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DIGEST PAPER

Features of the synthesis and biological evaluation of 3-(carboxyphenyl)chromones

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Abstract: Flavonoids and their derivatives have historically been a source of therapeutic agents. Every year, more and more data is published on new flavonoid compounds, both synthetic and isolated from natural sources, and their innumerable physiological and pharmacological activities. This review presents synthetic routes towards 3-(carboxyphenyl)chromones and evaluation of their biological activity as published in both journal and patent literature. We have focused specifically on the 3-(carboxyphenyl)chromones, because while methods of synthesis and biological activity of 2(3)-substituted and 2,3-disubstituted chromones are well studied, literature data on isoflavones containing a carboxyl, ester, or amide group in ring B is scarce and fragmentary. The presented generalization of synthetic strategies and biological activity of 3-(carboxyphenyl)chromone derivatives demonstrates that this class of compounds can be targeted for discovery of new drugs and can be readily prepared owing to recent advances in synthetic organic and medicinal chemistry.

Keywords: chromones; isoflavones; biological activity; synthesis.

Chromones are important structural motifs that serve as useful templates for a design of novel biologically important compounds. The majority of research activity in recent years has been focused on the synthesis of 2(3)-substituted (flavones and isoflavones respectively) and 2,3-disubstituted chromones [1-7]. The synthetic approaches to chromone-pyrazole-fused compounds [8], azachromones, and azachromanones [9] have been summarized. Among numerous currently known isoflavone derivatives, compounds **1** with a carboxyl group in the ring B constitute a small group of compounds (Figure 1).

Isoflavones of natural origin, due to peculiarities of their biogenesis, belong to the category of polyphenols. Any substituents in their structure other than hydroxyl, alkoxyl, and methyl groups are extremely rare [10].

Preparative synthesis of isoflavones mainly focused on making of natural compounds with biological activity as well as the synthesis of analogues and heteroanalogues of isoflavones – 3-hetarylchromones [11]. Methods to synthesize derivatives of pharmaceutically active molecules of 3-(carboxyphenyl)chromones and their synthetic intermediates have also been reported.

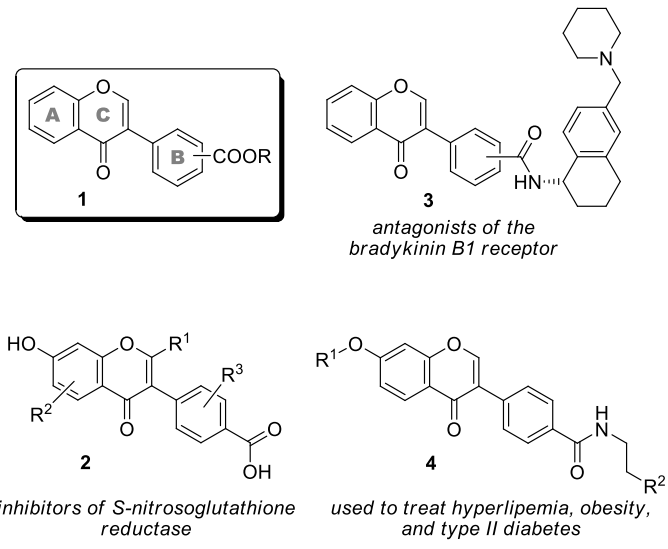

Figure 1. Examples of pharmaceutically active 3-(carboxyphenyl)chromones.

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For example, acids **2** are inhibitors of *S*-nitrosoglutathione reductase and can be used as immunomodulators, anti-inflammatory, and anti-asthma drugs [12]; isoflavone amides of type **3** are antagonists of the bradykinin B1 receptor [13]; and amides **4** are used to prevent or cure hyperlipemia, obesity, and type II diabetes (Figure 1) [14]. Yet, despite the obvious prospect, studies of synthesis of isoflavones containing a carboxyl, ester, or amide group in the B-ring have received little attention. These compounds are usually briefly mentioned in widely scoped publications and rarely feature as individual study objects. In addition, studies of the impact of introducing a highly acidic and reactive carboxyl group or its derivatives, e.g., various amides, on biological activity and approaches to constructing the isoflavone system are isolated.

