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The synthesis of angular hetarenochromones based on 7-hydroxy-8-carbonylchromones

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The present review highlights advanced strategies to the synthesis of the chromones annulated with *O*- and *N*-containing heterocycles at C(7)-C(8) bond. Due to the prevalence of such motives in different kinds of natural flavonoids and some alkaloids, fused chromones have attracted a great deal of attention so far. On the other hand a wide range of biological activities is displayed by the compounds of this type both among naturally occurring flavonoids and their synthetic analogues. 8-Carbonyl-7-hydroxychromones proved to be versatile synthones for the synthesis of angular hetarenochromones via approach of annulation of a heterocycle to the chromone core. It also addresses the question of the biological activity of naturally occurring and fused synthetic hetarenochromones.

Introduction

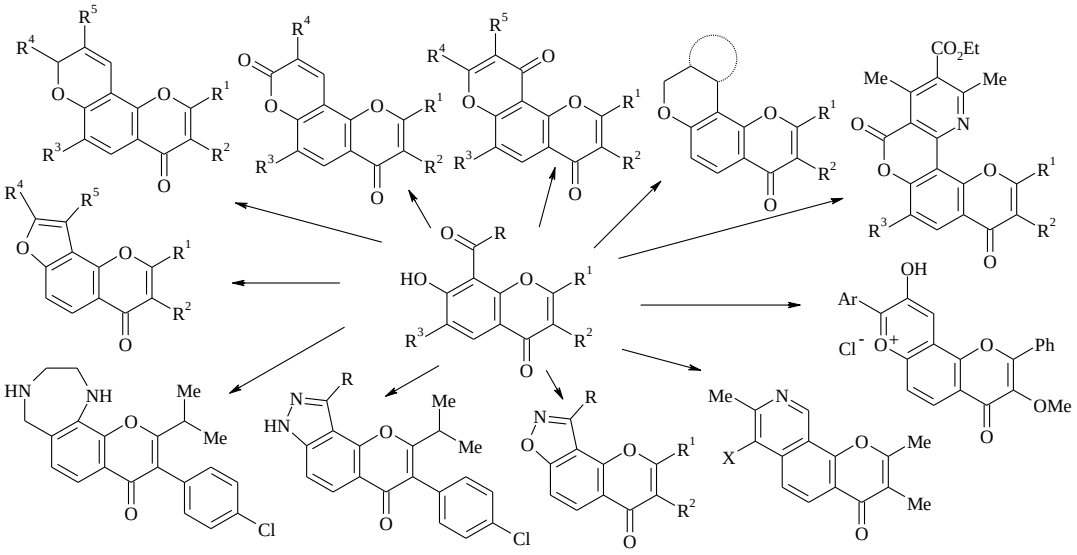
The chromone system is the core fragment of a group of natural flavonoids which are ubiquitous in nature and possess a wide spectrum of biological activity [1]. Chromones are worth studying in view of a wide scope of their transformations employed in organic synthesis and are reported to be a privileged scaffold in drug discovery [2]. Fused chromones have attracted a great deal of attention owing to a prevalence of such motives in different kinds of natural flavonoids and some alkaloids. Naturally occuring fused flavonoids are rather common to contain a pyran or furan ring annulated with chromene-4-one core. Natural furo[2,3-*h*]chromones and pyrano[2,3-*f*]chromones are known to possess antiviral, antimicrobial, insecticidal, fungicidal and psychotropic activity [3]. Some synthetic analogs of natural furo[2,3-*h*]chromones and pyrano[2,3-

f]chromones, containing instead of a furan or pyran ring, azole or azine cycle, are much more active, and in some cases, change the pharmacological profile of drugs [4].

Two approaches to the synthesis of chromones annulated with heterocycles at C(7)-C(8) bond such as annulation of heterocycle to the chromone core and annulation of γ-pyrone ring to benzohetarene core have been highlighted in the literature [3].

The introduction of the carbonyl group ortho to the hydroxyl group in 7-hydroxychromones promotes the annulation reaction at C(7)-C(8) bond of chromone cycle. This fact allows consideration 8-carbonyl-7-hydroxychromones as versatile synthones for the synthesis of angular hetarenochromones via the first approach.

The present review is focused on the syntheses of furo[2,3-*h*]chromones, pyrano[2,3-*f*]chromones and their elaborated fused derivatives, as well as their N-containing analogues, starting from the 7-hydroxy-8-formyl/acetyl/benzoyl-chromones and shows the current status of researches to date (**Scheme 1**).



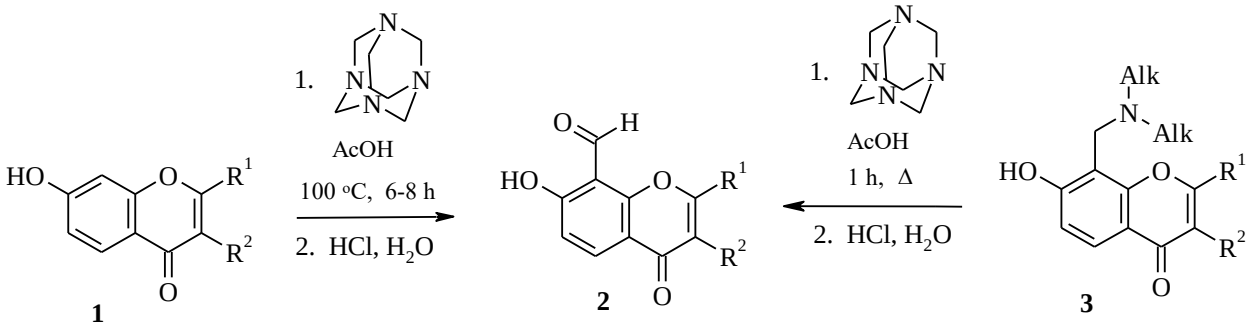
Scheme 1. Hetarenochromones based on 8-carbonyl-7-hydroxychromones

1. Synthesis of 8-formyl-, acetyl- and benzoyl-7-hydroxychromones

8-Formyl-, acetyl- and benzoyl-7-hydroxychromones, the convenient building blocks for annulation reactions, can be obtained by a concise and effective protocols, starting from cheap and readily available starting materials.

The Duff reaction have been employed to 7-hydroxychromones, flavones and isoflavones with great efficacy, allowing the formyl group introduction in one step only. According to the protocol 7-

hydroxychromones (**1**) easily undergo condensation with hexamethylenetetramine (HMTA) in glacial acetic acid solution and on subsequent hydrolysis with hydrochloric acid give comparatively good yields of 8-formyl derivatives (**Scheme 2**). For the first time this method was applied to 7-hydroxychromones and flavones in 1939 [5], and it remains the main method of synthesis for 8-formyl-7-hydroxychromones (**2**) up to date [6]. Thus, in 2015 a series of novel isoflavonoids, representing structural modifications of daidzein, an active ingredient of traditional Chinese medicine was synthesized and evaluated for its anti-influenza activity, *in vitro*, against H1N1 Tamiflu-resistant (H1N1 TR) virus in the MDCK cell line. Among them, 8-formyl-7-hydroxyisoflavones were most promising and demonstrated better activities and selectivities comparable to the reference ribarivin, a nucleoside antiviral agent. 3-(4-Bromophenyl)-8-formyl-7-hydroxychromone displayed the best inhibitory activity (EC50, 29.0 μM) and selectivity index (SI>10.3). Analysis of the structure-activity relationships (SAR) indicated that the presence of both the Bromine in 3-aryl substituent and appropriate CHO and OH groups in benzene core of chromone system might be critical for the activity and selectivity against H1N1 TR influenza viruses [7]. Having successfully accomplished the Duff reaction to 7-hydroxyisoflavones [8], we then employed the protocol to their 3-phenoxy- [9] and 3-hetaryl analogues, such as (3-(4-phenyl-4*H*-1,2,4-triazol-3-yl)- and 2-methyl-5-methoxycarbonylfuran-3-yl derivatives [10, 11]. 3-(4-Methylthiazol-2-yl)- and 3-(1-phenylpyrazol-4-yl) derivatives were synthesized via the Duff reaction in modified conditions upon stirring 3-hetaryl-7-hydroxychromones and HMTA in trifluoroacetic acid in a closed vial under argon at 110˚C for 40 min [12].

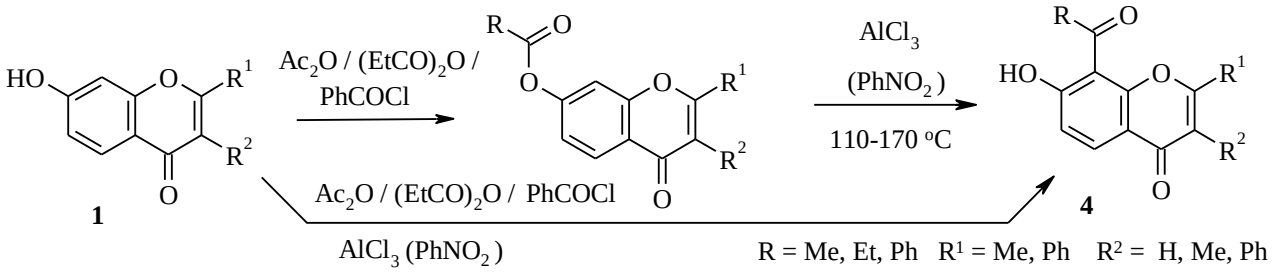


R^1 = H, Me, Ph, 2-furyl R^2 = H, Me, MeO, Et, Ph, Ar, ArO, Het

Scheme 2. The synthesis of 8-formyl-7-hydroxychromones

Under the Duff conditions the Mannich bases can also serve as starting materials in the 8-formyl-7-hydroxychromones' synthesis [13]. Heating of 8-dialkylamino-7-hydroxychromones (**3**) with HMTA in acetic acid during 1 h, followed by acid hydrolysis proved to be a convenient method for synthesis of 8-formyl-7-hydroxyisoflavones and their 3-hetaryl analogues (**2**) [10, 14] (**Scheme 2**).

The approach relied upon acylation of 7-hydroxychromones **1** with acetic anhydride, propionic anhydride or benzoyl chloride followed by the Friss rearrangement enabled to obtain 8-acyl-7-hydroxychromones (**4**) [15-17] (**Scheme 3**). Similarly the Friedel-Crafts acylation, propyonilation and benzoylation of 7-hydroxychromones **1** in $AlCl_3$ led to the corresponding 8-acetyl-, 8-propionyl and 8-benzoylchromones **4** in 60-70 % yields [17]. When the above reaction was carried out in nitrobenzene as a solvent, lower yields were obtained [17].

