Synthesis of linear hetarenochromones based on 7-hydroxy-6-formyl(acetyl)chromones

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Fused chromones are attracting increasing attention as novel therapeutic agents due to their wide distribution in nature, effective bioactivities and low toxicity. 6-Carbonyl-7-hydroxychromones proved to be versatile synthons for the synthesis of linear hetarenochromones by annulation of heterocycle to the chromone core. The present review is focused on the syntheses of furo[3,2-*g*]chromones, pyrano[3,2-*g*]chromones and some of their N-containing analogues, namely chromeno[6,7-d]isoxazoles, pyrano[3',2':6,7]chromeno[4,3-*b*]pyridine-5,11-diones and pyrano[3',2':6,7]chromeno[4,3-*c*]pyridine-5,11-diones based on the 7-hydroxy-6-formylchromones or 7-hydroxy-6-acetylchromones and shows the current state of research to date. The methods for the synthesis of the starting 7-hydroxy-6-formylchromones and 7-hydroxy-6-acetylchromones have been also mentioned. The biological activity of naturally occurring and modified synthetic linear hetarenochromones has been also represented.

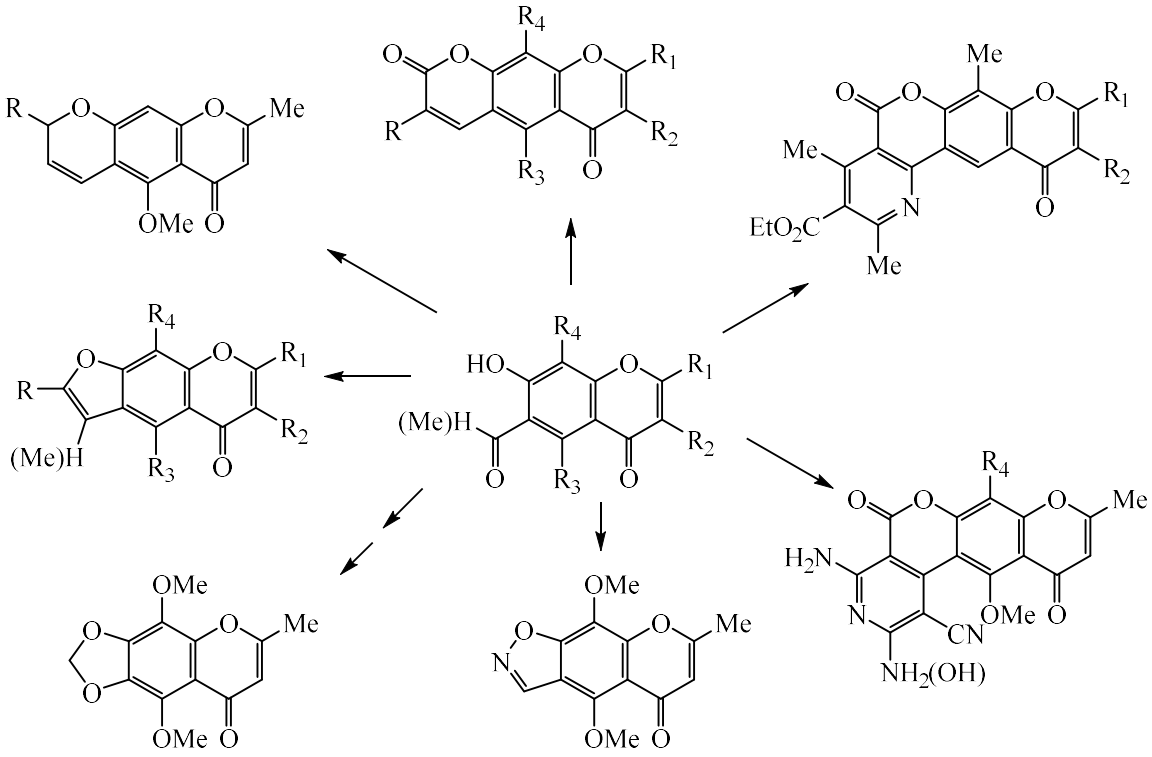
Introduction

Chromone derivatives represent an important class of naturally occurring compounds belonging to the flavonoid family with a wide range of biological activities and [illegible] [1]. The [illegible] high pharmacological potency made them a privileged scaffold in drug discovery [2, 3].

The first chromone to be used in pure form in clinical practice was a linear furochromone khellin [4]. Natural hetarenochromones are represented primarily by furochromone and pyranochromone derivatives. Benzopyranones and furobenzopyranones are compounds of considerable significance owing to their wide spread occurrence in plants and their potential [illegible] ticals in the treatment of renal colic, anginal syndromes, whooping cough, peptic ulcer, in photochemotherapy treatment of a variety of skin diseases such as psoriasis, vitiligo, mycosis fungoides, as antiviral, antitumor, antiproliferation and CNS agents [5].

Design of hetarenochromones can be accomplished both by annulation of heterocycle to the chromone core and by annulation of γ-pyrone cycle to the benzohetarene system. *ortho*-Hydroxy-formyl(acetyl)chromones are treated as attractive starting materials for the synthesis of angular and linear hetarenochromones by the first route. The syntheses of angular hetarenochromones have been highlited in reviews [6, 7].

We present here the current state of research on the synthesis of linear hetarenochromones namely furo[3,2-*g*]chromones, pyrano[3,2-*g*]chromones and some of their N-containing analogues based on the 7-hydroxy-6-formyl- and 7-hydroxy-6-acetylchromones (**Scheme 1**).



Scheme 1. Hetarenochromones based on of 6-formyl(acetyl)-7-hydroxychromones

1. Synthesis of 6-formyl- and 6-acetyl-7-hydroxychromones

It is interesting to note that several 7-hydroxy-6-formylchromones were isolated from natural sources. Two homoisoflavones: 5,7-dihydroxy-3-(4-methoxybenzyl)-8-methyl-4-oxo-4*H*-6-chromenecarbaldehyde (**1**) and 3-(1,3-benzodioxol-5-ylmethyl)-5,7-dihydroxy-8-methyl-4-oxo-4*H*-6-chromenecarbaldehyde (**2**), the former

showing marked cytotoxic activity against lung cancer cells being isolated from the roots of *Ophiopodon japonicus* [8, 9] (**Figure 1**).

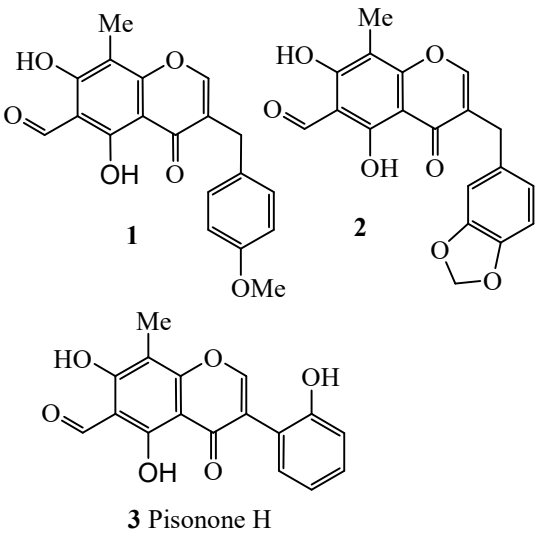
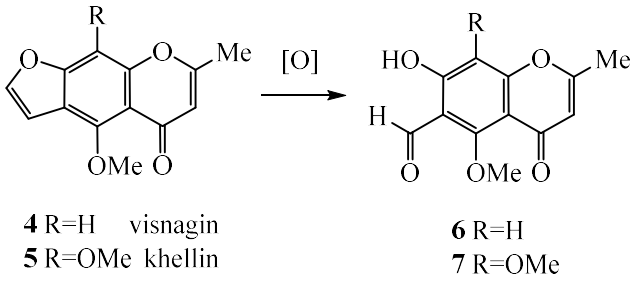


Figure 1. Natural 6-formyl-7-hydroxychromones from *Ophiopodon japonicus* and *Pisonia umbellifera*

5,7,2'-Trihydroxy-6-formylisoflavone (**3**), named as pisonone H, was identified in a study of the stems of *Pisonia umbellifera* used in Chinese folk medicine and tested for anti-inflammatory and cytotoxic activity[10] (**Figure 1**).

Usually, 7-hydroxy-6-formylchromones are synthesized by oxidation of natural linear furochromones: visnagin (**4**) and khellin (**5**) and their synthetic analogues [11-15] (**Scheme 2**).

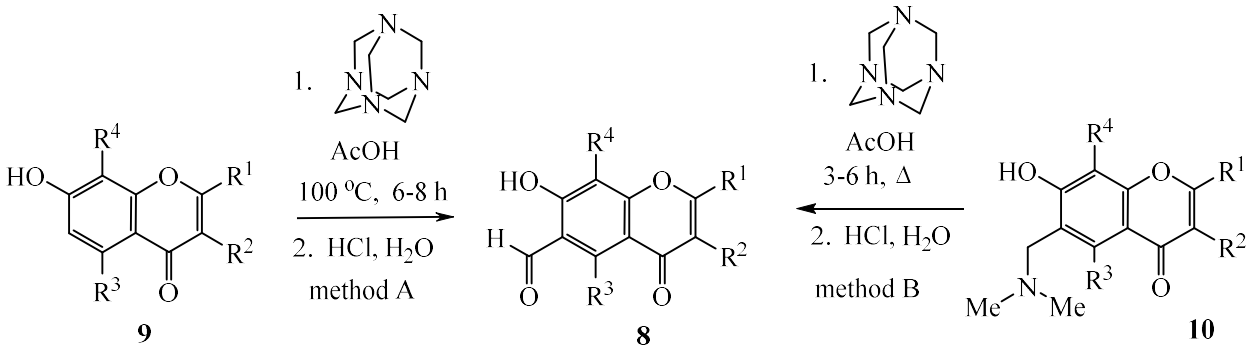


Scheme 2. Oxidation of visnagin (**4**) and khellin (**5**)

Oxidation of visnagin **(4)** with chromic acid afforded the hydroxy aldehyde **6** in good yield [11]. However, treatment of khellin (**5**) with chromic acid under identical conditions (and modifications thereof) failed to yield hydroxyaldehyde **7** [13]. The failure of the above oxidation is perhaps not surprising when one considers that chromic acid is known to effect oxidative demethylation of certain *p*-methoxy aromatics to yield quinones [13]. Oxidation of khellin with mercuric(II) nitrate ($Hg(NO_3)_2$) in aqueous THF followed by treatment with sodium metaperiodate ($NaIO_4$) afforded hydroxy aldehyde **7** in 24 % yield. Catalytic osmylation of khellin, using $NaIO_4$ to reoxidize the osmium, in THF at 50° C afforded hydroxy aldehyde **7** in 73 % yield [12, 13].