In this brief review, we present a compilation of the literature data published in the last years, concerning the synthesis and biological activity of the 3-(carboxyphenyl)chromones. Analysis of the data demonstrates that although the introduction of a carboxyl group can complicate the construction of the isoflavone system, these problems are easily overcome. Therefore, we hope that this review will help draw attention to such promising building blocks for medicinal chemistry as 3-(carboxyphenyl)chromones.

Biological activity of 3-(carboxyphenyl)chromones, their esters and amides

The summary of 3-(carboxyphenyl)chromones biological activity presented below illustrates that these compounds can be readily employed as precursors to new drugs with various pharmacological effects.

A series of acids **2** (Figure 2) was reported to inhibit *S*-nitrosoglutathione reductase (GSNOR) [12], which implied that these compounds were promising immunomodulators, anti-inflammatory, and anti-asthma drugs. Similar bioactivity was manifested by corresponding 1-thioisoflavones [15].

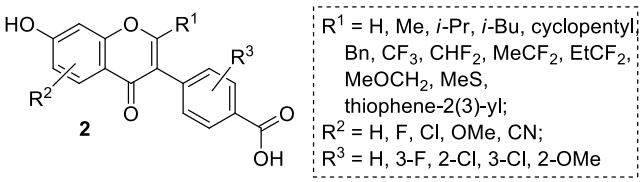
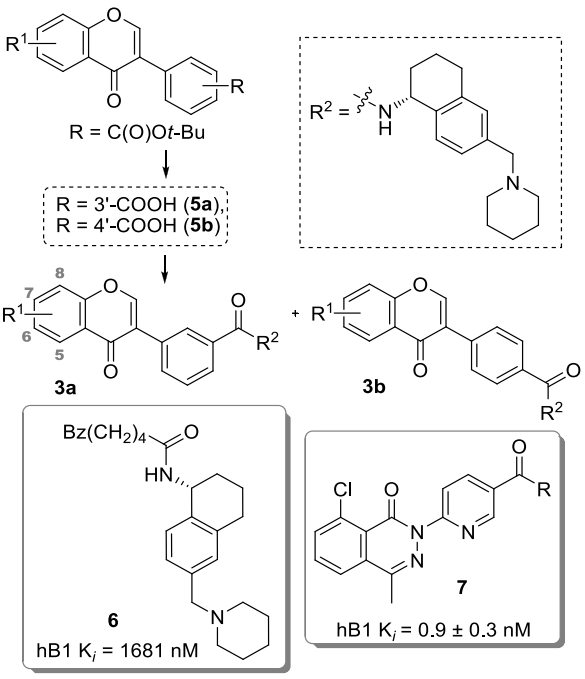


Figure 2. 4-(7-Hydroxy-4-oxo-4*H*-chromen-3-yl)benzoic acids **2** – inhibitors of *S*-nitrosoglutathione reductase.

A number of functionalized isoflavones, including those with carboxyl and carboxamide groups in 4'-position, and their heteroanalogues (at the ring A), featured as possible agents for the treatment of various kinds of mental disorders and addictions due to their ability to inhibit aldehyde dehydrogenase 2 (ALDH-2) [16-17].

Amides **3a,b**, produced from acids **5a,b**, were synthesized in the course of amide **6** modification in order to obtain new antagonists of the bradykinin B1 receptor (hB1) (Scheme 1) [13].

Despite *p*-isomer **3b** being less effective than its analogue with the phthalazinone cycle, it was selected as a promising compound for a more detailed study. It is interesting to note the significantly higher activity of *p*-isomer **3b** in comparison with *m*-isomer **3a**. The same pattern was observed not only for isoflavone derivatives but also for structurally related phthalazinones.