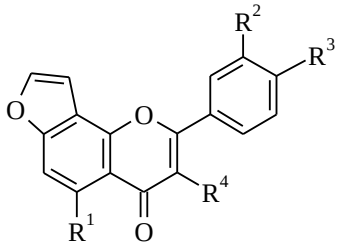


Scheme 3. The synthesis of 8-acyl- and 8-benzoyl-7-hydroxychromones

8-Formyl-, acetyl- and benzoyl-7-hydroxychromones have been successfully used for annulation of 5, 6 and 7 membered heterocycles to the chromone core.

2. Furo[2,3-*h*]chromones

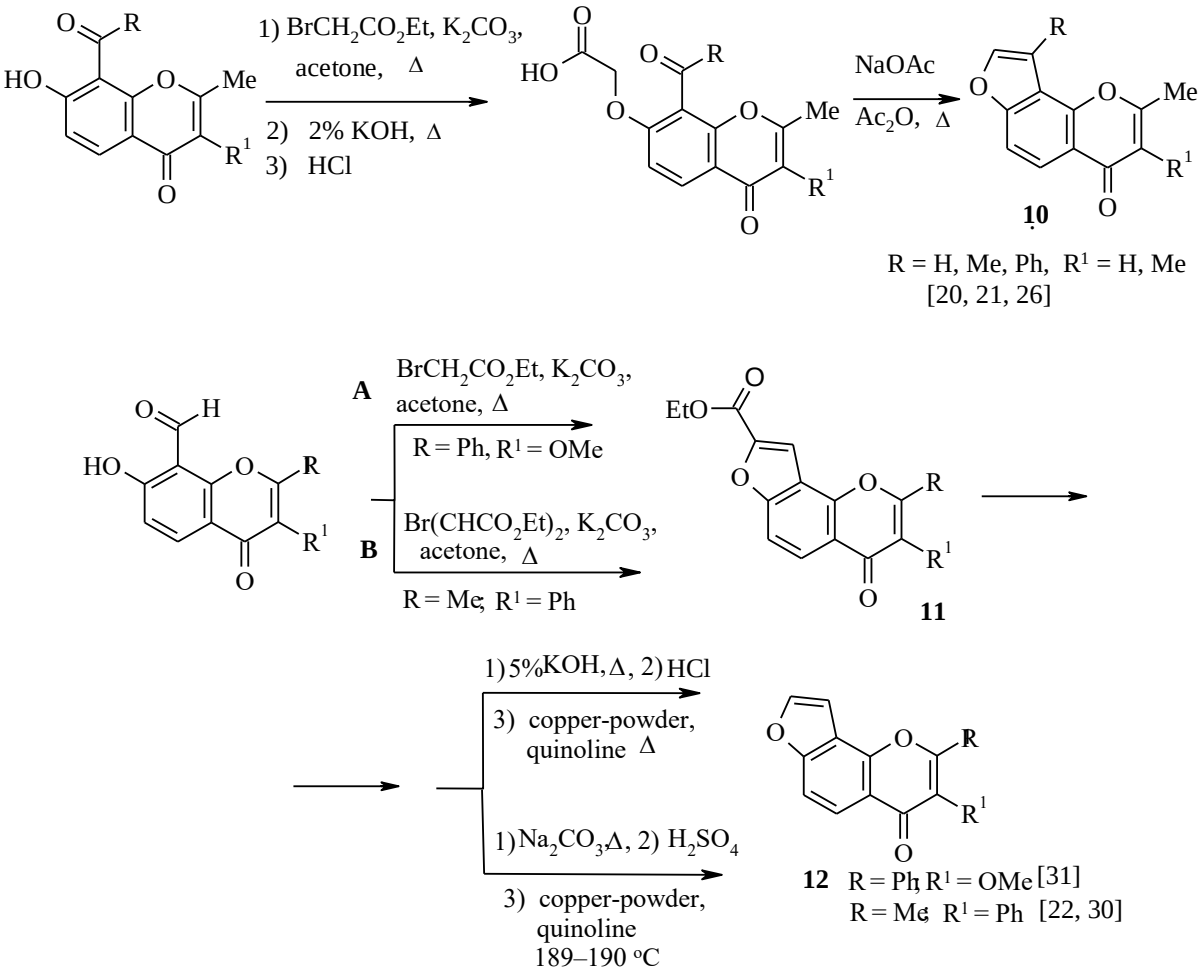
Chromones annulated with the furan ring are an abundant subclass of flavonoids, which are widely distributed in nature. Naturally abundant furo[2,3-*h*]flavones, such as lancheolatin B (**5**), pongoglabol (**6**), pongaglabol methyl ether (**7**), pongaglabrone (**8**) and karanjin (**9**) which are the major constituents of the *Pongamia* genus are known to possess antibacterial, antifungal and cytotoxic activity [18, 19] (**Figure 1**). Karanjin is used as bioinsecticide and biopesticide [19]. The wide range of biological properties of natural furo[2,3-*h*]chromones has stimulated interest in the synthesis of such system derivatives.



5. $R^1=R^2=R^3=R^4=H$ lancheolatin B
6. $R^1=OH$, $R^2=R^3=R^4=H$ pongaglabol
7. $R^1=OMe$, $R^2=R^3=R^4=H$ pongaglabol methyl ether
8. $R^1=R^4=H$, $R^2+R^3=$-O-CH^2-O- pongaglabrone
9. $R^1=R^2=R^3=H$, $R^4=MeO$ karanjin

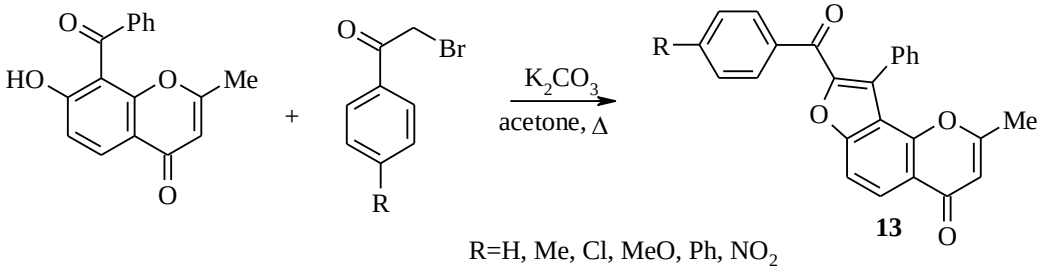
Figure 1. Natural furo[2,3-*h*]flavones

A number of furo[2,3-h]chromones/flavones/isoflavones **10**, **11**, **12** were prepared starting from 7-hydroxy-8-formyl- and 8-acetylchromones on alkylation with ethyl bromoacetate (Method A) [20-28] or diethyl bromomalonate (Method B) [27, 29-34] in anhydrous acetone or dioxane in the presence of K_2CO_3, followed by intramolecular condensation of 7-alkoxy derivatives on active methylene group with 8-acyl substituent as shown in examples (**Scheme 4)**. The method B has been improved recently by employment of tetrabutylammonium-bromide (TBAB) as phase transfer catalyst in toluene under dry nitrogen conditions in a Dean-Stark trap [27]. Ethyl furo[2,3-h]chromone-8-carboxylates **11** and ethyl 2-(2'-furyl)-3-methylfuro[2,3-h]chromone-8-carboxylate prepared by both methods A and B were identical [27]. Hydrolysis of 8-ester group in compounds **11**, followed by decarboxylation led to 8-unsubstituted furo[2,3-h]chromones **12** [22, 23, 30, 31]. 2,3,5,9- And 2,3,6,9-tetramethylfuro[2,3-h]chromones were proposed as potential photochemotherapeutic agents [26].



Scheme 4. The synthesis of furo[2,3-h]chromones

8-(*p*-Substituted benzoyl)-2-methyl-9-phenylfuro[2,3-h]chromones **13** have been prepared by condensation of 8-benzoyl-7-hydroxy-2-methylchromone with various *p*-substituted phenacyl bromides as potential antiimplantation agents. [35, 36] (**Scheme 5**).



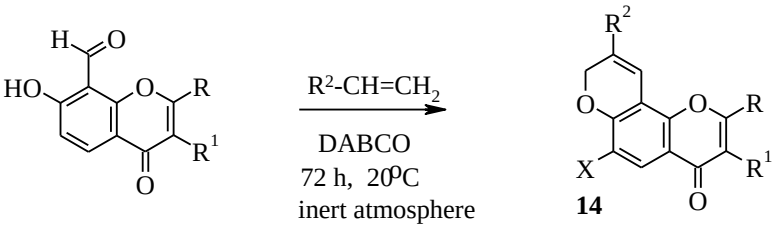
Scheme 5. The synthesis of 8-aroyl-2-methyl-9-phenylfuro[2,3-h]chromones **13**

3. Chromones annulated with pyrane cycle

This section includes the references on the annulation of pyrane, α-pyrone, γ-pyrone and fused pyrane rings to chromone core on the base of 8-carbonyl-7-hydroxychromones.

3.1. Pyrano[2,3-f]chromones

Condensation of 8-formyl-7-hydroxychromones, flavones, isoflavones and 8-formyl-7-hydroxy-2-(2'-furyl)-3-methylchromone with methyl vinyl ketone, acrolein and acrylonitrile in the presence of diazabicyclo[2.2.2]octane (DABCO) under N_2 atmosphere at room temperature using the Baylis-Hillman reaction conditions afforded 9-acetyl/formyl/cyano-substituted pyrano[2,3-f]chromones **14** in 65-81 % yields [37-40] (**Scheme 6**).