6-Formyl-7-hydroxychromones (**8**) can also be obtained from 7-hydroxychromones (**9**) *via* the Duff reaction (method A) by heating them with hexamethylene tetramine (from 1 equiv. [16] to 7 equiv. [17]) in glacial acetic acid at 100°C for 6-8 h followed by hydrolysis with

hot HCl and water (1:1) when heating for 15-30 min (**Scheme 3**). The Duff's method has been used successfully in a number of cases [16-18], however certain difficulties arise in the implementation of the reaction. Due to the low activity of position 6 in 7-hydroxychromones towards electrophilic attack, only 8-substituted 7-hydroxychromones (**9**) can be used in this reaction. With more complex molecules especially having a larger number of free hydroxyls groups in their structure, namely nor-wogonin (**9** R^1=Ph, R^2=H, R^3=R^4=OH) and 5,7,8-trihydroxy-2-methylchromone, it did not work and no aldehyde could be obtained [17].



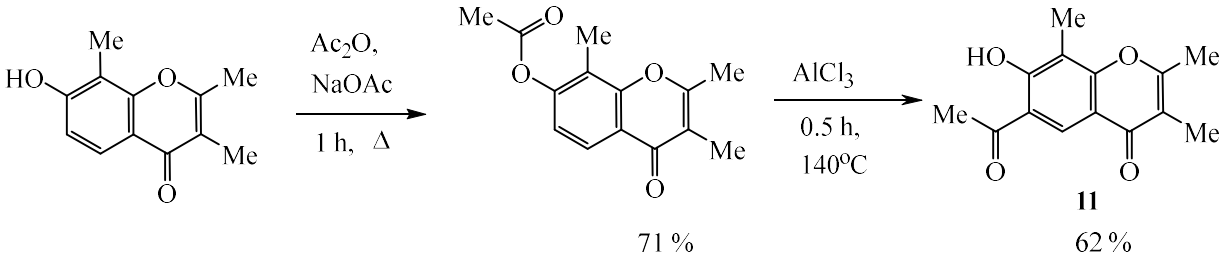
A R^1=R^2=R^4=Me, R^3=H (95 % crude product) [16]
R^1=Me, R^2=H, R^3=OH, R^4=OMe (63 %) [17]
R^1=Ph, R^2=H, R^3=OH, R^4=OMe (52 %) [17, 18]

B R^1=R^4=Me, R^2=OPh, R^3=H (35 %) [19]
R^1=R^3=H, R^2=4-MeOC_6H_4, R^4=Me (46 %) [20]

Scheme 3. The synthesis of 6-formyl-7-hydroxychromones *via* the Duff reaction

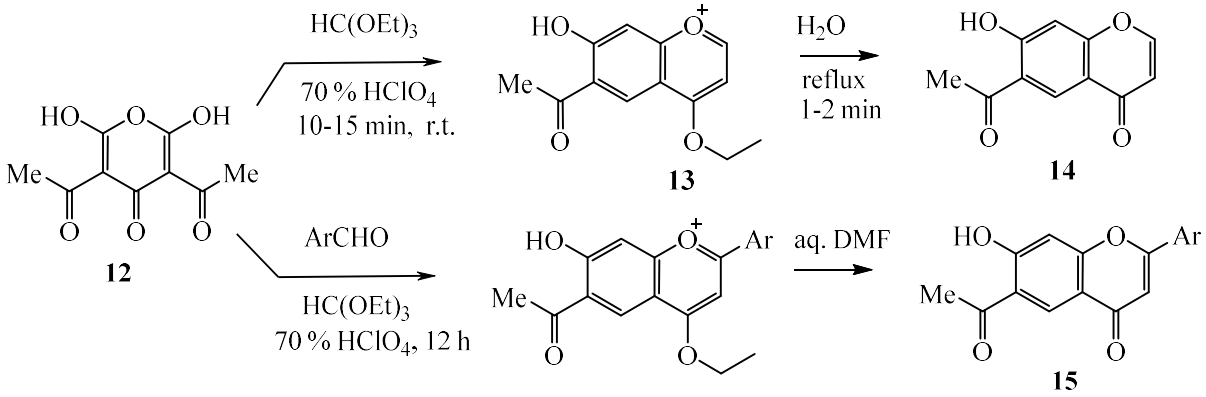
Another embodiment of 6-formyl-7-hydroxychromones (**8**) synthesis (method B) starting from 6-aminomethyl derivatives of 7-hydroxychromones (**10**) under modified Duff reaction conditions, namely refluxing **10** with 2 equiv. of hexamethylene tetramine in AcOH for 3-6 h followed by acid hydrolysis, has been reported in [19, 20] (**Scheme 3**). It should be noted that carrying out this reaction while heating in a water bath (100ºC) did not lead to the desired result. Under these conditions, only the hydrochloride of the aminomethyl derivative **10** was isolated [19].

The synthesis of 6-acetyl-7-hydroxychromones was realized *via* acetylation of 8-substituted-7-hydroxychromones with acetic anhydride containing anhydrous sodium acetate followed by Friss rearrangement with anhydrous aluminium chloride, as shown in the **Scheme 4** for 6-acetyl-7-hydroxy-2,3,8-trimethyl-chromone (**11**) [21].



Scheme 4. The synthesis of 6-acetyl-7-hydroxy-2,3,8-trimethylchromone

The reaction of resodiacetylacetophenone (**12**) with ethyl orthoformate (6 equiv.) in the presence of 70 % perchloric acid gave 4-alkoxybenzopyrylium salt **13**, which was converted to 6-acetyl-7-hydroxychromone **14** in almost quantitative yield on refluxing water [22] (**Scheme 5)**. Reaction of **12** with aromatic aldehydes in ethyl orthoformate followed by boiling in DMF and dilution with water resulted in 6-acetyl-7-hydroxyflavones **15** with hypolipidemic activity [23] (**Scheme 5)**.



Ar=4-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-MeO-3-OHC_6H_3, 3,4-$(MeO)_2C_6H_3$

Scheme 5. The synthesis of 6-acetyl-7-hydroxychromones from 4-alkoxybenzopyrylium salts

6-Formyl- and 6-acetyl-7-hydroxychromones have been extensively used in the synthesis of chromones, annulated with five- and six-membered heterocycles, namely furo[3,2-*g*]chromones, dioxolo[4,5-*g*]chromones, chromeno[6,7-*d*]isoxazoles, pyrano[3,2-*g*]chromones, pyrano[3',2':6,7]-chromeno[4,3-*b*]pyridines and pyrano[3',2':6,7]chromeno[4,3-*c*]pyridines.

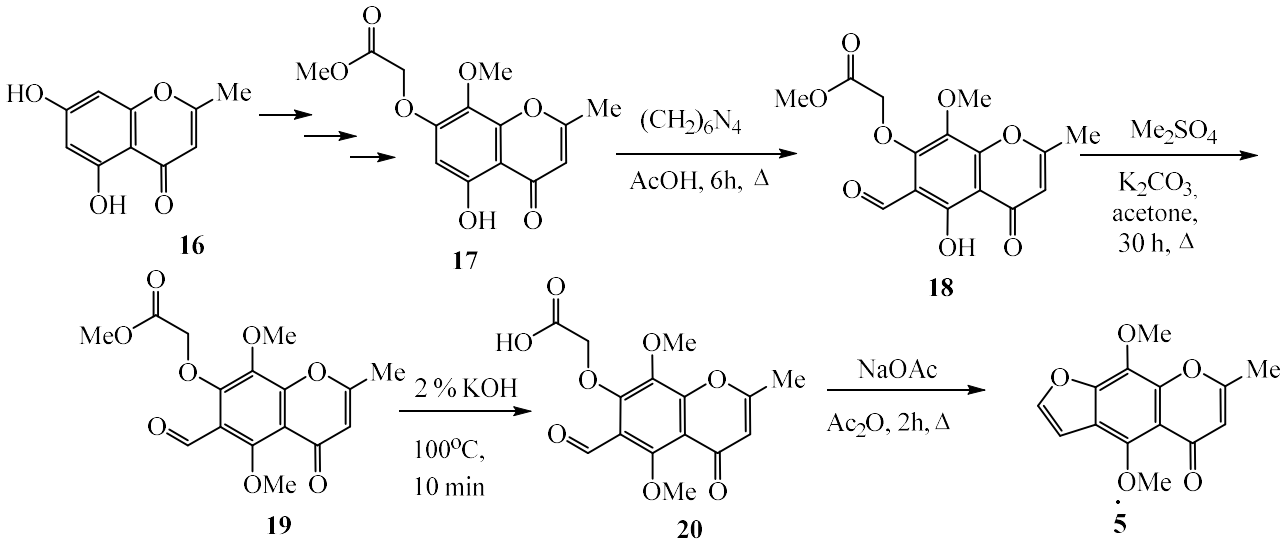
2. Chromones annulated with five-membered heterocycles

2.1. Furo[3,2-*g*]chromones

Khellin and visnagin (**Scheme 2**) are the most famous natural linear furo[3,2-*g*]chromones found in fruits and seeds of

Ammi visnaga, a plant belonging to the family *Umbelliferae* [24]. They were shown to possess phototoxic and genotoxic activities against various kinds of microorganisms, phototherapeutic properties similar to those of the psoralen, but with substantially lower phototoxic and DNA damaging effects, herbicidal and vasodilating activity. These results support their application in the photo-chemotherapeutic treatment of vitiligo and psoriasis, usefulness in the treatment of spasmodic conditions like asthma and intestinal colic and also for certain diseased conditions of the heart and their potential as bioherbicides or lead molecules for the development of new medicines [25-27].

