insignificant amounts [22].

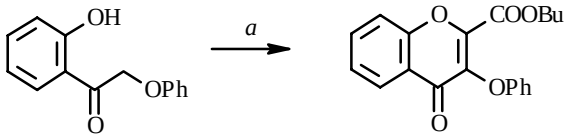
Switching formylating agents for acylating ones gives 2-substituted derivatives of 3-phenoxychromones. 2-Ethoxycarbonyl-3-phenoxy-7-hydroxychromones **14** were prepared using ethyloxalyl chloride and 2-hydroxyacetophenones **9** in pyridine at room temperature [8, 24-26]. Reaction of 2,4-dihydroxy-α-aryloxyacetophenones **9** with acetic, trifluoroacetic, propionic, and butyric anhydrides in the presence of triethylamine did not stop at acylation of the hydroxyls and heating of the reaction mixture closed the pyrone ring to form 3-phenoxychromones containing methyl (**15**), trifluoromethyl (**16**), ethyl (**17**), or propyl (**18**) groups in the 2-position of the benzopyran-4-one system [17, 27, 28]. Removal of the acyl protection to give 7-hydroxychromones was carried out by boiling alcohol solutions of the acylchromones in the presence of HCl.



The chromone ring can be constructed using acid catalysis by Vilsmeier reaction of the corresponding 2-hydroxyketones. The heterocycle was formed by adding boron trifluoride etherate to a solution of the corresponding 2,4-dihydroxy-α-phenoxyacetophenone **9** in DMF with subsequent addition of an acid chloride and further hydrolysis of the reaction mixture to **12a** [23, 28-30]. Methanesulfonyl chloride, phosphorus tri- and pentachlorides, phosphoryl chloride, and thionyl chloride were used as the acid chlorides.

It is assumed that $BF_3 \cdot Et_2O$ complexes all hydroxyls of the phenol of the starting ketone in the initial reaction step, simultaneously passivating them. Therefore, the Vilsmeier reagent will attack at the activated methylene. Furthermore, the 2-hydroxy-α-phenoxyacetophenones will not cyclize without $BF_3 \cdot Et_2O$ [29].

Of other approaches to heterocyclization of α-phenoxy-2-hydroxyacetophenones, a method based on reaction at 140°C of 2′-hydroxy-2-phenoxyacetophenone (**6**) with butoxydichloroacetate in the presence of catalytic amounts of powdered Pt, Pd, or Ru to form butyl 3-phenoxy-4-benzopyron-2-carboxylate (**19**) is notable [31]. Ester **19** was also formed using *o*-hydroxyacetophenone **6** and dibutyloxalate in the presence of NaH [32].