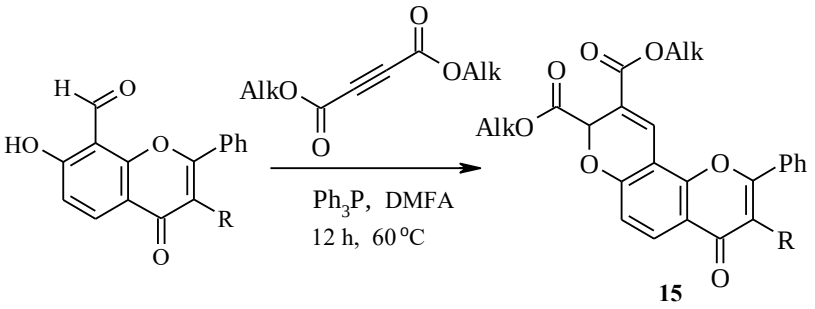


R = H, Me, Ph, 2-ClC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2'-furyl ;
R^1 = H, Me, Ph, 4-$MeOC_6H_4$, 3-ClC_6H_4, 4-BrC_6H_4, 2,4-$Cl_2C_6H_3$; R^2 =MeCO, CHO, CN
X= H, Cl, Br

Scheme 6. Synthesis of 9-acetyl/formyl/cyanopyrano[2,3-f]chromones **14** via the Baylis-Hillman reaction

A simple and efficient one-pot method has been developed for the synthesis of functionalized pyrano fused flavone derivatives, e.g., such as dialkyl 4-oxo-2-

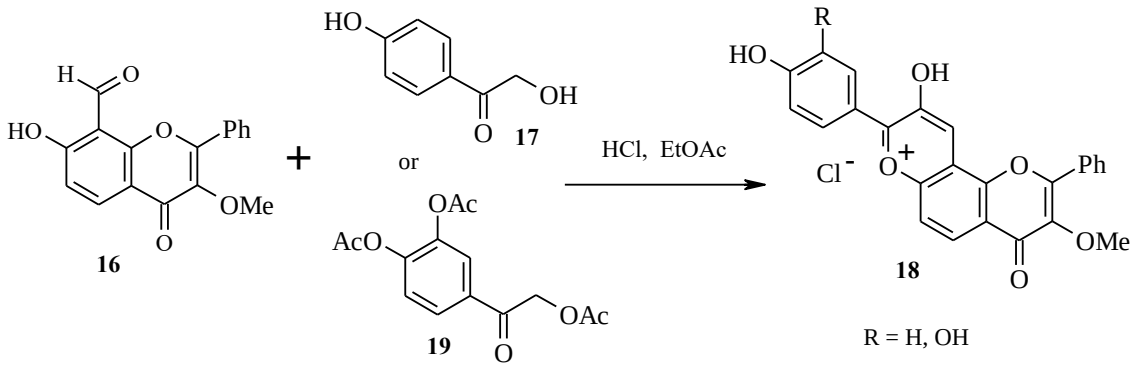
phenyl-4,8-dihydropyrano[2,3-f]chromene-8,9-dicarboxylates **15,** from 8-formyl-7-hydroxyflavones using dialkyl-acetalynedicarboxylates in the presence of triphenyl phosphine [41] (**Scheme 7**).



R = H, Me, Et ; Alk = Me, Et

Scheme 7. Synthesis of dialkyl 4-oxo-2-phenyl-4,8-dihydropyrano[2,3-f]chromene-8,9-dicarboxylates **15**

8-Formyl-7-hydroxy-3-methoxy-flavone (**16**) and 2-hydroxy-1-(4-hydroxyphenyl)-1-ethanone (**17**) in ethyl acetate in the presence of HCl was reported to give 9-hydroxy-8-(4-hydroxyphenyl)-3-methoxy-4-oxo-2-phenyl-4H-pyrano[2,3-f]chromen-7-ium chloride (**18**) (R=H). Its 3,4-dihydroxy analog **18** (R=OH) was obtained from flavone **16** and 2-[3,4-di(methylcarbonyloxy)phenyl-2-oxoethyl acetate (**19**) [42] (**Scheme 8**).



Scheme 8. Synthesis of 9-hydroxy-8-aryl-3-methoxy-4-oxo-2-phenyl-4H-pyrano[2,3-f]chromen-7-ium chlorides **18**

3.2. Chromones annulated with α-pyrone cycle

Annulated with α-pyrone cycle at the C7-C8 bound chromones were proposed as potential photoreagents for DNA [43]. α-Pyrono[2,3-f]flavones, their hetero analogues and isoflavones are known to display bacteriostatic activity [44, 45]. Partially hydrogenated derivatives of 4*H*,8*H*-pyrano[2,3-f]chromen-4,8-dione system which are clausenidin [46, 47] and calomelanol D [48, 49] occur naturally.

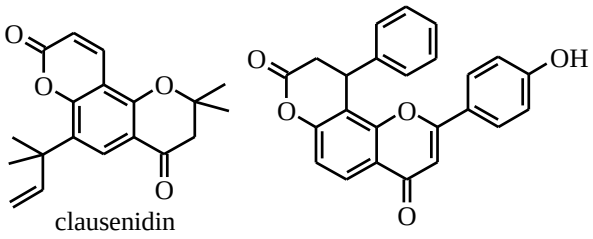
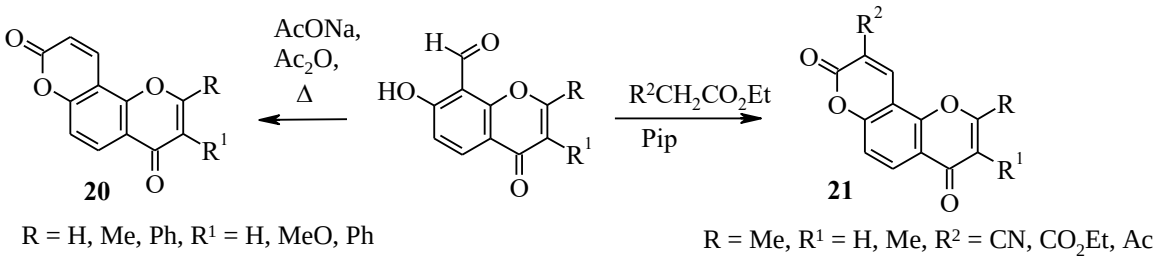


Figure 2. Natural α-pyrono[2,3-f]chromones

Annulation of α-pyrone cycle to chromone core at the C7-C8 bound starting from 7-hydroxy-8-formylchromones by the Perkin reaction yielded 9-unsubstituted 4*H*,8*H*-pyrano[2,3-f]chromen-4,8-diones **20** [9, 20], α-pyrono[2,3-f]flavones [5] and α-pyrono[2,3-f]isoflavones [50], while condensation with diethyl malonate, ethyl acetoacetate and cyanoacetic ester under the Knoevenagel conditions gave 9-carbethoxy, 9-acetyl and 9-cyano-4*H*,8*H*-pyrano[2,3-f]chromen-4,8-diones **21,** respectively [20, 43] (**Scheme 9**). 9-Carbethoxy derivatives **21** (R^2=CO_2Et) underwent hydrolysis followed by decarboxylation to give 9-unsubstituted pyrano[2,3-f]chromen-4,8-diones **21** [20, 43].

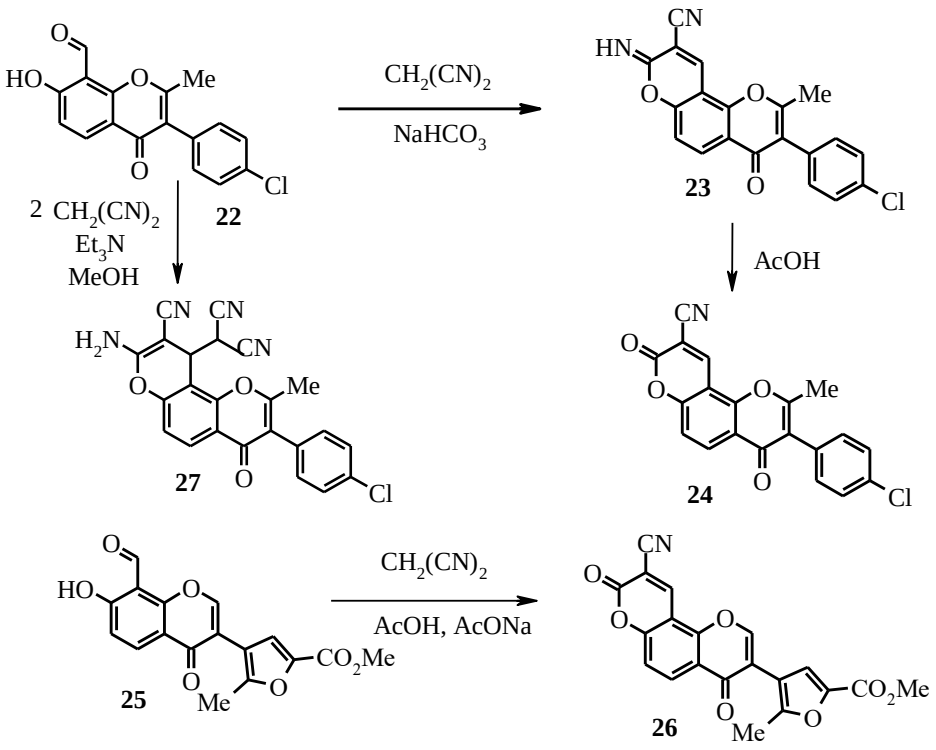


Scheme 9. The synthesis of 4*H*,8*H*-pyrano[2,3-f]chromen-4,8-diones

The Knoevenagel condensation of 7-hydroxy-8-formylchromones with malononitrile depending on the ratio of reagents and conditions used in the reaction led to the variety of the products [51]. Upon treatment of 8-formyl-7-hydroxychromone **22** with malononitrile (1:1) in aqueous solution of $NaHCO_3$ 8-iminopyranochromone **23** was isolated in 66% yield. Subsequent hydrolysis of the compound **23** via refluxing in AcOH resulted in pyranochromone **24** formation in 75% yield. (**Scheme 10**).