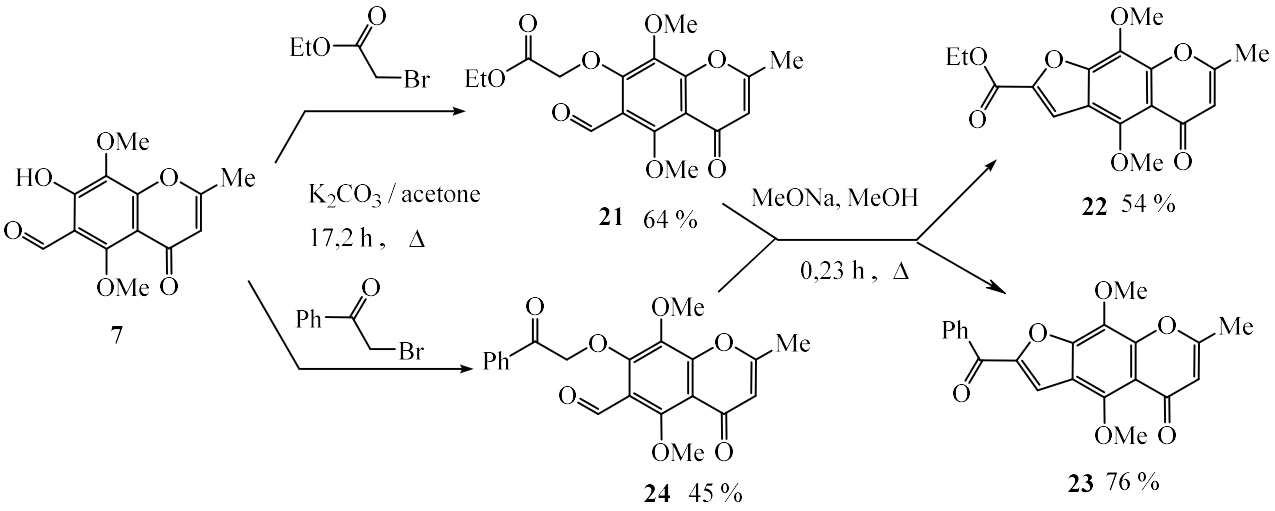
A facile synthesis of kellin (**5**) was implemented in 1949 starting from 2-methyl-5,7-dihydroxychromone (**16**) in 7 steps. The approach relied on formylation of 5-hydroxy-8-methoxy-7-O-carbomethoxy-methyl-2-methylchromone (**17**) with hexamine in glacial acetic acid solution yielding the 6-formyl derivative **18**, followed by complete methylation to the key intermediate aldehydo-ester **19** and gentle alkali hydrolysis to aldehydo-acid **20** which when boiled with acetic anhydride and sodium acetate formed the furan ring with the simultaneous evolution of carbon dioxide [27] (**Scheme 6**).



Scheme 6. The synthesis of kellin

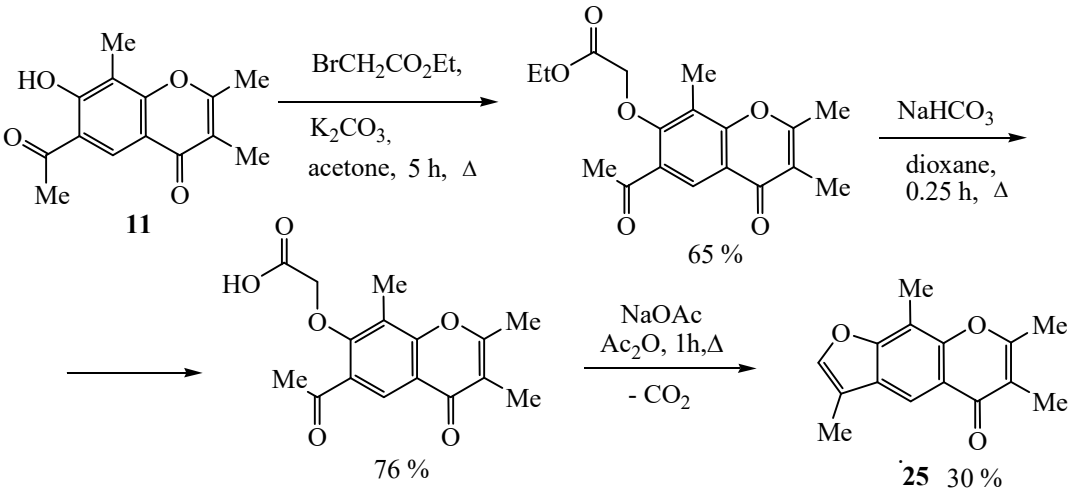
An alternative approach was realized by Gammill *et al* to obtain aldehydo-ester **21**. It was synthesized upon alkylation of 5,8-dimethoxy-7-hydroxy-2-methyl-6-formyl-chromone **7** with ethyl bromoacetate in the presence of K_2CO_3 in refluxing acetone [13]. Treatment of **21** with 1 equiv of sodium methoxide in methanol cleanly afforded 2-ethoxycarbonylkellin (**22)** in 54% yield [13] (**Scheme 6**). 2-Benzoylkellin (**23**) and its

precursor **24** were prepared under the same conditions using phenacyl bromide as an alkylating agent [13] (**Scheme 7**).



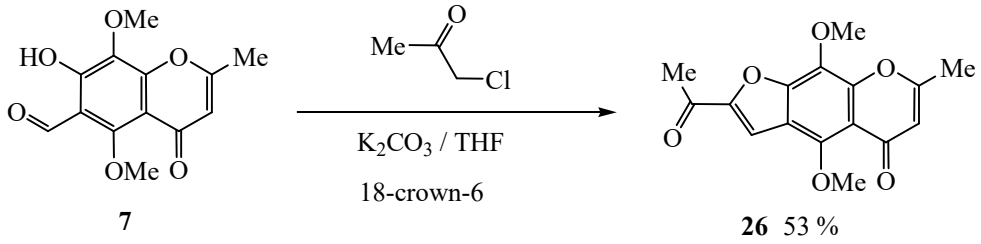
Scheme 7. The synthesis of 2-ethoxycarbonylkellin and 2-benzoylkellin

Tetramethylfuro[3,2-*g*]chromone **25**, proposed as potential photochemotherapeutic agent, was synthesized starting from 6-acetyl-7-hydroxy-2,3,8-trimethylchromone (**11**) by alkylation with ethyl bromoacetate in anhydrous acetone in the presence of K_2CO_3, followed by ester hydrolysis and subsequent intramolecular condensation as shown in **Scheme 8** [21].



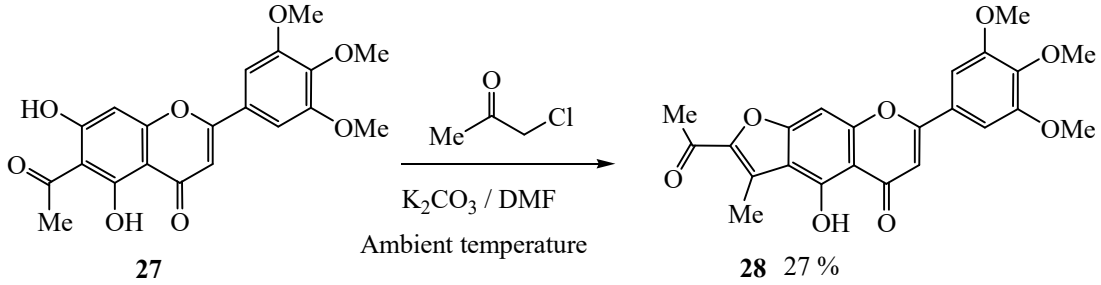
Scheme 8. The synthesis of tetramethylfuro[3,2-g]chromone **25**

In contrast to the aforecited examples, alkylation of 7-hydroxy-6-formylchromone **7** with chloroacetone in refluxing THF containing 18-crown-6/K_2CO_3 afforded the 2-acetylkellin **26** directly and in a good yield [12, 13] (**Scheme 9**).



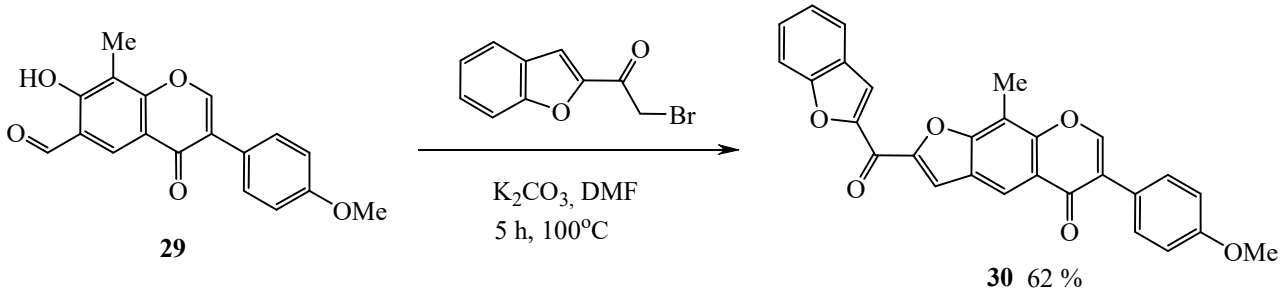
Scheme 9. The synthesis of 2-acetylkellin **26**

Treatment of 6-acetyl-5,7-dihydroxyflavone **27** with chloroacetone in DMF in the presence of K_2CO_3 at ambient temperature resulted in the formation of the 2-acetylfuroflavone **28** in 27 % yield [28] (**Scheme 10**).



Scheme 10. The synthesis of 2-acetylfuroflavone **28**

Alkylation of 7-hydroxy-6-formylisoflavone **29** with 2-bromoacetyl-benzofuran in DMF in the presence of K_2CO_3 when heating at 60ºC is accompanied by condensation along the carbonyl group to result in the annulation of the furan ring to the isoflavone core and formation of 2-benzo-[*b*]furan-2-ylcarbonyl-6-(4-methoxyphenyl)-9-methyl-5*H*-furo[3,2-*g*]chromone (**30**) in 62 % yield [20] (**Scheme 11**).