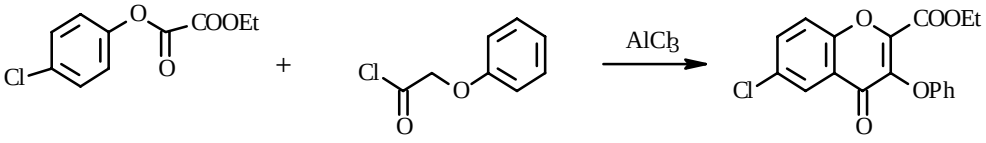


6 **19**

a. $Cl_2CHCOOBu$, Pt or $(COOBu)_2$, NaH

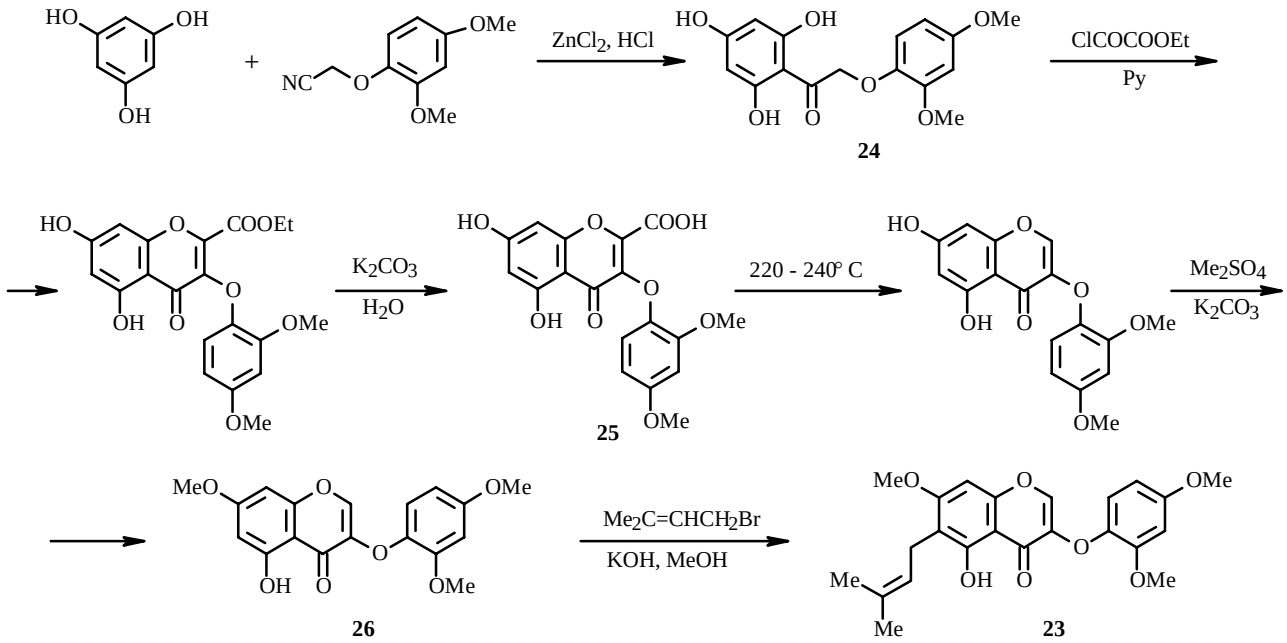
The general conclusion from an examination of synthetic methods for 3-aryloxychromones based on cyclization of various α-phenoxy-2-hydroxyacetophenones is that the latter are very convenient and unique precursors of phenoxy analogs of isoflavones. In the overwhelming majority of methods, precursors are converted to the target 3-phenoxychromones in one step and high yields.

A synthesis of ethyl-6-chloro-3-phenoxychromon-2-carboxylate (**20**) based on condensation of 4-chlorophenyl-ethyloxalate (**21**) and phenoxyacetyl chloride (**22**) in the presence of $AlCl_3$ has also been reported [33].



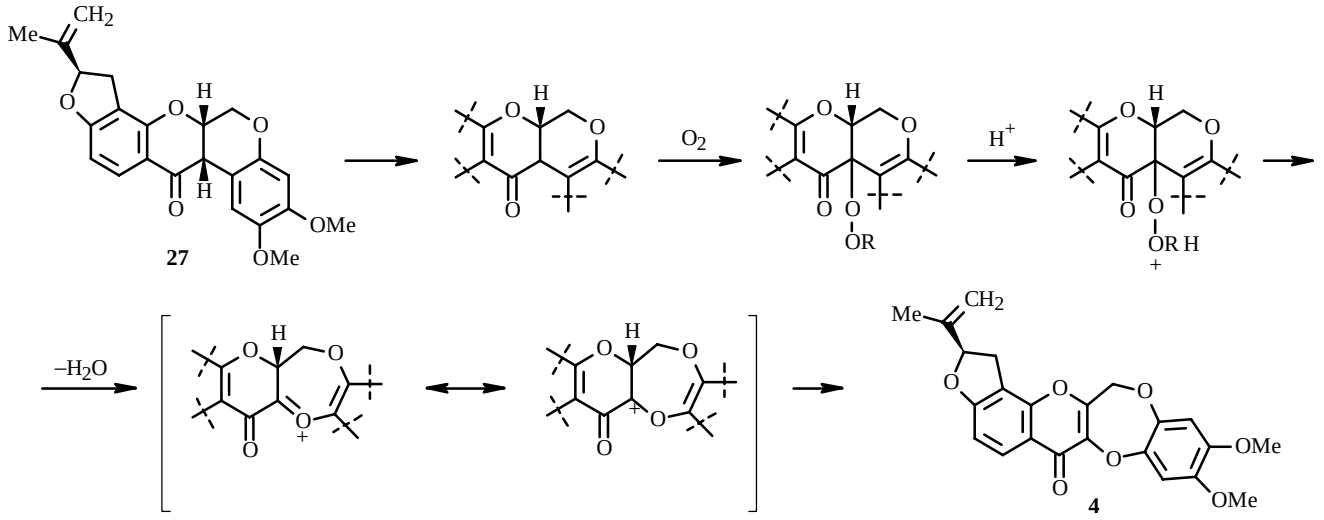
21 **22** **20**

The structure of glyasperin E (**1**) was established by total synthesis of its dimethylether **23** [8]. Key intermediate **24** was readily prepared by Hesch condensation of phloroglucinol and the appropriate phenoxyacetonitrile. The chromone system was constructed using the Baker method [34] that consists of cyclization of ketone **24** using chloroethyloxalate and thermal decarboxylation of 2-carboxycrhomone **25**. Selective methylation of the 7-hydroxyl, which is not involved in H-bonding, and subsequent C-prenylation of hydroxychromone **26** gave the dimethylether of glyasperin E.