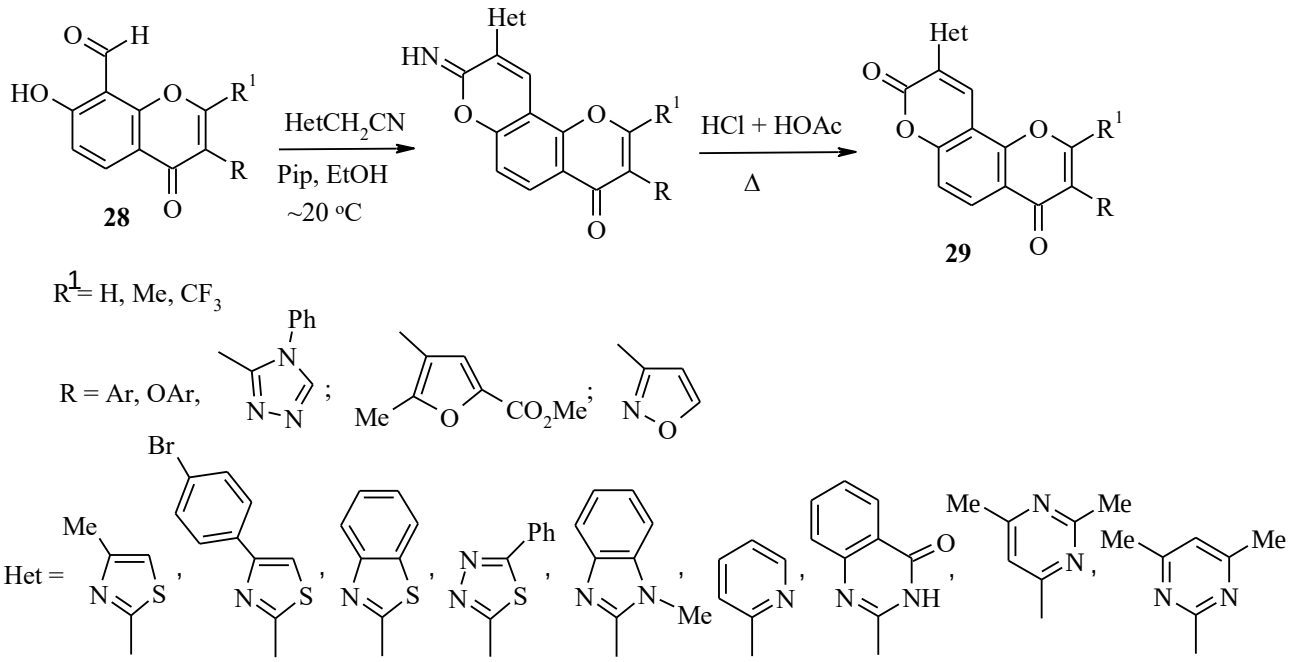
Conducting the Knoevenagel reaction of the compound **25** in acetic acid resulted in 4*H*,8*H*-pyrano[2,3-*f*]chromen-4,8-dione **26** in 50% yield without isolation of intermediate 8-imino derivative (**Scheme 10**).

Having already been isolated, 8-iminopyranochromone **23** was envisaged to be able to join another malononitrile molecule at C10 through the Michael addition. Thus, using of 2 equivalents of malononitrile in reaction with 8-formylchromone **22** in methanol and Et_3N gave the product **27** in 60% yield (**Scheme 10**).



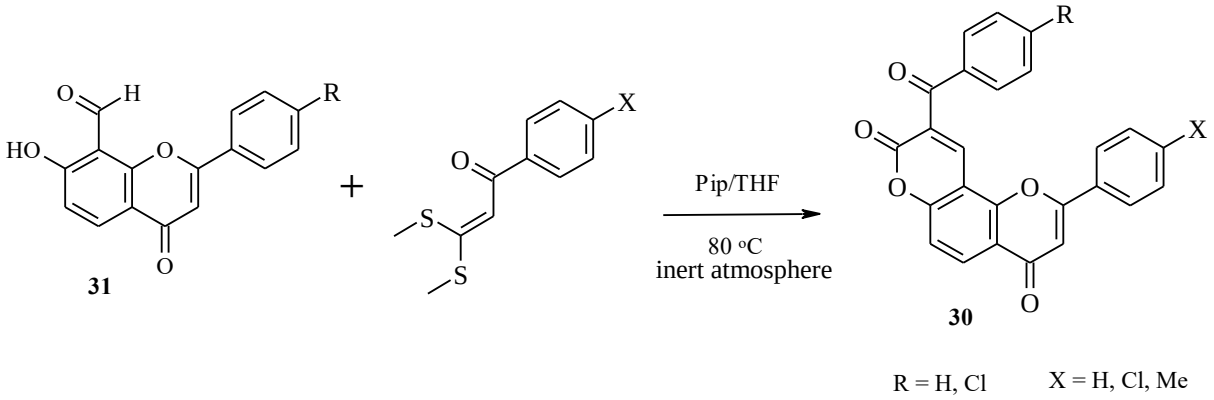
Scheme 10. The interaction of 8-formyl-7-hydroxychromones with malononitrile

Condensation of 8-formyl-7-hydroxyisoflavones and 8-formyl-7-hydroxy-3-aryloxychromones **28** with hetarylacetonitriles in the Knoevenagel conditions makes it possible to introduce heterocyclic substituent in 9-th position of 4*H*,8*H*-pyrano[2,3-*f*]chromen-4,8-diones **29** [8-11, 52-54] (**Scheme 11**). 3,9-Disubstituted with different heterocycles 4*H*,8*H*-pyrano[2,3-*f*]chromen-4,8-diones **29** can be synthesized by the reaction of 3-hetaryl-8-formyl-7-hydroxychromones **28** with hetarylacetonitriles**.** In a number of cases, the intermediates of this reaction 9-azahetaryl-8-iminopyrano[2,3-f]chromen-4-ones were isolated. The desired products **29** were obtained by hydrolysis of the latter in a mixture of hydrochloric and acetic acids (**Scheme 11**).



Scheme 11. The synthesis of 9-hetaryl-4*H*,8*H*-pyrano[2,3-*f*]chromen-4,8-diones **29**

A facile synthesis of 3-aroylcoumarin-flavone hybrids **30** was implemented by interaction of 8-formyl-7-hydroxyflavones **31** and α-oxoketene dithioacetals in the presence of a catalytic amount of piperidine [55] (**Scheme 12**).

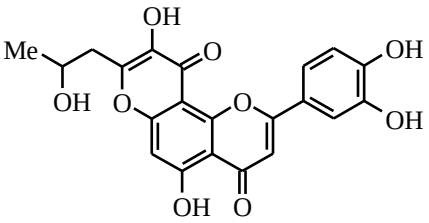


Scheme 12. The synthesis of 3-aroylcoumarin-flavone hybrids **30**

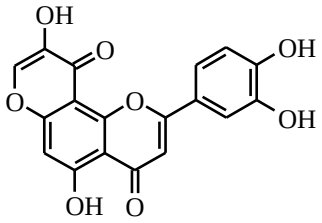
3.3. Chromones annulated with γ-pyrone cycle

4*H*,10*H*-Pyrano[2,3-f]chromen-4,10-dione system is a skeleton of light-yellow dyes for silk arthraxin and norarthraxin (**Figure 3**), which were isolated from *Arthraxon histidus Makino* and *Miscantus tinctorius Hacke* [56-59]. Derivatives of this system revealed higher light-stability than natural analogues [60, 61]. They have been

proposed as liquid crystals [62] and antiallergic agents [63, 64]. They were active in treating extrinsic allergic asthma, intrinsic asthma, hay fever, urticaria and auto-immune diseases [65] and were patented as antihistaminic [66] and antiasthmatic agents [67-69].



arthraxin



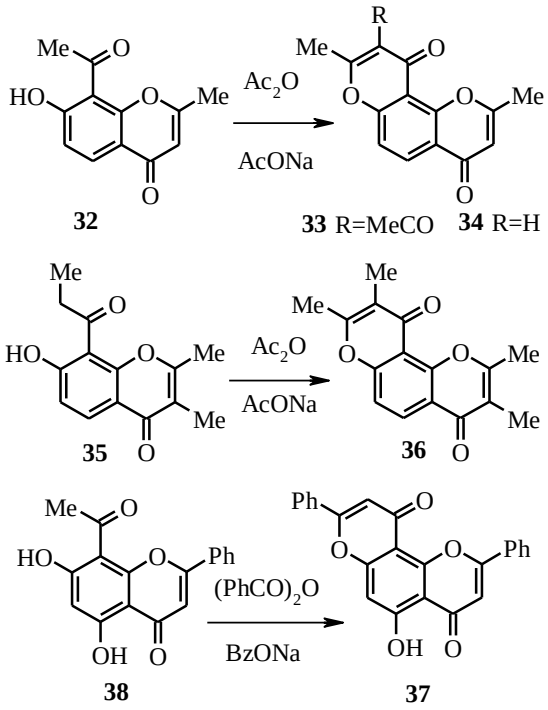
norarthraxin

Figure 3. Natural γ-pyrono[2,3-f]chromones

Design of 4*H*,10*H*-pyrano[2,3-f]chromen-4,10-dione system can be accomplished both by simultanious annelation of the two γ-pyrone rings to benzene core and by annelation of γ-pyrone ring to chromone system. The advantage of the second approach is a possibility to obtain the system with different substituents in pyrone cycles. Three ways to 4*H*,10*H*-pyrano[2,3-f]chromen-4,10-diones based on 8-acetyl-7-hydroxychromones are described in the literature.

The first one is the Kostanecki reaction. Condensation of 8-acetyl-7-hydroxy-2-methylchromone **32** with acetic anhydride and anhydrous sodium acetate yielded 9-acetoxy-2,8-dimethyl-4*H*,10*H*-pyrano[2,3-f]chromen-4,10-dione **33**, which underwent smooth deacetylation when boiling with aqueous sodium carbonate giving 9-unsubstituted product **34** [20, 70] (**Scheme 13**). 8-Propionylchromone **35** in the Kostanecki reaction conditions forms 2,3,8,9-tetramethyl-4*H*,10*H*-pyrano[2,3-f]chromen-4,10-dione **36** [15] (**Scheme 13**).

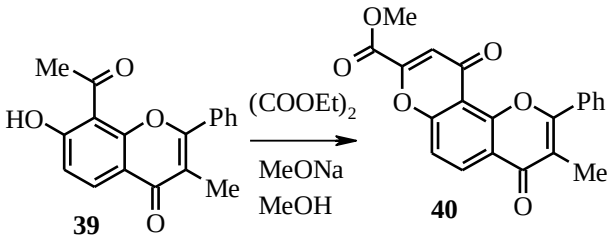
Flavon **37**, with a skeleton similar to artraxin, was prepared by heating 8-acetyl-5,7-dihydroxyflavon **38** with benzoic anhydride and BzONa at 180˚C [71] (**Scheme 13**).