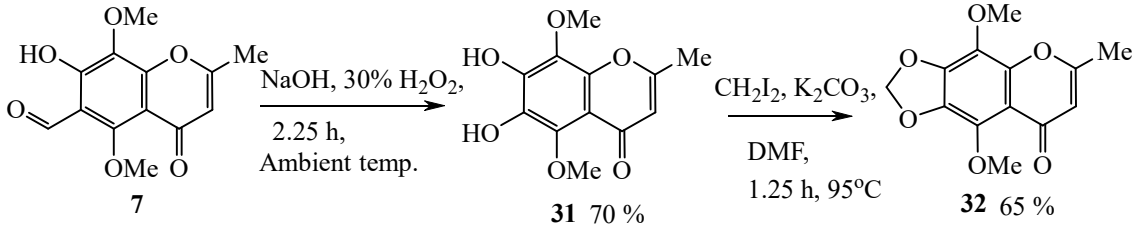


Scheme 11. The synthesis of 2-benzo[*b*]furan-2-ylcarbonyl-6-(4-methoxyphenyl)-9-methyl-5*H*-furo[3,2-*g*]chromone **30**

2.2. Dioxolo[4,5-*g*]chromone

Dioxolo[4,5-*g*]chromone system has been synthesized from 5,8-dimethoxy-2-methyl-7-hydroxy-6-formylchromone (**7**) in two steps. Hydroxy aldehyde **7** underwent a smooth Dakin oxidation ($NaOH/H_2O_2$) to yield diol **31**. Alkylation of **31** with diiodomethane (K_2CO_3/DMF) afforded 4,9-

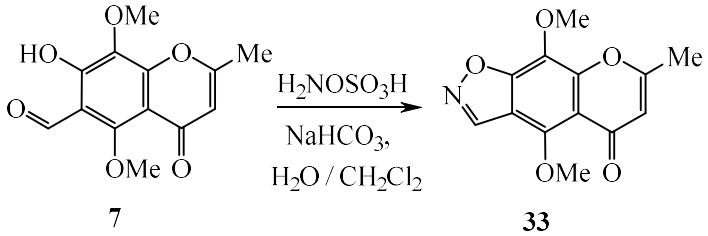
dimethoxy-6-methyl-8*H*-[1,3]dioxolo[4,5-*g*]chromen-8-one **32** in 65 % yield [13] (**Scheme 12**).



Scheme 12. The synthesis of 4,9-dimethoxy-6-methyl-8*H*-[1,3]dioxolo[4,5-*g*]chromen-8-one **32**

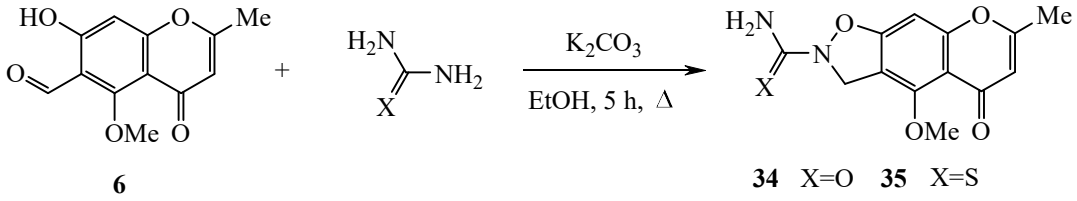
2.3. Chromeno[6,7-*d*]isoxazoles

Annulation of isoxazole cycle to the chromone system has been implemented on the basis of 6-formyl-7-hydroxychromones **6** and **7**. 4,9-Dimethoxy-7-methyl-5*H*-chromeno[6,7-*d*]isoxazol-5-one **33** was prepared in 79 % yield by slow addition of O-sulfonic acid hydroxylamine to the aldehyde **7** in a two phase system (H_2O / CH_2Cl_2) containing $NaHCO_3$ (2 equiv.) [12] (**Scheme 13**).



Scheme 13. The synthesis of 4,9-dimethoxy-7-methyl-5*H*-chromeno[6,8-*d*]isoxazol-5-one **33**

6-Formyl-7-hydroxy-5-methoxy-2-methylchromone (**6**), on treatment with urea and thiourea in ethanol in the presence of anhydrous potassium carbonate, gave 2,3-dihydroisoxazole derivatives **34, 35** [29] (**Scheme 14**).



Scheme 14. The synthesis of chromeno[6,8-*d*]isoxazol-2(3H)-carboamide **34** and carbothioamide **35**

3. Chromones annulated with six-membered heterocycles

3.1. 2*H*,6*H*-Pyrano[3,2-*g*]chromones

Among the naturally occurring chromones with antitumor potential, one can find compounds possessing the core structure of pyran or dihydropyran attached to the chromone skeleton belonging to pyranochromone derivatives [30]. 3,3-Dimethylallylspatheliachromene methyl ether (**36**), 3,3-dimethylallyl-spatheliachromene (**37**) and 5-*O*-methyl-cneorumchromone K (**39**) isolated from *Dictyoloma vandellianum* A. Juss (*Rutaceae*), were tested for cytotoxic activities towards tumor cell lines B16-F10, HepG2, K562 and HL60 and non-tumor cells PBMC. Compound **36** was the most active showing IC_{50} values ranging from 6.26 to 14.82 μg/ml in B16-F10 and K562 cell lines, respectively, and presented IC_{50} value of 11.65 μg/ml in PBMC cell line [31] (**Figure 2**).

3,3-Dimethylallylspatheliachromene (**37**) and pulverochromenol (**38**) isolated from two Spanish Cneoraceae, *Cneorum tricoccum* and *C. pulverulentum*, may be of potential interest as antitumorals showing an inhibitory activity on HeLa cells with ID_{50} of 5 and 1 μg/ml, respectively [32] (**Figure 2**).

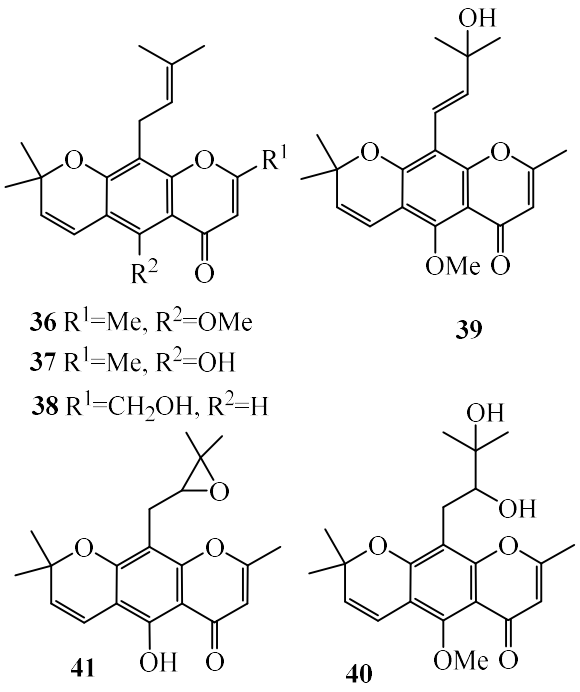
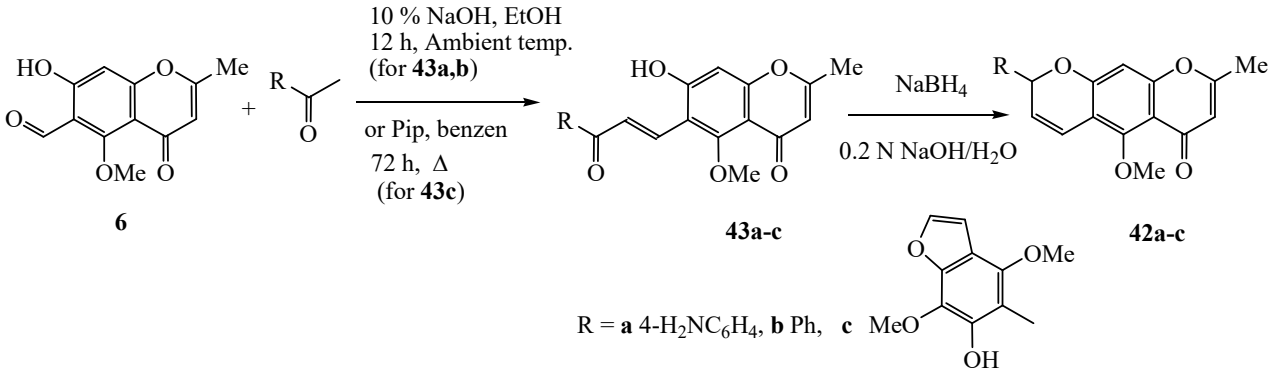


Figure 2. Natural linear pyranochromones

Phytochemical investigation from roots of *Spathelia excelsa* yielded the pyrano-chromones 10(2,3-dihydroxy-3-methylbutanyl)-methoxyspatheliacromen (5-methoxy-spatheliabischromen) (**40**) and 10(2,3-epoxy-3-methylbutanyl)spatheliachromen (**41**) [1, 33] (**Figure 2**). The latter, according to the results of assays against protozoan parasites, showed significant activity, mainly as trypanocidal [33].

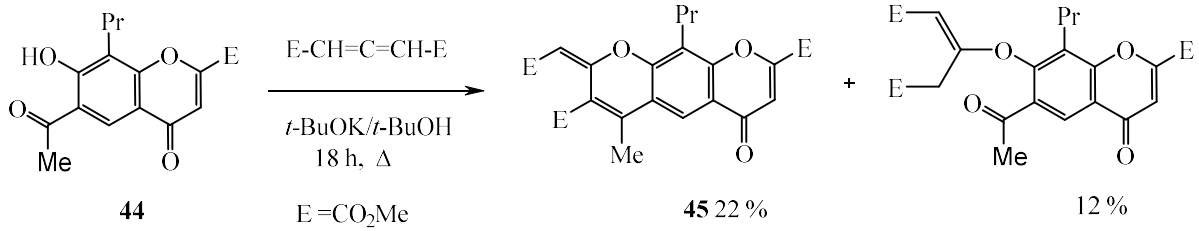
A facile synthesis of pyrano[3,2-*g*]chromones **42a-c** was implemented by condensation of 6-formyl-7-hydroxy-chromone **6** with aminoacetophenone, acetophenone and khellinone yielding the chalcones **43a-c**, which upon reduction with $NaBH_4$ afforded 5-methoxy-8-methyl-2-R-2*H*,6*H*-pyrano[3,2-*g*]chromen-6-ones **42a-c**. Compounds **42b**, **42c**, **43b** and **43c** were

tested for analgesic, antiinflammatory and ulcerogenic activities. Compounds **42b** and **42c** were found to be potent analgesics and **42c** showed minimal ulcerogenic effect. None of the compounds tested possessed antiinflammatory activity [29] (**Scheme 15**).