25 **26** **23**

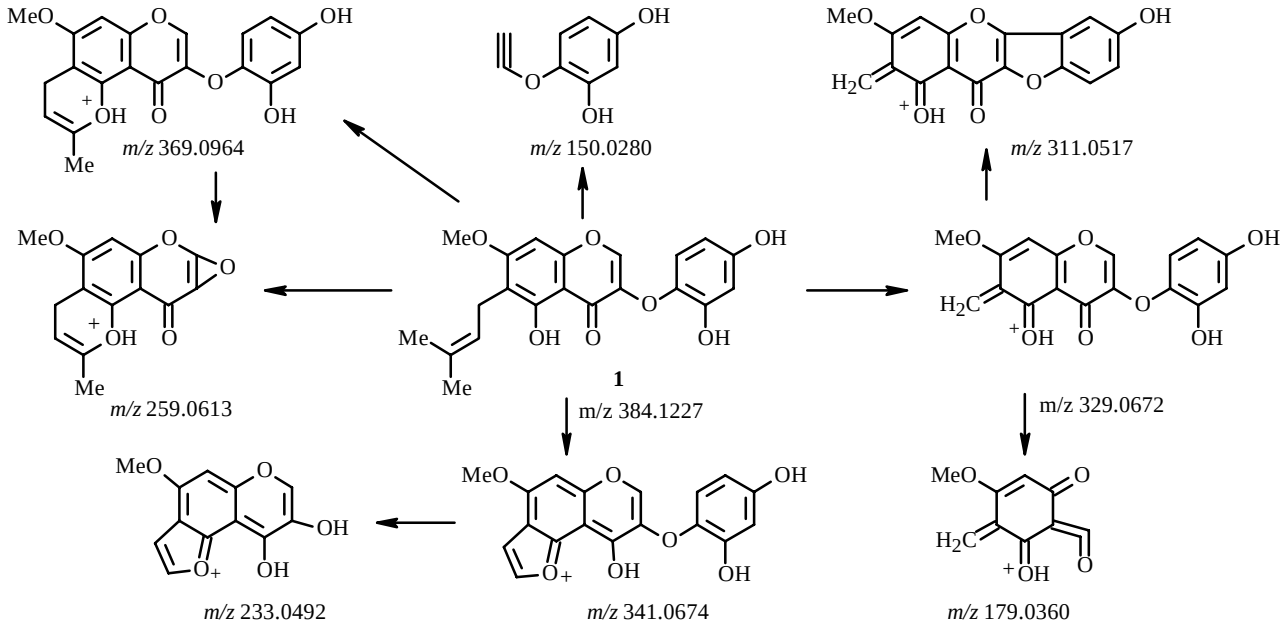
(-)-13-*Homo*-13-oxa-6a,12a-dehydrorotenone (**4**) was prepared in 9% yield by reaction of rotenone **27** with acetylchloride in DMF saturated with oxygen [11]. This process was analogous to the well-known auto-oxidation of cumene into phenol.



3. STRUCTURE DETERMINATION OF 3-ARYLOXYCHROMONES

The C=O stretching vibrations at 1650-1660 cm^{-1} are the most characteristic ones in IR spectra of 3-phenoxychromones, like those for all compounds based on the benzopyr-4-one skeleton [8, 16].

In most instances proton and carbon NMR spectroscopy can unambiguously establish the structures of 3-aryloxychromones. Signals for C-2, C-3, and C-4 in the ranges 147-151 ppm, 137-144, and 175-178 ppm, respectively, are characteristic of 3-phenoxychromone systems in ^{13}C NMR spectra [8, 10]. PMR spectroscopy enables definite conclusions to be made not only about the structure but also the conformation of 3-phenoxychromones [16]. The essentially invariable chemical shifts of protons in the 2- and 6-positions of the phenoxyl moiety and the direct dependence of chemical shifts of protons in the 3- and 5-positions on the electronegativity of the substituents located in the 4-position indicate that the 3-phenoxychromone contains a chromone ring lying in the plane of the molecule and a phenoxyl substituent that forms a torsion angle of 90° (270°) around the C–O–C bond of the 3-benzopyran situated at an angle of 90° relative to it.