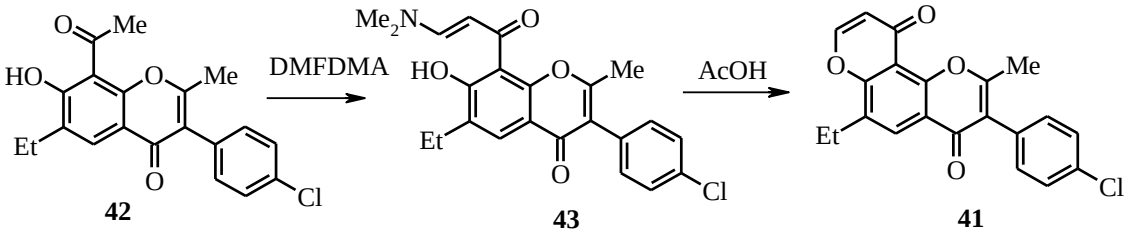
Scheme 13. The synthesis of 4*H*,10*H*-pyrano[2,3-f]chromen-4,10-diones via the Kostanecki reaction

The second way relies upon the Claisen reaction (the condensation of acetyl chromones with esters). 8-Acetyl-7-hydroxy-3-methylflavon **39** when heating with diethyloxalate in methanol in the presence of MeONa cyclized into 4*H*,10*H*-pyrano[2,3-f]chromen-4,10-dione **40** [64] (**Scheme 14**).

The third receiving path to 4*H*,10*H*-pyrano[2,3-f]chromen-4,10-dione system (**41**) is the enaminokethone method, which comprises in the interaction of 8-acetyl-7-hydroxyisoflavone **42** with N,N-dimethylformamide dimethyl acetal in toluene, followed by cyclization of 8-(3-dimethylamino-2-propenoyl)-7-hydroxy-4*H*-chromen-4-one **43** in acetic acid [72] (**Scheme 15**).



Scheme 14. The synthesis of 4*H*,10*H*-pyrano[2,3-f]chromen-4,10-dione **40** via the Claisen reaction



Scheme 15. The enaminokethone method of synthesis of 4*H*,10*H*-pyrano[2,3-f]chromen-4,10-dione **41**

3.4. Chromones annulated with the system of fused pyrane and other rings

Chromones annelated with pyran ring, fused with pyridin and piperidin cycles are represented by alkaloids, such as schumanniophytine **44**, schumannificine **45**, anhydrochumannificine **46**, schumagnine **47,** isolated from plants of *Schumanniophyton* genus in the family *Rubiaceae* [73-75] (**Figure 4**). The alkaloids of *Schumanniophyton* genus were found to possess antiviral activity against human immunodeficiency virus (HIV) [76].

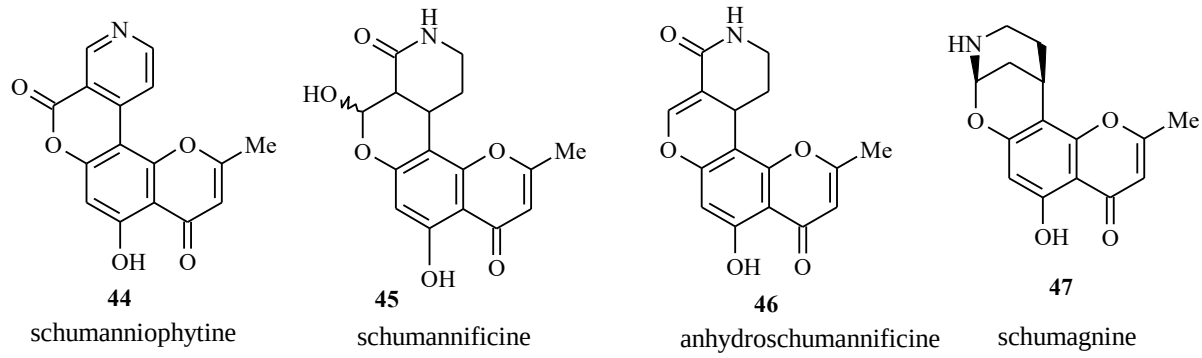
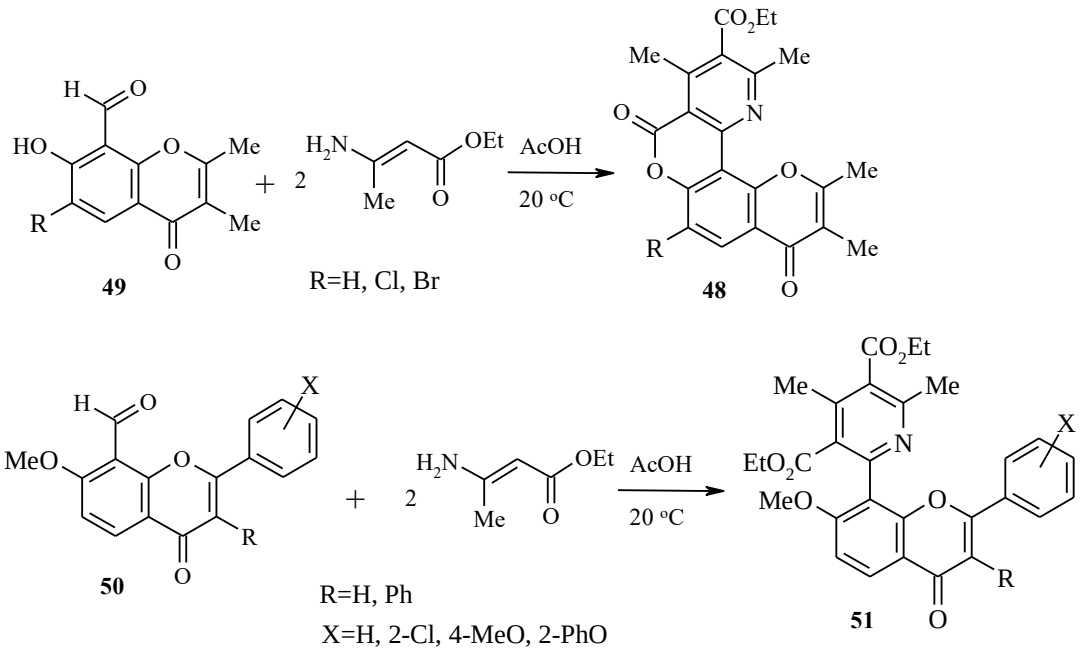


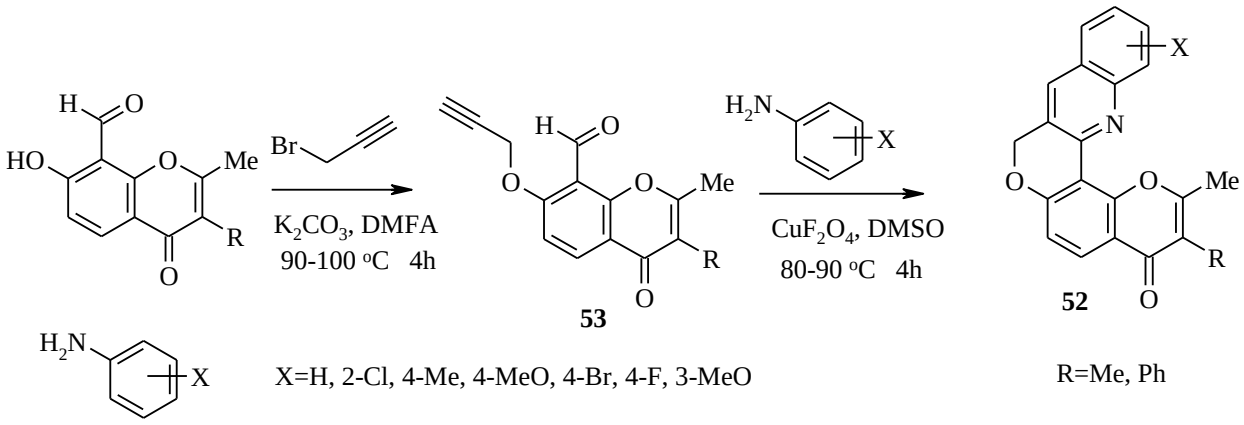
Figure 4. Structures of alkaloids from plants of *Schumanniophyton* genus

The Hantzsch reaction has been successfully employed to one-step assembling pyrano-pyridine fragment to chromone core to give isomeric to schumanniophytine skeleton structure **48** with antibacterial activity [77]. 8-Formyl-7-hydroxychromones **49** in the reaction with ethyl 3-aminocrotonate in acetic acid medium quantitatively yielded 5*H*,9*H*-pyrano[2′,3′:5,6]chromeno[4,3-b]pyridine-5,9-diones **48** [77], while 7-methoxy-8-formylflavones **50** under the same conditions afforded 7-methoxy-2-aryl-3-(phenyl/or-H)-8-[2-(4,6-dimethyl-3,5-dicarbethoxypyridyl)]-4*H*-1-benzopyran-4-ones **51** [78] (**Scheme 16**).



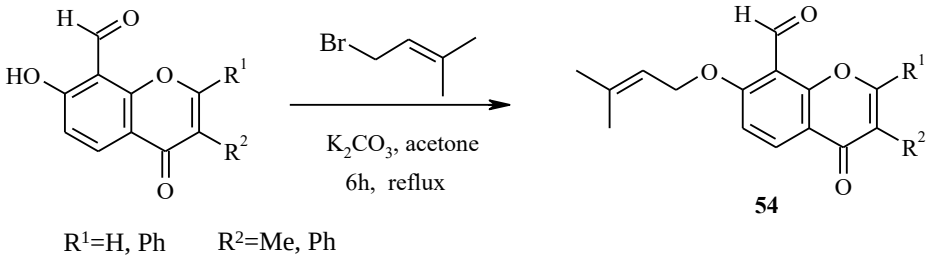
Scheme 16. The synthesis of 5*H*,9*H*-pyrano[2′,3′:5,6]chromeno[4,3-b]pyridine-5,9-diones **48** and 7-methoxy-8-[2-(4,6-dimethyl-3,5-dicarbethoxypyridyl)]-4*H*-1-benzopyran-4-ones **51** via the Hantzsch reaction

Pyrano[2′,3′:5,6]chromeno[4,3-b]-quinolin-4-ones **52** have been synthesized from 8-formyl-7-hydroxy-2-methylchromone and isoflavone in two steps: by alkylation with 2-propynyl bromide to give 8-formyl-7-(prop-2-ynyloxy)-2,3-disubstituted chromones **53** followed by intramolecular aza-Diels-Alder reaction of the azadienes generated *in situ* from aryl amines and 8-formyl-7-(prop-2-ynyloxy)chromones **53** using $CuFe_2O_4$ nanoparticles as a catalyst in DMSO at 80-90°C in good-to-excellent yields [79] (**Scheme 17**). 2-Chloranilines form 13-Cl-substituted products **52**, 4-substituted anilines form 11-substituted products **52** and 3-methoxyanilines give the mixture of 10-methoxy and 12-methoxypyrano[2′,3′:5,6]chromeno[4,3-b]quinolin-4-ones (**52**).