Scheme 15. Synthesis of 5-methoxy-8-methyl-2-R-2*H*,6*H*-pyrano[3,2-*g*]chromen-6-ones **43a-c**

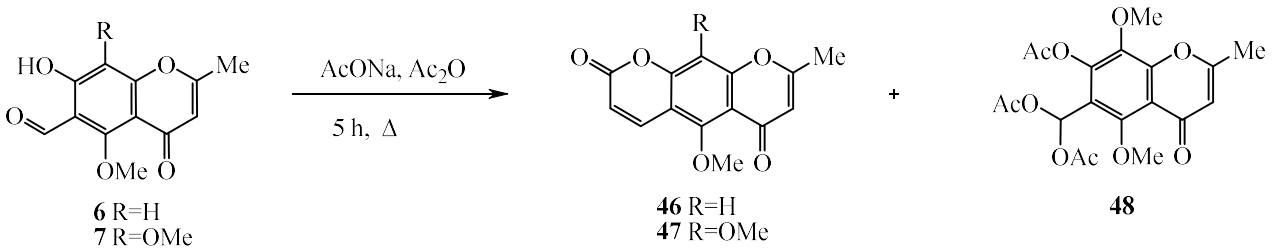
6-Acetyl-7-hydroxychromone **44** has been converted into pyrano[3,2-*g*]chromone **45** in 22 % yield by the reaction with allene-1,3-dicarboxylic ester when heating with potassium *tert*-butylate in *tert*-butyl alcohol for 18 h [34] (**Scheme 16**).



Scheme 16. Synthesis of dimethyl 2-(2-methoxy-2-oxoethylidene)-4-methyl-6-oxo-10-propyl-2*H*,6*H*-pyrano[3,2-*g*]chromen-3,8-dicarboxylate **45**

3.2. *2H,6H*-pyrano[3,2-*g*]chromene-2,6-diones

The availability of the *o*-hydroxyformylchromones also provided the opportunity to prepare the α-pyronochromone derivatives**.** Treatment of **6** with an excess of sodium acetate in refluxing acetic anhydride for 5 h afforded a 36 % yield of the 5-methoxy-8-methyl-*2H,6H*-pyrano[3,2-*g*]-chromene-2,6-dione (**46**) *via* the Perkin reaction [35] (**Scheme 17**)**.** In a similar case, the *o*-hydroxyformylchromone **7** was found to afford α-pyronochromone **47** in 16.5 % yield and triacetate **48** in 65% yield [13] (**Scheme 17**)**.**



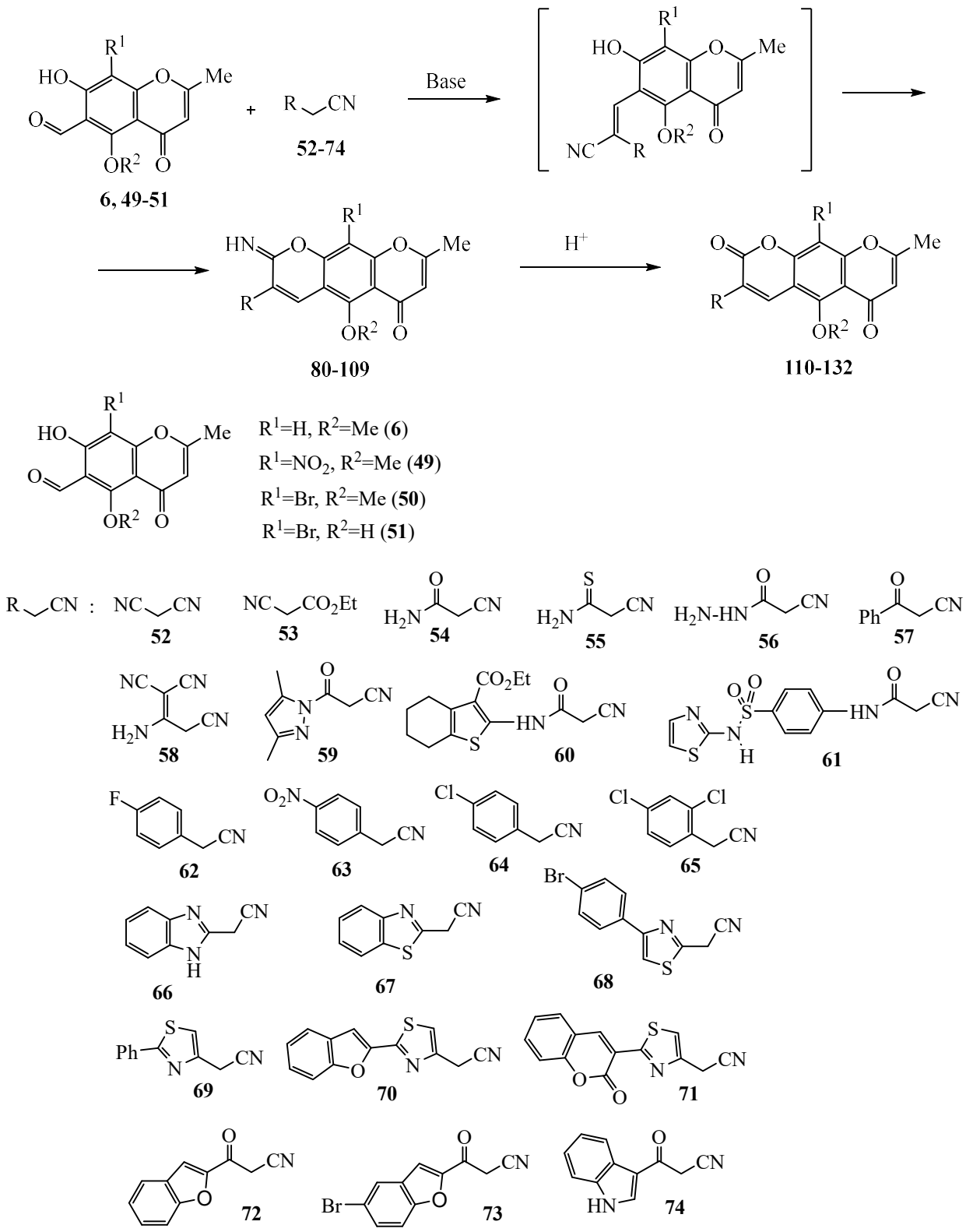
6 R=H
7 R=OMe

46 R=H
47 R=OMe

48

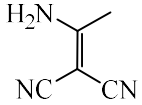
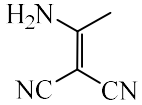
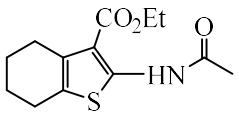
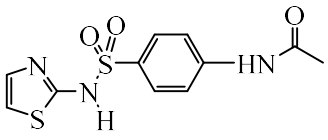
Scheme 17. Synthesis of pyrano[3,2-*g*]chromene-2,6-diones (**46**, **47**) *via* the Perkin reaction

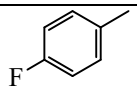
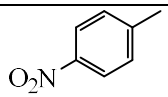
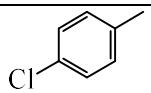
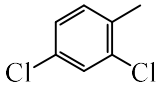
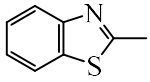
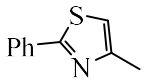
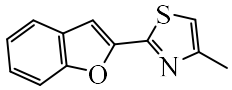
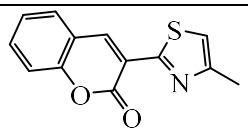
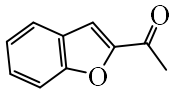
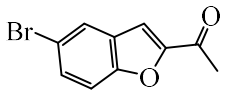
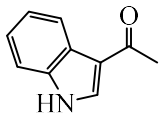
Knoevenagel condensation, based on the interaction of salicylic aldehydes or their more complex derivatives and compounds with an active methylene group, for example, substituted acetonitriles, proved to be the most versatile method for the synthesis of coumarins and their condensed analogs. Thus, the introduction of 6-formyl-7-hydroxychromones into this reaction led to the annulation of α-pyrone cycle to the chromone system. The reaction proceeds in several stages and depending on the reaction conditions, intermediate products can be isolated. 6-Formyl-7-hydroxy-5-methoxy-2-methylchromone (**6**), its 8-nitro (**49**) and 8-bromo (**50**) derivatives as well as 8-bromo-6-formyl-5,7-dihydroxy-2-methylchromone (**51**) were chosen as the carbonyl component (**Scheme 18**). Substituted acetonitriles **52-74** used as the methylene component are presented in the **Scheme 18**. Usually the reaction was carried out in EtOH in the presence of piperidine as a base catalyst, resulting in the formation of 2-iminopyrano[3,2-g]chromen-6-one, which, upon subsequent acid hydrolysis, was converted to pyrano[3,2-g]chromen-2,6-dione. In some cases triethylamine and ammonium acetate were used as base. Diethyl malonate (**75**), ethyl acetoacetate (**76**) and benzoyl acetate (**77**) as well as esters **78** and **79** can also act as a methylene component in the Knoevenagel condensation with 6-formyl-7-hydroxychromones, yielding the corresponding pyrano[3,2-*g*]chromene-2,6-diones (**Scheme 19**). The resulting products, their yields and reaction conditions are shown in **Tables 1-3**.