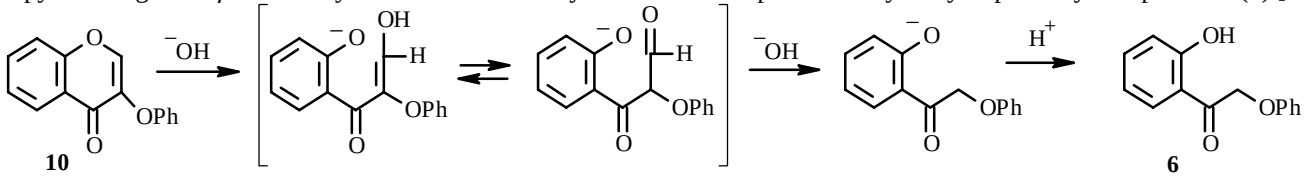
In reports on 3-phenoxychromones, the data are primarily limited to indications of the mass numbers and elemental compositions of the molecular ions, sometimes giving fragment ions and data on the relative intensities. The mass spectrum of the natural 3-aryloxychromone glyasperin E **(1)** has been studied in the most detail. Its fragmentation pattern has been published [8].

X-ray structure analyses of 3-aryloxychromones have not been reported.

4. CHEMICAL PROPERTIES AND METHODS OF MODIFYING 3-ARYLOXYCHROMONES

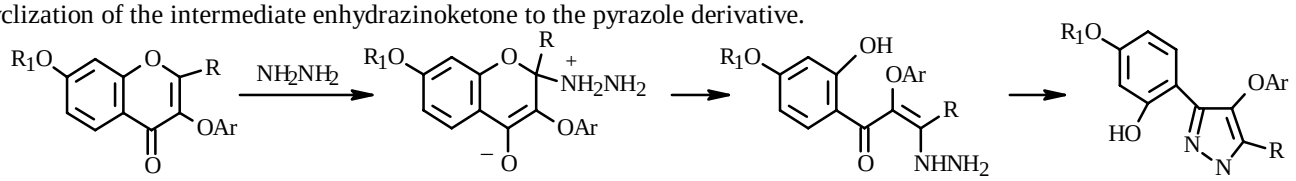
Reactions at the phenol hydroxyl, electrophilic substitution on the chromone ring, and the effect of nucleophilic reagents have been studied in order to prepare new physiologically active compounds based on 3-aryloxychromones and to study their chemical and biological properties.

Nucleophilic reagents add to the 2-position of 3-phenoxychromones. Heating **10** with base in aqueous alcohol opens the pyrone ring. The β-dicarbonyl derivative formed by this then decomposes to 2-hydroxy-α-phenoxyacetophenone (**6**) [35].



10 **6**

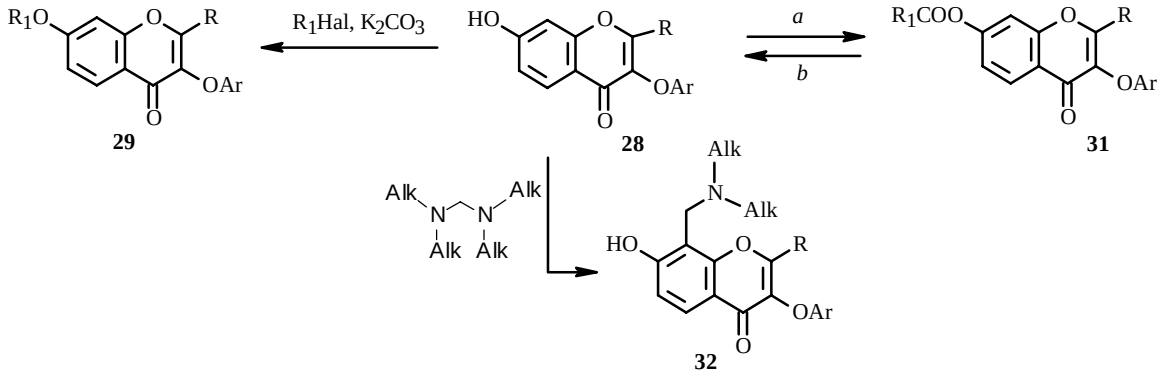
Reaction of hydrazine with compounds containing a chromone system can take two main directions. Hydrazones can form or the chromone system can recyclize. Hydrazine reacts with 7-hydroxy- and 7-alkoxy-3-phenoxychromones **28** and **29** analogously to isoflavone and 3-hetarylchromones to recyclize exclusively into the corresponding 3-(2,4-dihydroxyphenyl)-4-aryloxypyrazole **30** [27]. The recyclization mechanism caused by hydrazine can be represented as the result of nucleophilic attack of hydrazine at the 2-position of the benzopyrone ring, which leads to opening of the γ-pyrone ring and subsequent cyclization of the intermediate enhydrazinoketone to the pyrazole derivative.