Scheme 1. Isoflavone amides **3** – antagonists of the bradykinin B1 receptor.

Interestingly, subsequent studies of isoflavone amides **3a,b** showed that their inhibitory activity significantly depends on the presence of substituents in the A-ring of isoflavone [18]: *p*-amide **3b** with a F or Cl atom introduced into the 5th position of the chromone ring is quite capable of competing in terms of activity with the most successful inhibitor **7** in a series of phthalazinones from a previous study [13]. Table 1 shows the efficiency of the bradykinin B1 receptor inhibition by the indicated compounds; as a numerical parameter, the inhibitory constant (K_i) is used.

Table 1. The efficiency of inhibition of the hB1 receptor.

Compd	R^1	hB1 K_i (nM)	Compd	R^1	hB1 K_i (nM)
3aa	H	64 ± 11	**3ba**	H	184 ± 32
3ab	5-Cl	29 ± 12	**3bb**	5-Cl	4 ± 2
3ac	6-Cl	767 ± 225	**3bc**	6-Cl	1616 ± 498
3ad	6-F	398 ± 44	**3bd**	7-Cl	42 ± 4
3ae	8-Cl	322 ± 126	**3be**	8-Cl	481 ± 87
			3bf	5-F	17 ± 8
			3bg	5-Me	15 ± 2

A variety of amides **4** of 7-hydroxy-isoflavone 4'-carboxylic acid was presented in a patent development [14] as medicines for preventing or curing hyperlipemia, obesity, or type II diabetes (Figure 3).

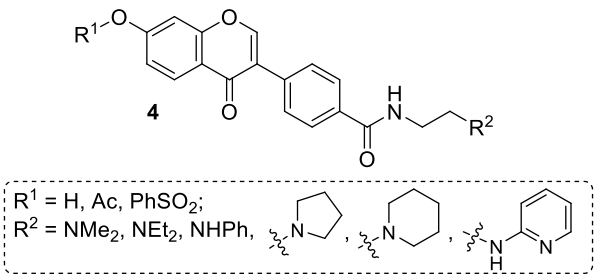


Figure 3. Isoflavone amides **4** – products for the treatment of hyperlipemia, obesity, and type II diabetes.

Of the four synthesized amides (Figure 4), the amide **8d** exhibited transactivation activity and induced the expression of farnesoid X receptor (FXR). The latter is known to regulate a series of target genes, including short heterodimer partner (SHP), bile salt export pump (BSEP) and sterol regulatory element-binding protein 1c (SREBP-1c).

Although the effect of **8d** in modulating FXR gene expression was less pronounced than that of GW4064 – synthetic FXR agonist, **8d** showed less toxicity in HepG2 cells. Overall, results obtained by the authors indicated that **8d** could act as a promising lead compound for the design of novel FXR modulators against dyslipidemia [19]. Moreover, amidation turned out to be a necessary condition for the high level of biological activity as the acid itself and its ester demonstrated much more modest performance. Functionalized isoflavones similar to the depicted ones have been patented for preventing or treating hyperlipidemia, type II diabetes, atherosclerosis, and non-alcoholic fatty hepatitis [20].

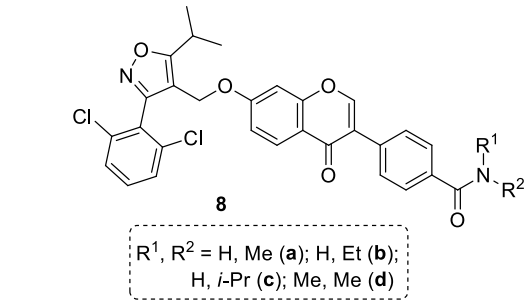


Figure 4. Isoflavone amides **8** – FXR modulators against dyslipidemia.