Scheme 18. Synthesis of pyrano[3,2-*g*]chromene-2,6-diones *via* the Knoevenagel reaction based on substituted acetonitriles

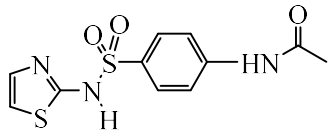
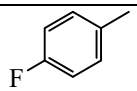
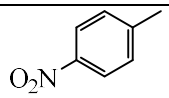
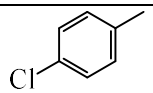
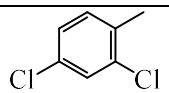
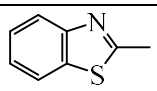
Table 1. The synthesis of 2-iminopyrano[3,2-*g*]chromen-6-ones **80-109**, their yields and reaction conditions

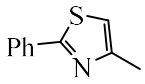
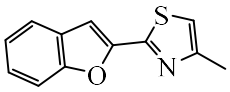
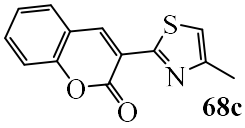
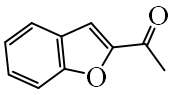
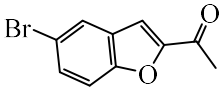
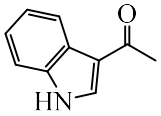
N	R^1	R^2	R	Reaction conditions	Yield, %	Ref
80	H	Me	CN	**6**+**52**, *A:* NH_4OAc, EtOH, 1 h, r.t. *B:* NH_4OAc, EtOH, 1 h, Δ	85 *	[36] [37]
81	NO_2	Me	CN	**49**+**52,** Pip, EtOH, 10 h, Δ	75	[38]
82	Br	Me	CN	**50**+**52,** Pip, EtOH, 10 h, Δ	80	[38]
83	Br	Me	CO_2Et	**50**+**53,** Pip, EtOH, 2 h, r.t.	54	[39]
84	Br	H	CO_2Et	**51**+**53,** Pip, EtOH, 2 h, r.t.	84	[39]
85	H	Me	$CONH_2$	**6**+**54**, NH_4OAc, EtOH, 15 min, Δ	79	[39]
86	Br	Me	$CONH_2$	**50**+**54**, NH_4OAc, EtOH, 15 min, Δ	82	[39]
87	Br	H	$CONH_2$	**51**+**54**, NH_4OAc, EtOH, 15 min, Δ	83	[39]
88	H	Me	$CSNH_2$	**6**+**55**, NH_4OAc, EtOH, 1 h, Δ	80	[37]
89	H	Me	$CONHNH_2$	**6**+**56**, NH_4OAc, EtOH, 1 h, Δ	70	[37]
90	Br	Me	$CONHNH_2$	**50**+**56,** Pip, EtOH, 4 h, Δ	70	[38]
91	NO_2	Me	$CONHNH_2$	**49**+**56,** Pip, EtOH, 4 h, Δ	55	[38]
92	H	Me	PhCO	**6**+**57a,** *A*: Pip, EtOH, 1h, Δ *B*: Pip, EtOH, 15 min, r.t. *C*:Pip (2 drops), granding, 5 min, r.t.	70 45 45	[37] [40] [40]
93	NO_2	Me	PhCO	**49**+**57,** Pip, EtOH, 4 h, Δ	62	[38]
94	Br	Me	PhCO	**50**+**57,** Pip, EtOH, 4 h, Δ	60	[38]
95	NO_2	Me		**49**+**58,** Pip, EtOH, 4 h, Δ	80	[38]
96	Br	Me		**50**+**58,** Pip, EtOH, 4 h, Δ	85	[38]
97	H	Me		**6**+**60,** Pip, EtOH, 0.5 h, 80°C	67	[41]
98	H	Me		**6**+**61,** NH_4OAc, EtOH, 2 h, Δ	67	[42]

99	H	Me		**6**+**63,** Pip, EtOH, 5 h, Δ	85	[5]
100	H	Me		**6**+**64,** Pip, EtOH, 5 h, Δ	90	[5]
101	H	Me		**6**+**65,** Pip, EtOH, 5 h, Δ	90	[5]
102	H	Me		**6**+**66,** Pip, EtOH, 5 h, Δ	80	[5]
103	H	Me		**6**+**67**, *A*: Pip, EtOH, 5 h, Δ *B*: Pip, EtOH, 15 min, r.t. *C*:Pip (2 drops), granding, 5 min, r.t.	97 70	[5] [40]
104	H	Me		**6**+**69,** *A*: Pip, EtOH, 15 min, r.t. *B*:Pip (2 drops), granding, 5 min, r.t.	70 70	[40] [40]
105	H	Me		**6**+**70,** *A*: Pip, EtOH, 15 min, r.t. *B*:Pip (2 drops), granding, 5 min, r.t.	70	[40]
106	H	Me		**6**+**71,** *A*: Pip, EtOH, 15 min, r.t. *B*:Pip (2 drops), granding, 5 min, r.t.	70 70	[40] [40]
107	H	Me		**6**+**72,** *A*: Pip, EtOH, 15 min, r.t. *B*:Pip (2 drops), granding, 5 min, r.t.	80 80	[40] [40]
108	H	Me		**6**+**73,** *A*: Pip, EtOH, 15 min, r.t. *B*:Pip (2 drops), granding, 5 min, r.t.	55 55	[40] [40]
109	H	Me		**6**+**74,** *A*: Pip, EtOH, 15 min, r.t. *B*:Pip (2 drops), granding, 5 min, r.t.	90 90	[40] [40]

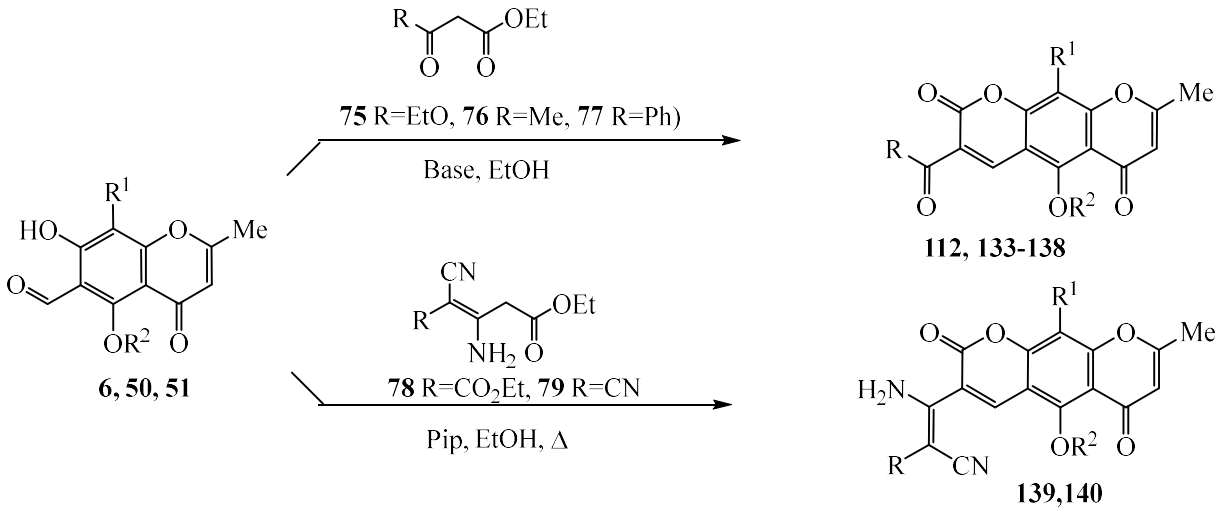
*yield not shown

Table 2. The synthesis of pyrano[3,2-g]chromen-2,6-diones **110-132**, their yields and reaction conditions

N	R^1	R^2	R	Reaction conditions	Yield, %	Ref
110	H	Me	CN	**6**+**52**, NH_4OAc, AcOH, 1 h, r.t. **6**+**53,** Pip, EtOH, 1 h, Δ **6**+**59,** Pip, EtOH, 1,5 h, Δ	80 85 68	[36] [36] [43]
111	Br	Me	CN	**50**+**53,** Pip, AcOH, 10 h, Δ	60	[38]
112	Br	Me	CO_2Et	**50**+**53,** Pip, EtOH, 0,5 h, Δ **77**, AcOH, Δ	*	[39]
113	H	Me	$CONH_2$	**6**+**54**, NH_4OAc, AcOH, 20,5 h, Δ **79**, AcOH, Δ	78 *	[39]
114	Br	Me	$CONH_2$	**50**+**54**, NH_4OAc, AcOH, 20,5 h, Δ	73	[39]
115	Br	H	$CONH_2$	**51**+**54**, NH_4OAc, AcOH, 20,5 h, Δ	64	[39]
116	H	Me	$CSNH_2$	**88**, conc. HCl, EtOH, 1 h, Δ	85	[37]
117	H	Me	$CONHNH_2$	**89**, conc. HCl, EtOH, 1 h, Δ	80	[37]
118	Br	Me	$CONHNH_2$	**90,** AcOH, 0,5 h, Δ	60	[38]
119	H	Me	PhCO	**92**, *A*: conc. HCl, EtOH, 1 h, Δ *B*: 10 % HCl, 1-2 min	60 85	[37] [40]
120	NO_2	Me	PhCO	**93,** AcOH, 0,5 h, Δ	50	[38]
121	H	Me		**6**+**61**, NaOAc, AcOH, 2 h, Δ **98**, conc. HCl, dioxane, 2 h, Δ	58	[42]
122	H	Me		**99,** AcOH, 1h, Δ	85	[5]
123	H	Me		**100,** AcOH, 1h, Δ	80	[5]
124	H	Me		**101,** AcOH, 1h, Δ	85	[5]
125	H	Me		**102,** AcOH, 1h, Δ	95	[5]
126	H	Me		**103,** *A*: AcOH, 1h, Δ *B*: 10 % HCl, 1-2 min	95 90	[5] [40]

127	H	Me		**104**, 10 % HCl, 1-2 min	*	[40]
128	H	Me		**105**, 10 % HCl, 1-2 min	85	[40]
129	H	Me	 **68c**	**106**, 10 % HCl, 1-2 min	70	[40]
130	H	Me		**107**, 10 % HCl, 1-2 min	70	[40]
131	H	Me		**108,** 10 % HCl, 1-2 min	80	[40]
132	H	Me		**109,** 10 % HCl, 1-2 min	85	[40]

*yield not shown



Scheme 19. Synthesis of pyrano[3,2-*g*]chromene-2,6-diones *via* the Knoevenagel reaction based on esters