28, 29 **30**

Many reactions of substituted 3-aryloxychromones with hydrazine have shown that the pyrone ring opens very easily and in high yields. This enables this reaction to be used for preparative purposes to produce 4-aryloxypyrazoles with alkyl and aryl substituents in the 3- and 5-positions that are unaccessible if other methods are used.

3-Phenoxychromones **28** that contain free hydroxyls are easily alkylated using the Williamson reaction resulting from reaction of the corresponding alkylating reagent in acetone solution in the presence of anhydrous potash to form 7-alkoxychromones **29**. Dialkylsulfates and alkylhalides were used for the alkylation [8, 18, 28]. The ester group can be introduced into 3-phenoxychromone to form acyl derivatives **31** by reacting its hydroxy derivatives with anhydrides or acid chlorides in pyridine [17, 18, 28]. The ester can be cleaved by HCl in ethanol.



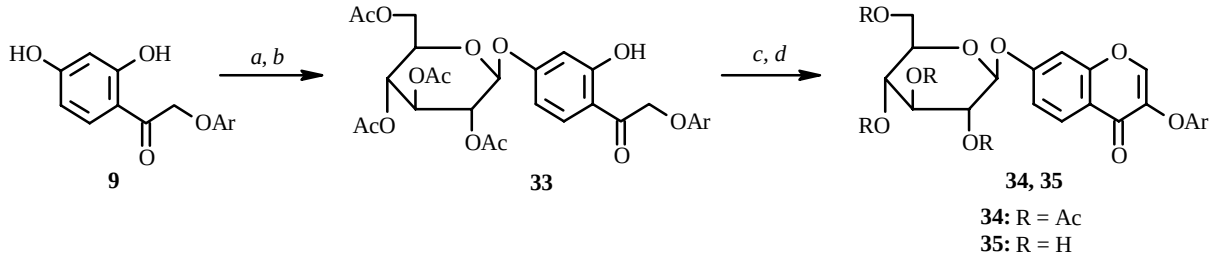
29 **28** **31**

32

a. $(R_1CO)_2O$ or R_1COCl, Py; *b*. HCl, EtOH

The Mannich reaction (C-aminomethylation) was carried out by heating 3-phenoxy-7-hydroxychromones **28** and substituted 1,1-diaminomethanes in absolute dioxane [36]. The synthesis produced Mannich bases **32**. The pharmocologically important aminomethyl group is added exclusively in the 8-position of the chromone.

A method to glycosylate the hydroxyl was developed in order to prepare water-soluble biologically active compounds based on 3-aryloxychromones [15]. Condensation of acetobromoglucose (Ac_4Glu*p*Br) with potassium salts of 2,4-dihydroxyacetophenones **9** in aqueous acetone or DMF:acetone:water at 20°C produced the peracetates of 2-hydroxyacetophenon-4-*O*-β-D-glucopyranosides **33**. The glycosylated ketones were heterocyclized into the target chromones **34** by the Bass method [37] and reaction with $BF_3 \cdot Et_2O$:DMF:methanesulfonyl chloride. Acetates **34** were deacetylated by a modified Zemplen method (reaction with NaOMe in MeOH) or reaction with aqueous NaOH (2 N) and the acetates in MeOH solution to give 3-aryloxychromon-7-*O*-β-D-glucopyranosides **35**.

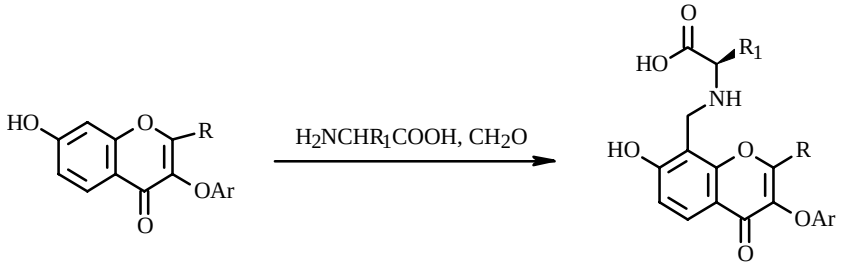


9 **33** **34, 35**

34: R = Ac
35: R = H

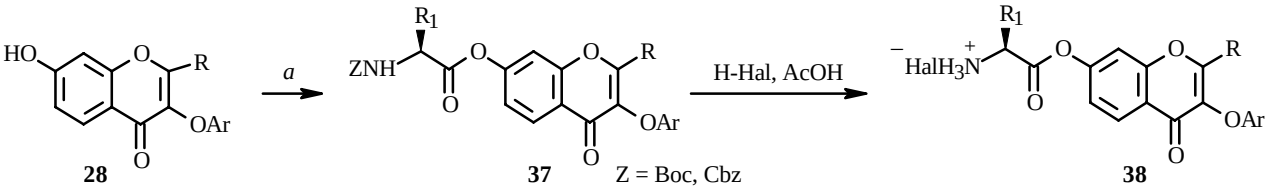
a. Ac_4Glu*p*Br, KOH; *b*. DMF, MeCOMe, H_2O; *c*. DMF, $MeSO_2Cl$, $BF_3 \cdot OEt_2$; *d*. MeONa, MeOH