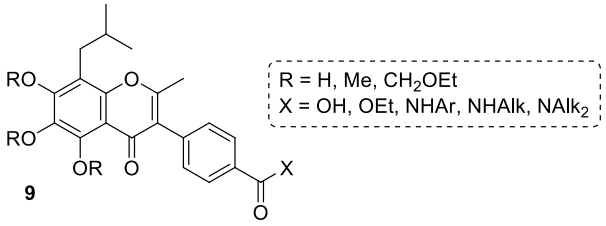


Figure 5. Series of isoflavones **9** – a new class of apoptosis inhibitors.

A large array of isoflavones modified with functional groups, as well as additional aromatic and heterocyclic fragments, were announced to be a new class of apoptosis inhibitors [21]. Compounds with carboxyl and carboxamide groups are represented mainly by structures **9** (Figure 5); several structures with a carboxyl group at the 3'-position of the isoflavone are shown.

Pyranoisoflavones were shown to function as butyrylcholinesterase inhibitor and can therefore be used in the treatment of Alzheimer's disease [22]; one of the studied derivatives was compound **10** with an ester group, the publication focused more on carbamate derivatives of hydroxyisoflavones, in particular, compound **11** – one of the most active substances (Figure 6).

The site docking data given in this work is interesting. Calculations showed that multiple ways of binding pyranoisoflavones to the active site of the enzyme exist depending on the nature and location of the substituents. In one of them, the carbonyl fragment of the chromone ring and π-interaction with the isoflavone ring B plays an important role, which is another argument in favor of the pharmacophoric potential of the isoflavone system. It should also be noted that the removal of the annelated pyran ring led to a noticeable drop in isoflavone activity, while the variation of substituents in ring B was not critical. This confirms the assumption that the B ring substituents can be easily varied (in particular, by obtaining amides of the carboxyl group) in order to introduce required physicochemical properties into a compound, while at the same time preserving the active action of the heterocyclic system itself.

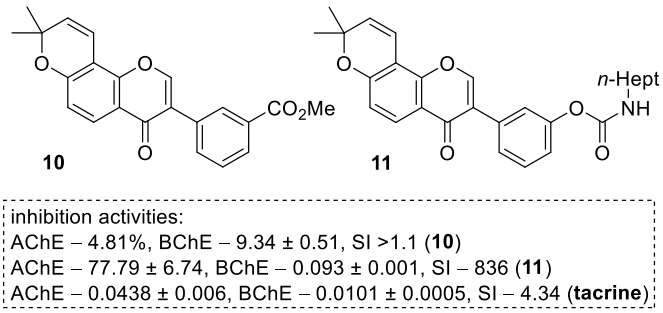
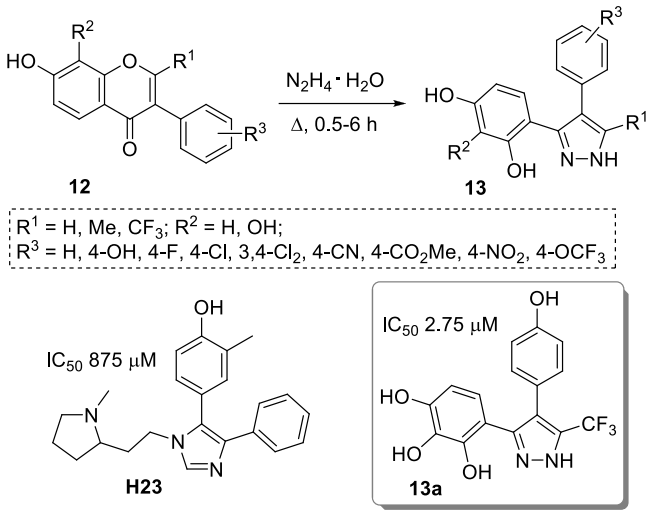


Figure 6. Pyranoisoflavones as butyrylcholinesterase inhibitor. The inhibition activities are expressed as IC_{50} (μM) or as a percentage of inhibition at 10 μM, and the IC_{50} values are the mean of three independent experiments ± SEM; SI represents selectivity index which is determined as ratio AChE IC_{50} / BChE IC_{50}; AChE – Acetylcholinesterase, BChE – butyrylcholinesterase.