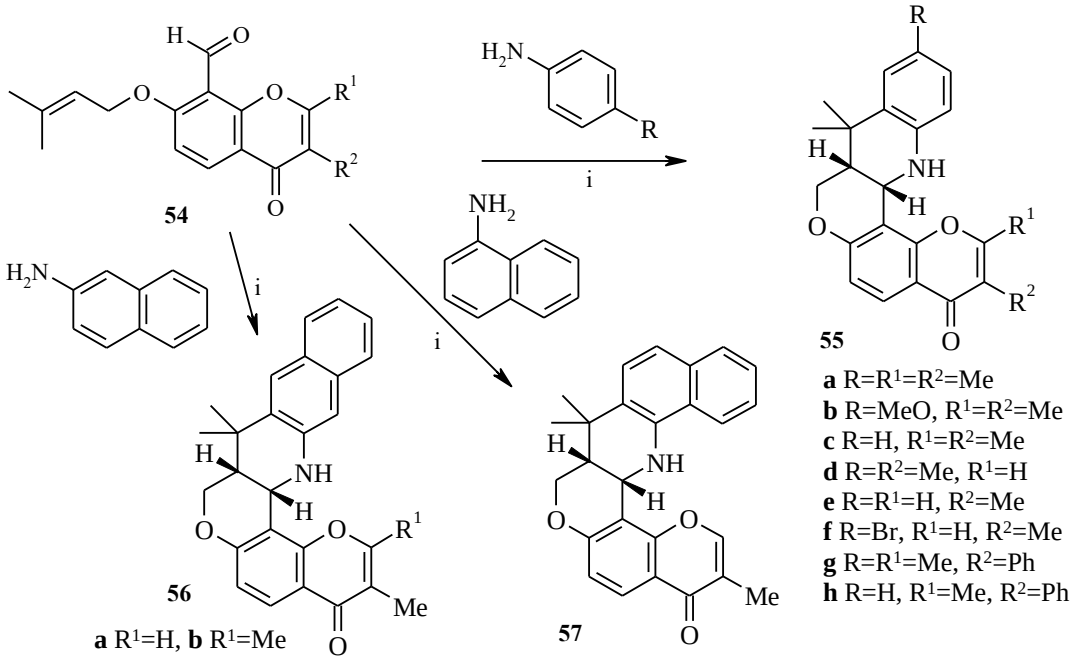
Scheme 17. The synthesis of pyrano[2′,3′:5,6]chromeno[4,3-b]quinolin-4-ones **52**

7-*O*-prenyl derivatives of 8-formyl-2,3-disubstituted chromones **54**, synthesized by alkylation of subsequent 8-formyl-7-hydroxychromones with prenyl bromide, as well as 7-(prop-2-ynyloxy) derivatives **53** are usefull synthones for intramolecular hetero Diels-Alder reaction [80].



Scheme 18. The synthesis of 7-*O*-prenyl-8-formyl-2,3-disubstituted chromones **54**

A series of articles [80-83] is devoted to the synthesis of *O,N*-containing hetarenopyrano[2,3-f]chromones via intramolecular hetero Diels-Alder reaction and their biological activity. *Cis*-fused tetrahydrochromeno[4,3-b]quinolines **55-57** have been synthesized by intramolecular [4+2] imino-Diels-Alder reactions of 2-azadienes derived *in situ* from aromatic amines and 7-*O*-prenyl derivatives of 8-formyl-2,3-disubstituted chromones **54** in the presence of 20 mol % $Yb(OTf)_3$ in acetonitrile under reflux in good to excellent yields [81] (**Scheme 19**).



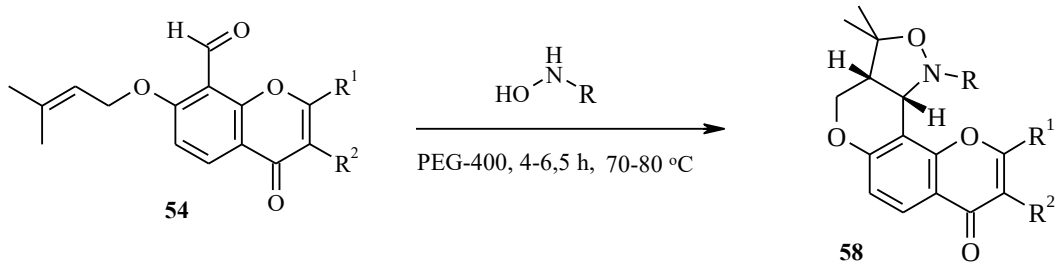
i: $Yb(OTf)_3$, acetonitrile, 3-3,5 h, reflux

Scheme 19. The synthesis of *cis*-fused tetrahydrochromeno[4,3-b]quinolines **55- 57** via intramolecular [4+2] imino-Diels-Alder reaction.

These compounds were evaluated for their antiproliferative activity against MDA-MB-231 and MCF-7 breast cancer cells. The results showed that compounds **57**, **55a** and **55h** exhibit significant antiproliferative activity against MCF-7 breast cancer cells and low inhibitory activity against MDAMB-231 breast cancer cell lines. Compound **56a** displayed activity as comparable to tamoxifen on both the cell lines [81].

Cis-fused chromeno pyrano[4,3-c]isoxazole derivatives **58** have been synthesized by intramolecular [1,3]-cycloaddition of the nitrones generated *in situ* from hydroxylamine derivatives and 7-*O*-prenyl-8-formyl-2,3-disubstituted chromones **54** using PEG-400 as a reaction medium under catalyst-free conditions in 72-90 % yields [82] (**Scheme 20**). The results showed that compounds **58b**, **58c**, **58d**, **58e** and **58k**

exhibit very potent antiproliferative activity against MDA-MB-231 breast cancer cells. Compounds **58a**, **58c**, **58e**, **58i** and **58k** displayed potent inhibitory activity against human MCF-7 breast cancer cell lines. Compounds **58h** and **58i** exhibited significant antiproliferative activity against human cervical cancer cell line, HeLa. While **58b**, **58d** and **58j** were active against human lung cancer cell line, A549. Compound **58j** was found to be the most promising against A549 (Lung cancer) with IC50 value of 0.194 μM [82].



54

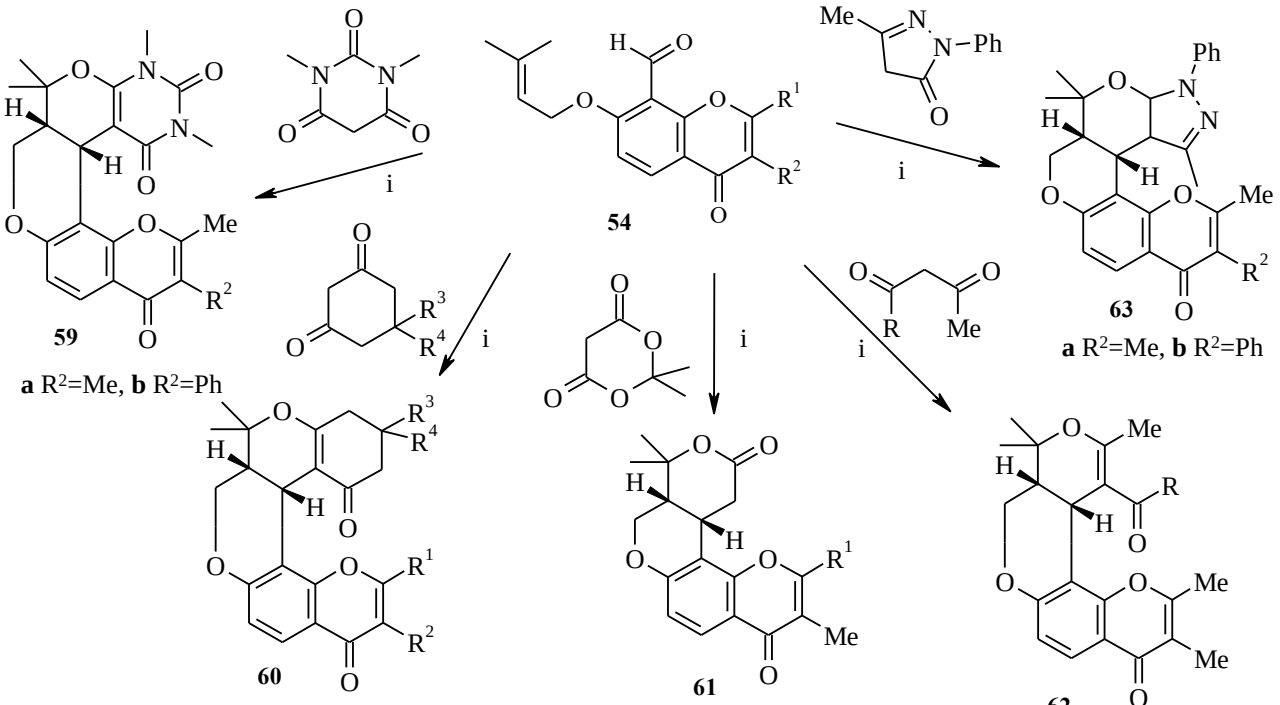
58

72-90 %

58 a R=$PhCH_2$, R^1=R^2=Me; **b** R=cyclohexyl, R^1=R^2=Me; **c** R=4-$MeOC_6H_4CH_2$, R^1=R^2=Me;
d R=4-$MeC_6H_4CH_2$, R^1=R^2=Me; **e** R=i-$PrC_6H_4CH_2$, R^1=R^2=Me; **f** R=4-$FC_6H_4CH_2$, R^1=R^2=Me;
g 2,3,4-$(MeO)_3C_6H_2CH_2$, R^1=R^2=Me; **h** R=$PhCH_2$, R^1=H, R^2=Me; **i** R=cyclohexyl, R^1=H, R^2=Me;
j R=4-$MeOC_6H_4CH_2$, R^1=H, R^2=Me; **k** R=4-$MeC_6H_4CH_2$, R^1=H, R^2=Me; **l** R=4-$MeOC_6H_4CH_2$, R^1=Me, R^2=Ph

Scheme 20. The synthesis of chromeno-annulated *cis*-fused pyrano[4,3-c]isoxazole derivatives **58** via intramolecular nitrone cycloaddition