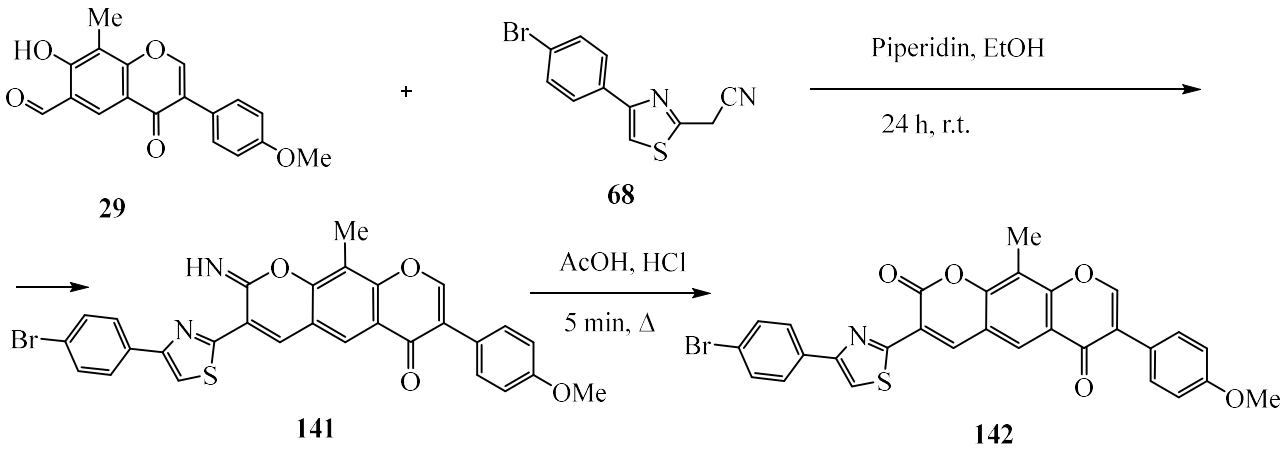
Table 3. The resulting products **112**, **133-140** in Knoevenagel reaction with esters, their yields and reaction conditions

N	R^1	R^2	R	Reaction conditions	Yield, %	Ref
112	Br	Me	EtO	**50**+**75,** Pip, EtOH, 0,5 h, Δ	53	[39]
133	H	Me	EtO	**6**+**75,** Pip, EtOH, 0,5 h, Δ	81	[39]
134	H	Me	Me	**6**+**76,** Pip, EtOH, 0,5 h, r.t.	70	[44]
135	Br	Me	Me	**50**+**76,** Pip, EtOH, 0,5 h, Δ	75	[39]
136	Br	H	Me	**51**+**76,** Pip, EtOH, 1 h, r.t.	53	[39]
137	H	Me	Ph	**6**+**77,** *A:* Pip, EtOH, 0,5 h, r.t. *B:* NH_4OAc, EtOH, 0,5 h, Δ	83	[39]
138	Br	Me	Ph	**50**+**77,** Pip, EtOH, 0,5 h, r.t.	80	[39]
139	H	Me	CO_2Et	**6**+**78,** Pip, EtOH,3 h, Δ	85	[45]
140	H	Me	CN	**6**+**79,** Pip, EtOH,1 h, Δ	90	[37]

Some points should be emphasized and some of the reactions should be discussed separately. Carrying out the Knoevenagel reaction in acetic acid led to the isolation of α-pyronochromones **110, 111, 113-115, 121** in one stage [36, 38, 39, 42] (**Table 2**).

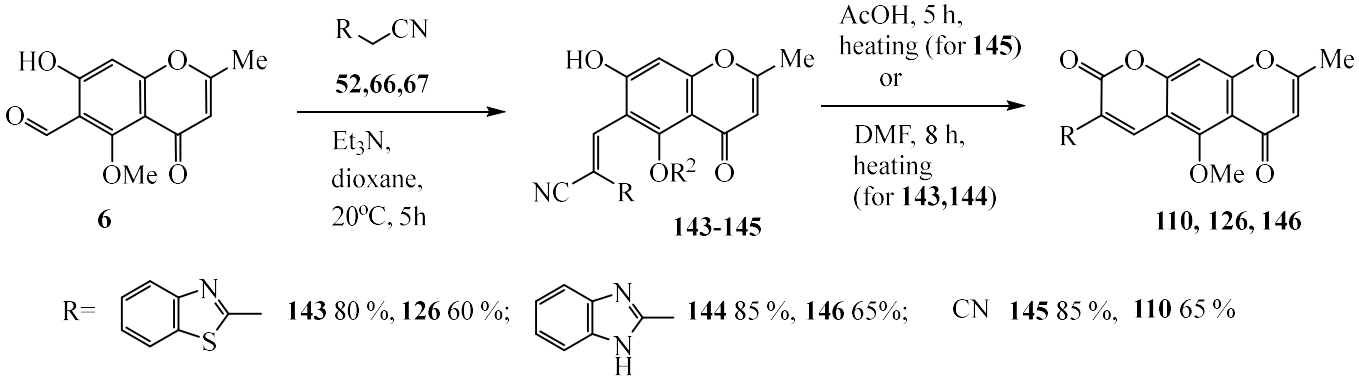
O. H. Hishmat *et al* reported that 8-bromo-6-formyl-7-hydroxy-5-methoxy-2-methylchromone (**50**), when treated with ethyl cyanoacetate (**53**) in ethanol in the presence of piperidine while stirring, gave the corresponding 3-carbethoxy-2-imino-pyranochromone **83** [39] (**Table 1**). When this reaction was repeated in ethanol while refluxing for 30 min, 3-carbethoxy-5-methoxy-8-methyl-10-bromo-6-oxo-2H,6H-benzo[1,2-b;5,4-b']dipyran (**112**) was formed [39] (**Table 2**). The latter compound was also obtained by either refluxing **83** with glacial acetic acid (**Table 2**) or by treating **50** with diethyl malonate in the presence of piperidine [39] (**Scheme 19, Table 3**). At the same time, it is surprising that, as previously described by the same authors, interaction of 6-formyl-7-hydroxy-5-methoxy-2-methylchromone (**6**) with ethyl cyanoacetate (**53**) in ethanol in the presence of piperidine while refluxing for 1 h led to the corresponding 3-cyano derivative **110** [36] (**Table 2**).

Condensation of 6-formyl-7-hydroxy-8-methyl-4'-methoxyisoflavone (**29**) with 2-[4-(4-bromophenyl)-1,3-thiazol-2-yl]-acetonitrile in the presence of a few drops piperidine afforded 2-iminopyrano[3,2-*g*]isoflavone **141**, which gave the corresponding pyranochromenedione **142** by hydrolysis with acetic acid [20] (**Scheme 20**).



Scheme 20. Synthesis of pyrano[3,2-*g*]isoflavones **141**, **142**

By the same manner, when **6** was condensed with benzothiazole-2-ylacetonitrile (**67**), the corresponding iminopyrano[3,2-*g*]chromone **103** and α-pyrono[3,2-*g*]chromone **126** were obtained [5] (**Scheme 19, Tables 1, 2**). It should be noted that when carrying out reactions of **6** with benzothiazol-2-ylacetonitrile (**67**), benzimidazol-2-ylacetonitrile (**66**) and malononitrile (**52**) in dioxane at 20°C for 5 h, in the presence of Et_3N as a catalyst, Yakuout El-S.M.A. was able to isolate intermediate ylidene compounds **143-145**, that were confirmed by C≡N absorption peak in IR spectra [46] (**Scheme 21**). Compound **145** was converted to pyrano[3,2-g]chromen-2,6-dione **110** upon heating in acetic acid for 5 h and 3-hetarylpyrano[3,2-g]chromen-2,6-diones **126** and **146** were obtained from **143** and **144**, when heating in DMF for 8 h [46] (**Scheme 21**).



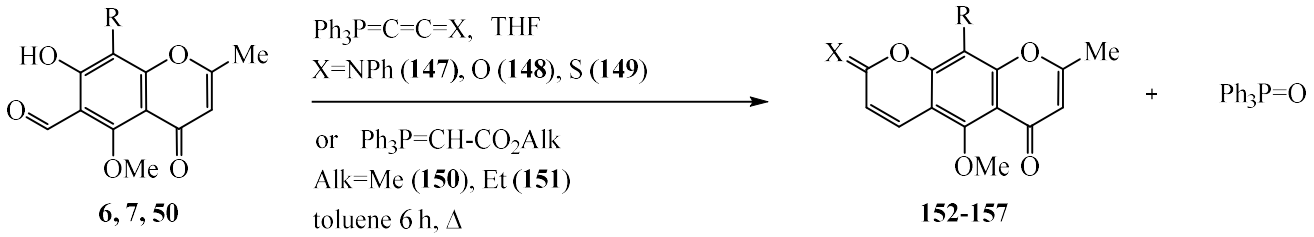
Scheme 21. Synthesis of pyrano[3,2-*g*]chromene-2,6-diones **110**, **126**, **146** by Yakuout El-S.M.A.

The obtained chromone derivatives were tested for molluscicidal and antitumor activities [46]. 6-(2-Cyanoacrylonitrile) derivative **145** was found to have significant molluscicidal activity with LC_{50} 18.7 ppm against *Biomphalaria alexandrina* snails as well as significant antitumor activity against all cell lines i.e. brest cancer, leukaemia cancer and renal cancer having ED_{50} in range of 7-10 μg/ml [1, 46].

Abdel-Aziem *et al* [40] showed that 3-(het)aroyl- (**92**, **107-109**) and 3-hetaryl-2-iminopyrano[3,2-g]chromen-6-ones **103-106** were formed not only under classical Knoevenagel reaction procedure (**Scheme 19, Table 1**), but also when a mixture of 6-formyl-7-hydroxychromone **6** and the appropriate acetonitrile derivatives **57**, **67**, **69-74** containing two drops of piperidine was ground in a mortar with a pestle at room temperature for 2–3 min. After completion of the reaction (5 min), the mixture was transferred by ethanol then filtered off. Compounds **92, 103-109** were subjected to hydrolysis *via* their reaction with 10% of hydrochloric acid under stirring to furnish 2*H*,6*H*-pyrano[3,2-g]chromene-2,6-diones **119, 126-132**. Compounds **92, 103-109** and **119, 126-132** were tested *in vitro* towards a panel of approximately 60 human tumors cell lines derived from nine different cancer types including leukemia, breast, ovarian, prostate, non-small cell lung, colon, CNS, melanoma and renal cancers. The result indicate that, compounds **109, 103, 126, 131** and **128** showed mild activity with growth inhibition (GI) of 28.90, 28.98, 27.29, 25.39 and 28.52%, respectively on the Renal Cancer UO-31; whereas **130** showed moderate activity toward the same cancer cell with growth inhibition (GI) of 35.7%. Besides, compounds **109** exerted moderate growth inhibition (GI) activity towards Non-Small Cell Lung Cancer (HOP-92) by 31.64%. In addition, compound **126** showed moderate growth inhibition (GI) activity against Melanoma (UACC-62) by 32.28% [40].