Biological activity of 3-(carboxyphenyl)chromone derivatives

Approaches to obtaining biologically active substances from isoflavones can be based not only on the modification of functional groups but also on the recyclization of the labile pyrone fragment. For example, article [23] proposed pyrazoles **13** as an alternative to substance H23 – a previously known inhibitor of glycogen synthase. The pyrazoles **13**, including a compound with an ester group in the ring B (R^1 = OH, R^2 = Me, R^3 = 4-CO_2Me, Scheme 2), were obtained *via* recyclization of 2-substituted (R^1 = H, Me, CF_3) isoflavones **12**. The *p*-hydroxy derivative **13a** exhibited the highest activity (Scheme 2, inhibitory IC_{50} values against human glycogen synthase GS 1 (hGYS1)).



Scheme 2. Isoflavones **12** – precursor inhibitors of glycogen synthase.

Saturated analogs of isoflavones with carboxyl, carboxamide, and ester groups are also mentioned among biologically active substances. Isoflavans **14**, in particular, were investigated as compounds that exhibited valuable pharmacological properties, especially for the treatment of vascular diseases (Figure 7) [24].

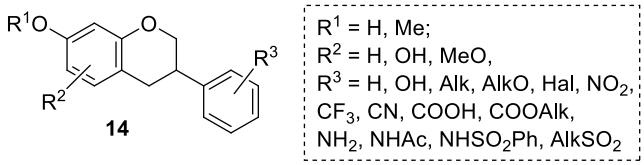
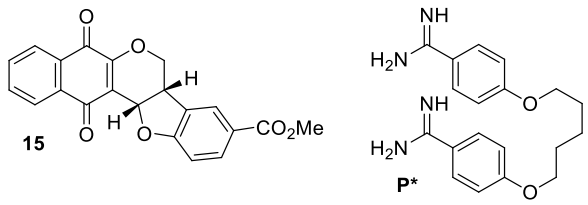


Figure 7. Isoflavans **14** – products for the treatment of vascular diseases.

It was also discovered that the antineoplastic activity on human malignant cell lines and antileishmanial activity on *Leishmania amazonensis* [25] is inherent in quinoid pterocarpans, including substance **15** with an ester group (Table 2).

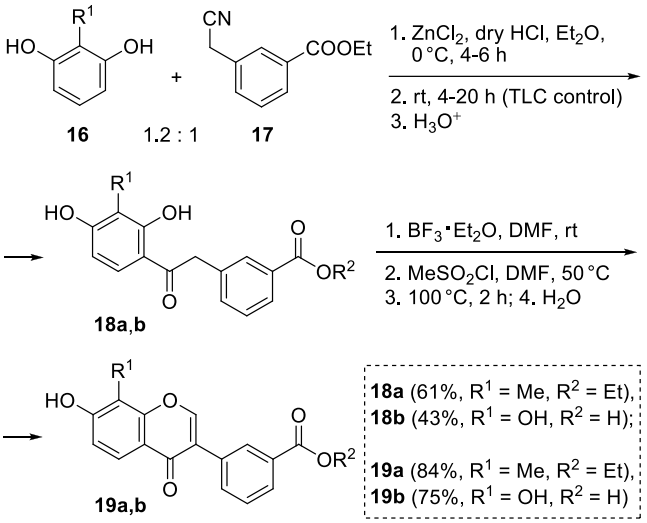
Table 2. Comparison of antileishmanial activity of compound **15** and pentamidine (**P***) on promastigote and amastigote forms of *L. amazonensis* and toxicity for M J774 cells (IC_{50} in μM).