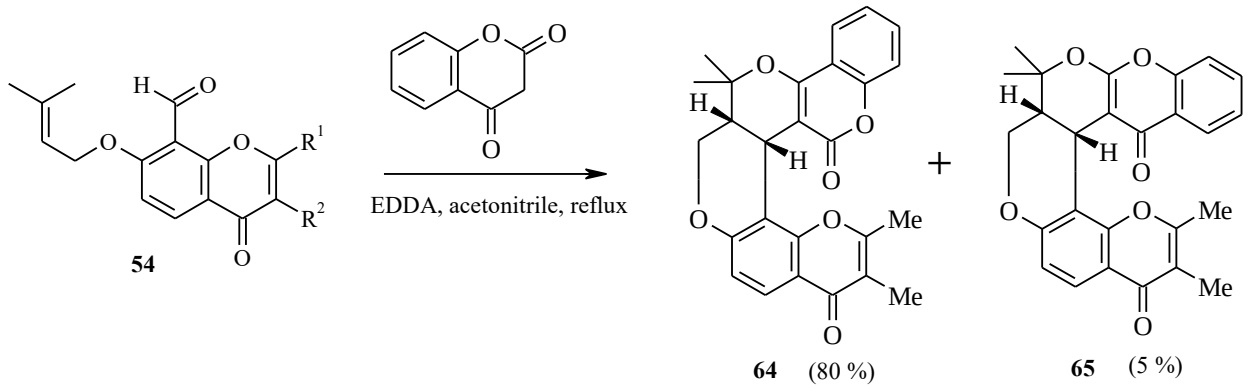
A series of chromeno-annulated *cis*-fused pyrano[3,4-c]pyran derivatives **59-63** have been synthesized by intramolecular [4+2] domino Knoevenagel-hetero-Diels-Alder reactions of 1-oxa-1,3-butadienes derived *in situ* from 1,3-dicarbonyls/active methylenes and 7-*O*-prenyl derivatives of 8-formyl-2,3-disubstituted chromenones **54** in the presence of 20 mol.% ethylenediamine diacetate (EDDA) in acetonitrile under reflux in 80-95 % yields [80] (**Scheme 21**).



Scheme 21. The synthesis of chromeno-annulated *cis*-fused pyrano[3,4-c]pyran derivatives **59**-**63** via intramolecular [4+2] domino Knoevenagel-hetero-Diels-Alder reaction

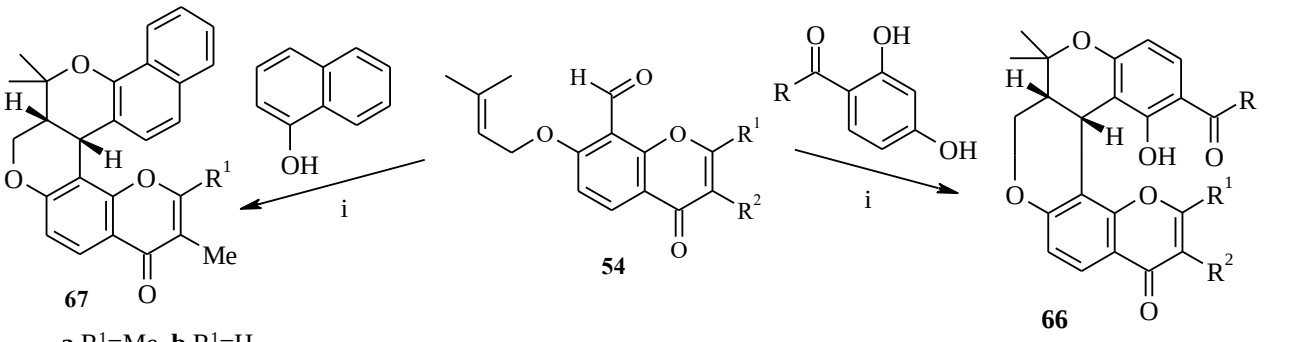
These compounds were evaluated for their antiproliferative activity using an *in vitro* MTT cytotoxicity assay. The results clearly demonstrated that compounds **59a**, **59b**, **60a**, **61b**, **62a**, **62b**, **63a** and **63b** exhibited significant anti-proliferative activity against human A549 lung cancer and non-cancer MRC-5 cell lines along with potent inhibitory activity against human neuroblastoma SK-N-SH cancer cell lines. Among these, compounds **59a**, **59b** and **61b** displayed the most potent anti-proliferative activity against human lung cancer A549 cell lines, while **59a** and **59b** displayed activity against neuroblastoma SK-N-SH cancer cell lines when compared to the standard doxorubicin [80].

Reaction of **54** and 2,4-chromanedione gave the mixture of the fused pyranobenzopyranones **64** (80 %) and **65** (5 %) (**Scheme 22**) [80].



Scheme 22. The synthesis of fused pyranobenzopyranones **64**, **65**.

Chromeno-annulated *cis*-fused pyrano[3,4-c]benzopyran **66** and naphthopyran **67** derivatives have been synthesized from 7-*O*-prenyl-8-formylchromones **54** and resorcinols or naphthols under the same conditions in good yields [83]. The compounds **66g** and **67b** exhibited very potent cytotoxicity against human cervical cancer cell line (HeLa). Compound **66g** displayed good inhibitory activity against both breast cancer cell lines, MDA-MB-231 and MCF-7. Further, the compound **66h** exhibited good cytotoxicity against only MDA-MB-231, and compound **67b** showed promising activity against human lung cancer cell line, A549 with IC50value of 2.53 ±0.07 μM, which was comparable to the standard doxorubicin (IC50 = 1.21 ± 0.1 μM).



a R^1=Me, **b** R^1=H

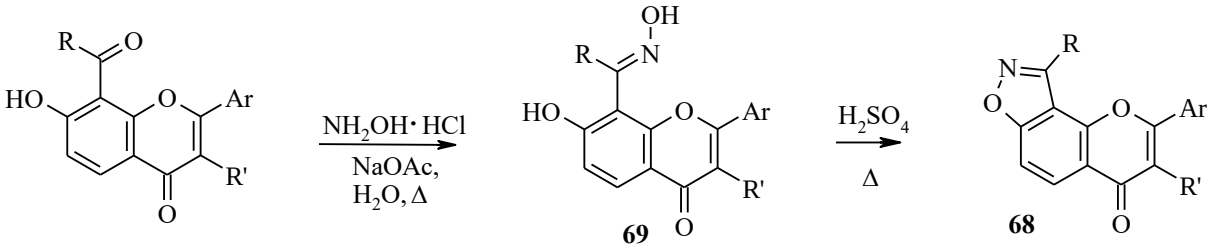
i: EDDA, acetonitrile, reflux 12 h, 80-85 °C

66 a R=Et, R^1=R^2=Me; **b** R=Me, R^1=R^2=Me;
c R=$PhCH_2$, R^1=R^2=Me; **d** R=Ph, R^1=R^2=Me;
e R=Et, R^1=H, R^2=Me; **f** R=Me, R^1=H, R^2=Me;
g R=$PhCH_2$, R^1=H, R^2=Me; **h** R=Ph, R^1=H, R^2=Me;
i R=Et, R^1=Me, R^2=Ph; **j** R=R^1=Me, R^2=Ph

Scheme 23. The synthesis of chromeno-annulated *cis*-fused pyrano[3,4-c]benzopyran **66** and naphthopyran **67** derivatives via domino aldol-type/hetero Diels-Alder reaction

4. N-Containing fused chromones

In respect that furanochromones have been shown to posses a wide range of physiological properties [18, 19], on analogy of these, the synthesis of a few isoxazolo[7,8-d]flavones **68** has been undertaken with the expectation that these compounds may possess biological activity [84]. Isoxazolo[7,8-d]flavones **68** have been synthesized from 8-acetyl- and 8-formyl-7-hydroxyflavones and hydroxylamine hydrochloride via preparing the oximes **69** and next following cyclizing with concentrated sulphuric acid at room temperature. In the case of 3-metylflavones, warming on the water-bath has been found to be necessary to effect cyclization. [84] (**Scheme 24**).

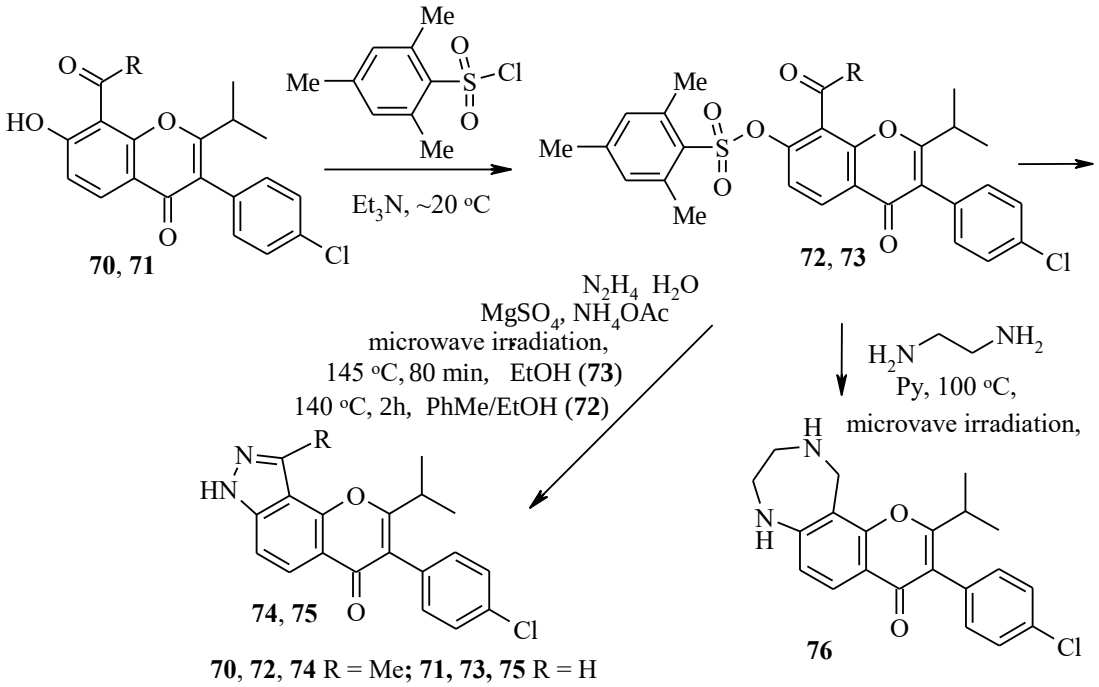


R=H, Me; R'=H, Me;
Ar=Ph, 4-ClC_6H_4, 4-Me C_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 3,4,5-$(MeO)_3C_6H_2$,

Scheme 24. The synthesis of isoxazolo[7,8-d]flavones **68**

The antibacterial activity of isoxazolo[7,8-d]flavones **68** have been evaluated using *Staphylococcus aureus*, *Bacillus coli* and *Bacillus subtilis*. Of the compounds tested, 3-methylisoxazolo[7,8-d]flavone and 4'-chloroisoxazolo[7,8-d]flavone exhibited the maximum activity, inhibiting the growth of all the bacteria at 10 ppm. In general, the 3-methylisoxazolo[7,8-d]flavone derivatives **68** have shown greater activity than thous without this substituent [84].