Considering the important role of amino acids in life processes of organisms, several methods for modifying 3-phenoxychromones with amino-acid-type molecules have been proposed [38]. The first method of amino-acid modification was based on Mannich aminomethylation. 7-Hydroxy-8-(*N*-aminoacyl)methyl-3-phenoxychromones **36** were formed by heating a mixture of **28**, an equivalent amount of formaldehyde, and the corresponding amino acid in aqueous alcohol solutions [39].



28 **36**

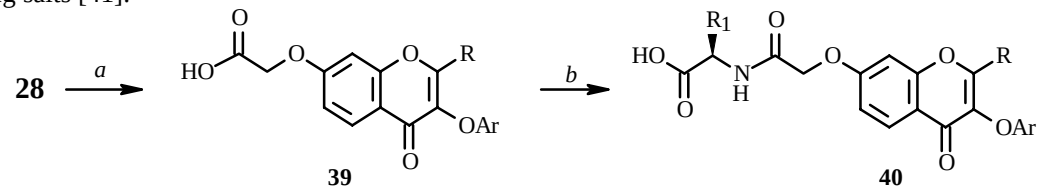
The second modification method is based on formation of an ester between the amino acid and the phenolic hydroxyl [18, 19, 40, 41]. The amino-acid amines are blocked by *t*-butyloxycarbonyl (Boc) or benzyloxycarbonyl (Cbz) groups. The protected amino acids are condensed by two different pathways. The first consists of acylation of **28** by symmetric anhydrides of *N*-protected amino acids at 0°C or room temperature in the presence of catalytic amounts of 4-dimethylaminopyridine (DMAP). The second method for preparing *N*-protected 7-*O*-aminoacyl-3-phenoxychromones **37** consists of condensation of **28** with *N*-protected amino acids in the presence of the condensing agent *N*,*N*′-*bis*-(2-oxo-3-oxazolidinyl)phosphodiamide (Bop-Cl) and triethylamine as the base. Acidolysis using HCl (3 M) in glacial acetic acid at 0°C (for Boc-derivatives) or saturated HBr in glacial acetic acid (for Cbz derivatives) removed the protecting group and formed the 7-*O*-aminoacyl-3-phenoxychromone hydrohalides (**38**).



28 **37** Z = Boc, Cbz **38**

a. $(ZNHCHR_1CO)_2O$, DMAP or $ZNHCHR_1COOH$, Bop-Cl, Et_3N

A third method of amino-acid modification was based on activated esters. Alkylation of **28** by ethylchloroacetate formed the ester, saponification of which gave the corresponding acid **39**. Reaction of the resulting chromonyloxyacetic acid **39** and *N*-hydroxysuccinimide in the presence of the condensing agent dicyclohexylcarbodiimide (DCC) produced the activated ester. *N*-[2-(3-Phenoxychromon-7-yloxy)acetyl]amino acid **40** was prepared by condensation of the activated ester of the acid with sodium salts of the corresponding amino acids in a water:dioxane mixture at room temperature with subsequent acidolysis of the resulting salts [41].

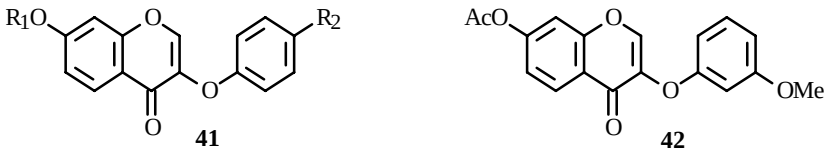


a. $ClCH_2COOEt$, K_2CO_3/H_2SO_4, AcOH; *b*. SuOH, DCC/NH_2CHR_1COONa/HCl

5. PHARMACOLOGICAL PROPERTIES OF 3-ARYLOXYCHROMONES

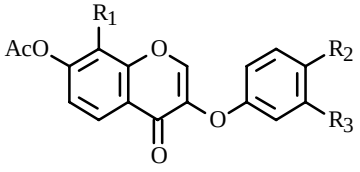
Like all compounds with the flavonoid structure, 3-aryloxychromone derivatives possess a broad spectrum of biological activity and low toxicity. Thus, biological tests have been carried out to reveal structure—activity trends in series of 3-phenoxychromone derivatives with respect to analgesic, anti-oxidant, hepatoprotective, hypolipidemic, and cholegogic activity [16, 28, 42].