Another method for the preparation of linear α-pyronochromones is based on the reaction of 8-formyl-7-hydroxychromones with ylide-phosphoranes **147-151**. Treatment of the chromene carbaldehyde **6** with (*N*-phenyliminovinylidene)triphenylphosphorane (**147**) or (2-oxovinylidene)triphenyl-phosphorane (**148**) in THF at room temperature for 10 h in the case of **147** and for 15 h in the case of **148** led to the formation of 5-methoxy-2-methyl-8-phenylimino-*8H*-pyrano[3,2-*g*]chromen-4-one (**152**) and 5-methoxy-8-methylpyrano[3,2-*g*]chromen-2,6-dione (**153**), in 70 % and 45 % yield, respectively, together with triphenylphosphine oxide [47] (**Scheme 22**). When **6** was allowed to react with **148** in THF, at the reflux temperature for 2 h, pyrano[3,2-*g*]chromen-2,6-dione **153** was

obtained in 80 % yield [48]. Reaction of **6** with thioketenylidenetriphenylphosphorane **(149)** proceeded in 6 h to give **154**. 10-Bromopyrano[3,2-*g*]chromen-2,6-diones **155, 156** were isolated in 75 % yield under the same experimental conditions [48] (**Scheme 22**).



152 R=H, X=NPh; **153** R=H, X=O; **154** R=H, X=S; **155** R=Br, X=O; **156** R=Br, X=S; **157** R=OMe, X=O

Scheme 22. The reaction of 8-formyl-7-hydroxychromones with ylid-phosphoranes

Compound **153** and triphenylphosphine oxide were similarly produced upon reacting **6** with alkoxycarbonylmethylenetriphenylphosphoranes **150, 151** in boiling toluene for 6 h. The reaction of **7** with alkoxycarbonyl-methylenetriphenylphosphoranes proceeded under the same conditions to give 10-methoxypyrano[3,2-*g*]chromen-2,6-dione **157** [49, 50] (**Scheme 22**).

3.3. Pyrano[3',2':6,7]chromeno[4,3-b]-pyridine-5,11-diones and pyrano[3',2':6,7]chromeno[4,3-*c*]pyridine-5,11-diones

The chromone alkaloids bear structural similarities with flavonoids. The chromone alkaloids isolated from the root bark of *Schumanniophytum magnificum* Harms. (*Rubiaceae*) consist of a chromone moiety, noreugenin, linked with either a pyridine or a piperidine ring, and were found to possess antiviral activities [51-53]. Among them, isoschumanniophytine **158** (**Figure 3**) was reported to have the structure of 12-hydroxy-9-methyl-*5H*,11*H*-pyrano[3',2':6,7]-chromeno[4,3-*c*]pyridine-5,11-dione, which was confirmed by the synthesis [54].

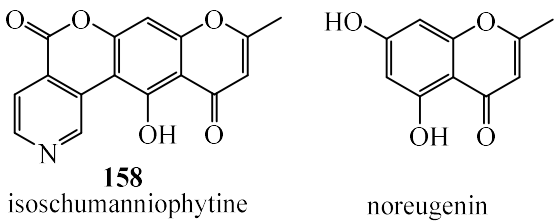
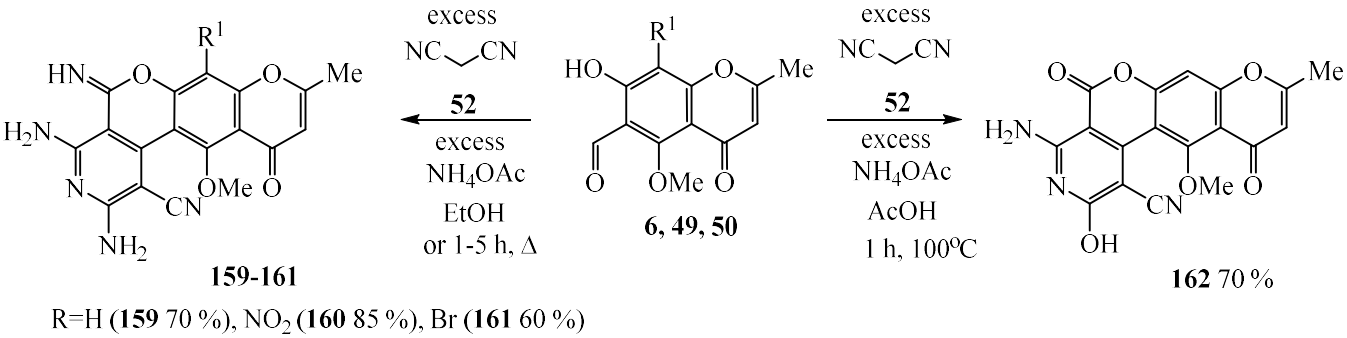


Figure 3. Structures of isoschumanniophytine and noreugenin

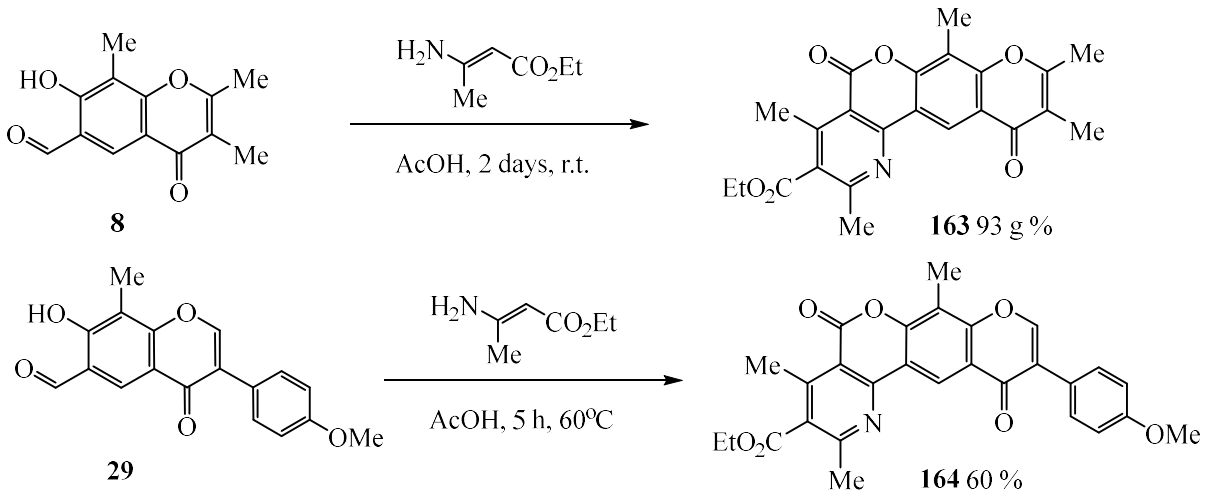
Hishmat O. H. *et al* reported on the synthesis of the pyrano[3',2':6,7]-chromeno[4,3-*c*]pyridine system derivatives

159-162 on the basis of 6-formyl-7-hydroxychromones **6**, **49, 50** [36, 38] (**Scheme 23**). Their treatment with an excess of malononitrile (**52**) in ethanol in the presence of an excess of ammonium acetate led to the formation of 2,4-diamino-9-methyl-5-imino-11-oxo-5*H*,11*H*-pyrano[3',2':6,7]-chromeno[4,3-*c*]pyridine-1-carbonitriles **159-161** *via* the 3-cyano-2-iminopyrano[3,2-g]chromen-6-ones **80-82** which reacted with another molecule of malononitrile in the presence of ammonium acetate through the Michael addition followed by cyclization [36, 38]. When the reaction of 6-formyl-7-hydroxychromone **6** with malononitrile (**52**) took place in glacial acetic acid it yielded 4-amino-2-hydroxy-9-methyl-5,11-dioxo-5*H*,11*H*-pyrano[3',2':6,7]chromeno[4,3-*c*]pyridine-1-carbonitrile **162** [36].



Scheme 23. The synthesis of the pyrano[3',2':6,7]chromeno[4,3-*c*]pyridine-5,11-diones **159-162**

Design of pyrano[3',2':6,7]chromeno-[4,3-*b*]pyridine-5,11-dione system isomeric to isoschumanniophytine skeleton has been accomplished starting from 6-formyl-7-hydroxychromone **8** and isoflavone **29** in reaction with an excess of ethyl 3-aminocrotonate in acetic acid [16, 20] (**Scheme 24**). It should be noted that while the reaction of 6-formyl-7-hydroxy-2,3,8-trimethylchromone (**8**) proceeded at room temperature for 2 days to give ethyl 2,4,7,9,10-pentamethyl-5,11-dioxo-5*H*,11*H*-pyrano[3',2':6,7]chromeno[4,3-*b*]pyridine-3-carboxylate (**163**) [16], success in obtaining ethyl 10-(4-methoxyphenyl)-2,4,7-trimethyl-5,11-dioxo-5*H*,11*H*-pyrano[3',2':6,7]-chromeno[4,3-*b*]pyridine-3-carboxylate (**164**) was achieved only upon heating to 60°C [20].



Scheme 24. The synthesis of the pyrano[3',2':6,7]chromeno[4,3-*b*]pyridines **163**, **164**

Compound **163** was tested *in vitro* for antibacterial activity against *Staphylococcus aureus* and *Escherchia coli* and showed weak activity against both the bacterial strains [16].

Conclusions

In conclusion, it should be noted that when chromone ring is fused with other rings, a synergistic effect of both the rings in their biological activities could be obtained. This is confirmed by the high biological activity of natural linear furochromones and pyranochromones. The biological data prompted organic and medicinal chemists to synthesize new chromone derivatives annulated with hetareno moieties to investigate their activities. Taking into account this fact, the development of methods for the synthesis of linear hetarenochromones is an urgent task. The literature data summarized in the present review clearly showed that cyclocondensations based on 6-formyl(acetyl)-7-hydroxychromones proved to be a convenient, simple and versatile approach for the synthesis of chromones fused with heterocycles at C(6)-C(7) bond, which will be useful to provide scaffolds for drug development.

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