Annulation of pyrazole cycle to chromone system has been implemented on the basis of 8-acetyl- and 8-formyl-7-hydroxychromones **70, 71**. Their treatment with 2-(mesitylene)sulfonyl chloride in dry CH_2Cl_2 in the presence of Et_3N and catalytic amount of 4-dimethylamino pyridine resulted in esters **72** and **73,** which under nucleophilic substitution by hydrazine hydrate in EtOH (**73**) or in the mixture of toluene and EtOH (**72**) in the presence of $MgSO_4$ and $AcONH_4$ on heating in microwave tube at 145˚C (80 min) or 140˚C (2 h), respectively, provided the corresponding (un)substituted at position 9 pyrano[2,3-e]indazol-4-(7H)-one **74** и **75** [85] (**Scheme 25**).



Scheme 25. The synthesis of chromones annelated with pyrazole and diazepine cycles

A mixture of 2,4,6-trimethylbenzenesulfonic acid 3-(4-chlorophenyl)-8-formyl-2-isopropyl-4-oxo-4H-chromen-7-yl ester (**73**) and ethylene diamine in anhydrous pyridine in a sealed microwave tube was heated under microwave irradiation to give hexahydrochromeno[7,8e][1,4]diazepin-4-one **76** [85] (**Scheme 25**). Chromones annulated with pyrazole (**74**, **75**) and diazepin rings (**76**) at C(7)-C(8) bond were patented as antagonists of VRI receptors [85].

In 2003, a novel tricyclic angular chromone, containing pyridine ring was isolated from the marine fungus *Aspergillus versicolor*. It was reported to have the structure **77** and named aspergillitine [86] (**Figure 5**).

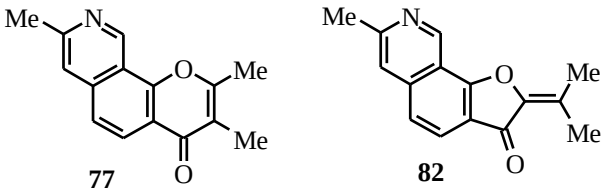
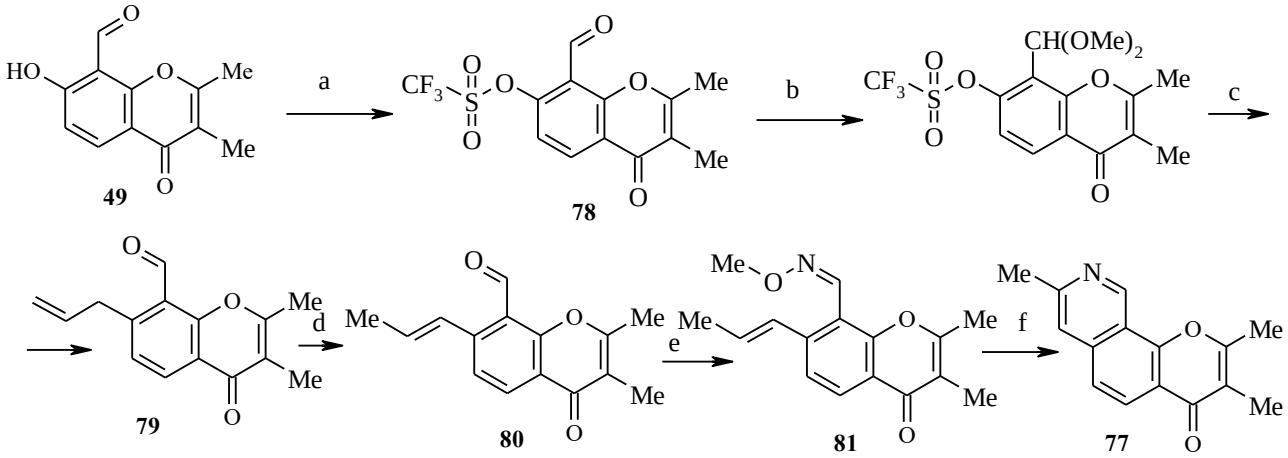


Figure 4. Structures of aspergillitine and alkaloid TMS-120 B from *Aspergillus versicolor*

The synthesis of aspergillitine (**77**) was achieved by Simonetti et al. in 11 steps and in 15 % overall yield from 2,4-dihydroxypropiophenone, through the intermediacy of 2,3-dimethyl-7-hydroxy-8-

formylchromone **49** [87]. Triflation of 7-hydroxy-8-formylchromone **49** and subsequent acetalization of the compound **78** set the stage for Stille allylation to the product **79**. Construction of the nitrogen-bearing heterocyclic ring involved a Stille cross-coupling reaction with *n*-$Bu_3SnCH_2CH{=}CH_2$, followed by double bond isomerization to derivative **80**, oxidation of the chromone carbonyl (**81**), and a final microwave-assisted electrocyclization of the thus formed 6π-electron aza-triene system [87] (**Scheme 26**).



a) *N*-phenyltriflimide, NaH, THF-DMF;
b) $HC(OMe)_3$, CSA, MeOH, 40 ºC;
c) 1. PPh3, LiCl, BHT, $Bu_3SnCH_2CH{=}CH_2$, $Pd(PPh_3)_2Cl_2$, DMF; 2. H+ (workup);
d) $Pd(PPh_3)_2Cl_2$, $CHCl_3$, reflux;
e) $MeONH_2$.HCl, NaOAc, EtOH, reflux;
f) 1,2-Cl_2-C_6H_4, MW.

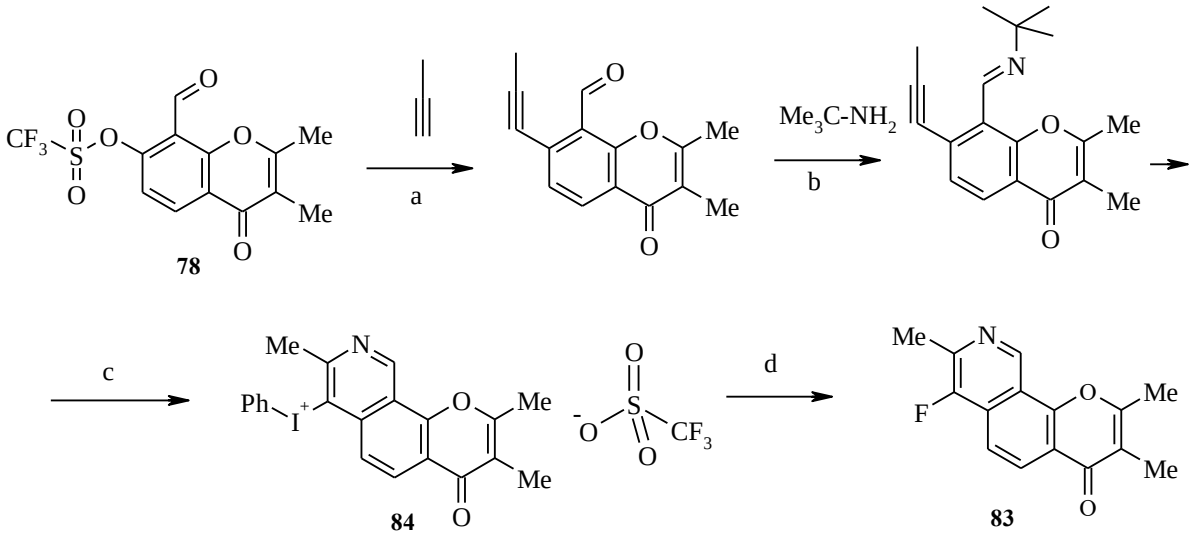
Scheme 26. The synthesis of aspergillitine **77**

The ^1H and ^{13}C NMR spectroscopic data of aspergillitine synthesized by Simonetti did not match with the data for the natural product reported in [86]. The latter being close to the data recorded for natural alkaloid TMC-120 B (**82**) [87]. Therefore, the initially proposed structure of aspergillitine (**77**) remains unobserved among natural products [87, 88].

7-Fluoro-analog of aspergillitine **83**

was synthesized from the corresponding phenyliodonium salt **84**, which was obtained from the ester **78** according to the **Scheme 27** [89, 90].

The ^{18}F-labeled analog of **83** was synthesized analogously using [^{18}F]-tetrabutylammonium fluoride at the final stage [89, 90].



a: triphenylphosphine-palladium(II) chloride, copper(l) iodide, triethylamine in N,N-dimethyl-formamide, Time=12h, T= 70 °C , Inert atmosphere
b: 20 °C / |Molecular sieve
c: 1. silver nitrate / N,N-dimethyl acetamide / 0.33 h / 20 °C
2. 3 h / 20 °C
d: potassium fluoride; 18-crown-6 ether / N,N-dimethyl-formamide / 0.67 h / 100 °C / Schlenk technique; Autoclave; Inert atmosphere

Scheme 27. The synthesis of 7-fluoro-2,3,4-trimethyl-4H-pyrano[3,2-h]isoquinolin-4-one **83**

Conclusions

In conclusion, the evidence from the literature data suggests that the wide spectrum of biological activities of naturally occurring heterocyclic ring fused chromones has stimulated interest in the development of synthesis methods of compounds, containing such skeletons. It is rather important to choose an appropriate starting material, which enables obtaining a wide range of required products. 8-Carbonyl-7-hydroxychromones proved to be versatile synthones for the synthesis of chromones fused with heterocycles at C(7)-C(8) bond, whereas the availability of the carbonyl group ortho to the hydroxyl group in the chromone cycle enables annulation reactions. The present review represented the advances in the synthesis of chromones annulated with *O*-containing 5- and 6-membered heterocycles, such as furan, pyrane, α- and γ-pyrone and their more complicated derivatives, as well as their *N*-

containing 5-7-membered analogues, such as oxazole, pyrazole, pyridine and diazepine rings based on the 7-hydroxy-8-formyl/acetyl/benzoylchromones. The biological activity of angular hetarenochromones has been also mentioned. There is much scope in the reported synthetic strategies and it is anticipated that the observed approach would give rise to design of molecules with enhanced biological properties.

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