3-Phenoxychromones **41** and **42** exhibit analeptic activity [43-46]. These compounds may be used in medicine to stimulate the central nervous system during serious infections, exhaustion of the organism, or depressive states.



R_1 = H, CH_3CO; R_2 = H, OH, Br, I, OEt

3-Phenoxychromone derivatives **43** and **44** exhibited strong anabolic activity, sometimes exceeding the magnitude of the effect from diiodotyrosine, and can be used in medicine as cell-growth stimulators and in agriculture as growth stimulators for farm animals [44, 47-51].

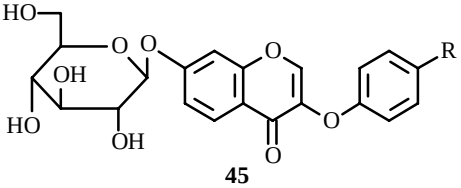


43, 44

43: $R_1 = R_2$ = H, R_3 = Me

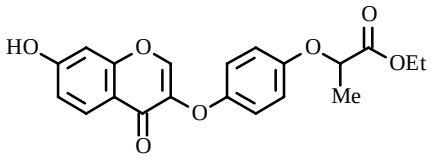
44: R_1 = Me, R_2 = H, Cl, Br, I, R_3 = H

3-Phenoxychromone 7-*O*-β-D-glucopyranosides **45** possess anti-inflammatory activity [52]. 3-(4-Fluorophenoxy)-chromon-7-*O*-β-D-glucopyranoside was also characterized as having anabolizing activity [53].



R = F, OMe

Ester **46** exhibited antioxidant activity [54]. 1,4-*Bis*-[3-(4-fluorophenoxy)chromon-7-yloxycarbovinyl]benzene (**47**) possesses distinct neuroleptic activity and can be used to treat neurological diseases [55].



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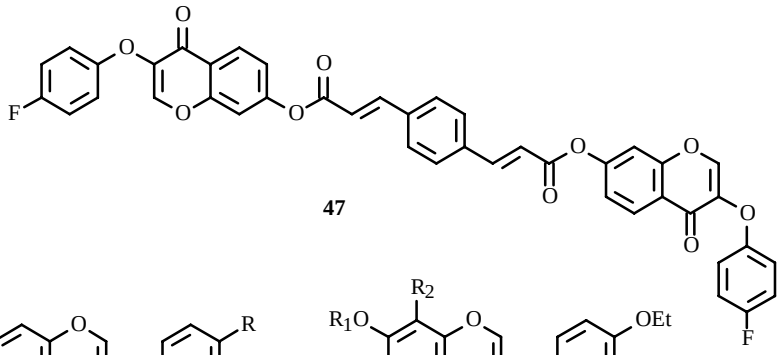

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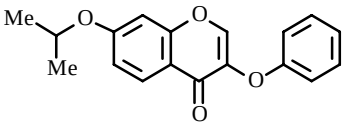

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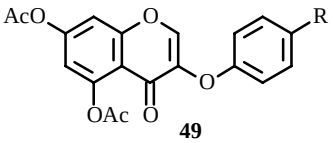
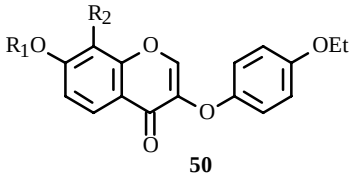


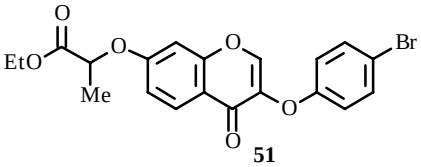
49

R = F, OMe



50

R_1 = H, CH_3CO, CHMeCOOMe, CHMeCOOEt
R_2 = H, Me



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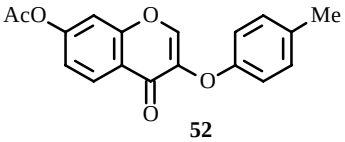

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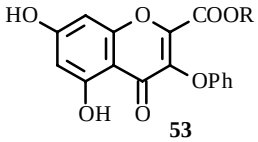


53

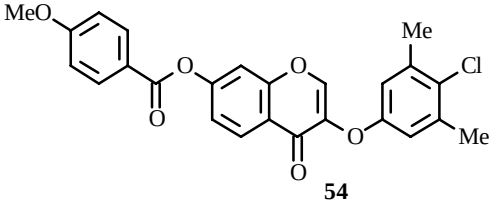
Complex activity was found for certain compounds, i.e., compounds exhibiting several interrelated activities. Thus, 3-phenoxy-7-isopropoxychromone (**48**) stimulates growth of animals and exhibits anti-oxidant and hepatoprotective activity and high antiviral activity, lowering the infectiousness of virus B 386/79 [56]. 3-Aryloxy-5,7-diacetoxychromones **49**, 3-(4-ethoxyphenoxy)-7-acetoxychromone, and 3-(4-ethoxyphenoxy)-7-hydroxychromone **50** derivatives exhibited high analeptic and hypolipidemic activity [47, 57-59]. 3-(4-Bromophenoxy)-7-(1-methyl-1-ethoxycarbonyl)-methoxychromone (**51**) possesses hepatoprotective and hypolipidemic activity [60]. 3-(4-Methylphenoxy)-7-acetoxychromone (**52**) possesses simultaneously both hypocholesterolemic and analeptic and anabolic activities. In particular, this compound exhibited a regulating effect on lipid exchange, decreasing the cholesterol level in blood (hypocholesterolemic activity), as a result of which it improved brain activity (analeptic activity) and increased both the total body mass and mass of internal organs (anabolic activity) [44].

Esters of 5,7-dihydroxy-4-oxo-3-phenoxychroman-2-carboxylic acid **53** act as inhibitors of testosteron-5α-reductase and aldosereductase and can be used in therapy to treat diabetes and other illnesses [25, 26].

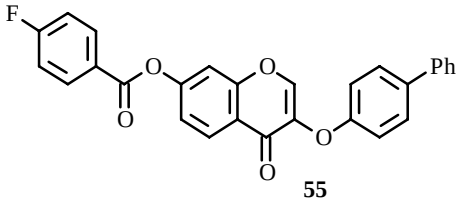
Mannich base **36** and 7-*O*-aminoacyl-3-phenoxychromone hydrochlorides **38** possess bactericidal activity against *Salmonella typhymurium* LT2, *Escherichia coli*, and *Candida albicans* [61].

(-)-13-*Homo*-13-oxa-6a,12a-dehydrorotenone (**4**) exhibited antitumor activity as an inhibitor of oxidoreductase [11, 62]. Certain synthetic and semisynthetic derivatives of 5,7-dihydroxy-3-phenoxychromone possess moderate cytotoxic activity against normal, cancer, and HIV-infected cells [63].

3-Phenoxychromone benzoates **54** and **55** inhibit the activity of proteinkinase CK2 at IC_{50} = 18.8 μM and IC_{50} = 22.4 μM, respectively, and are promising antitumor preparations [64].

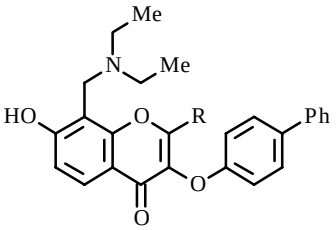


54



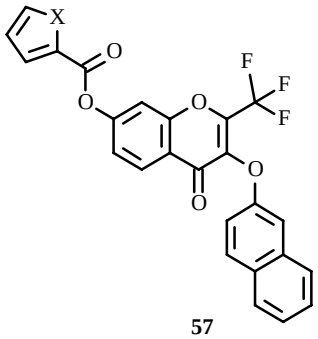
55

Certain derivatives of 3-aryloxychromone were tested for anticancer activity in vitro against 60 lines of human cancer cells. It was found that **56**-**58** inhibited proliferation of cancer cells in the range GI_{50} 3.44-41.1 μM and exhibited cytotoxic activity against cancer cells (LC_{50} from 49.5 μM) [36, 65].



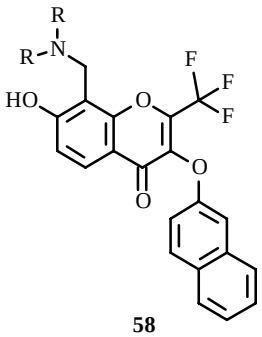
56

R = H, CF_3



57

X = O, S



58

In conclusion, it should be noted that the information presented attests to the promise of further research on the synthesis and chemical transformations of natural and synthetic 3-aryloxychromone derivatives. Modified 3-phenoxychromone derivatives are very interesting both in the search for new preparations with high biological activity and in solving problems of synthetic organic chemistry.

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