	15	P*
Promastigote	2.8	2.2
Amastigote	0.5	1.5
MJ774	22.5	70
M J774/amastigote	45	46

Synthesis of 3-(carboxyphenyl)chromones, their esters and amides

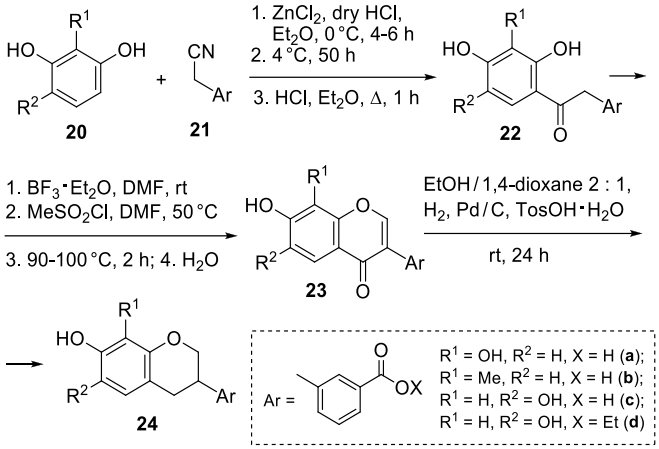
The most obvious "classical" solution to the problem of obtaining isoflavones with a carboxyl group in ring B is the Houben-Hoesch reaction using (carboxyphenyl)acetonitriles as key reagents, followed by formylation and ring-closure of the chromone system. However, the reactivity of phenylacetonitriles with a carboxyl function is questionable and, when ester protection of the carboxyl group is used, the ester fragment stability in both reaction and subsequent isolation conditions is of concern. Paper [26] described the preparation of 2-hydroxyphenylbenzyl ketones **18a,b** (and their analogues with alkoxy, CF_3, and CO_2Et groups) *via* the classical Houben-Hoesch reaction. Substituted phenols **16** and 3-(carboxyphenyl)acetonitrile (**17**) reacted under the action of $ZnCl_2$ in Et_2O, and underwent subsequent ring-closure into the corresponding isoflavones **19a,b** according to the method described by Bass – with $BF_3 \cdot Et_2O$ followed by formylation with $MeSO_2Cl$-DMF reagent (Scheme 3) [27].



Scheme 3. Synthesis of 3-(carboxyphenyl)chromones **19a,b**.

In two cases when Houben-Hoesch reaction of ethyl 3-(cyanomethyl) benzoate with 2,6-dihydroxytoluene or 1,2,3-trihydroxybenzene was used, the isolation of reaction products was accompanied by partial hydrolysis and the formation of a mixture of ester and acid **18**. Isolation and purification of the main product were based on the acid's solubility in the aqueous solution of $NaHCO_3$. The main product was the ester **18a** in the first case and the acid **18b** in the second. During formylation and heterocyclization, despite treating the reaction mixture with water at a certain stage of the process, hydrolysis of the ester group of derivative **19a** did not occur.

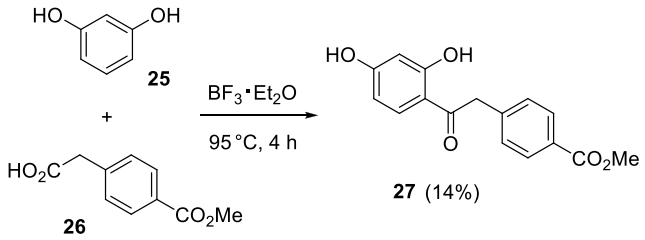
Notably, the conversion of deoxybenzoin to isoflavone is accompanied by partial or complete acylation of free OH-groups, and subsequent addition of water is necessary to remove the acyl residue from the hydroxyl group. Therefore, it can be assumed that the hydrolytic stability of the ester group in ring B is significantly higher; several similar examples are given later in the review.



Scheme 4. Synthesis of isoflavans **24**.

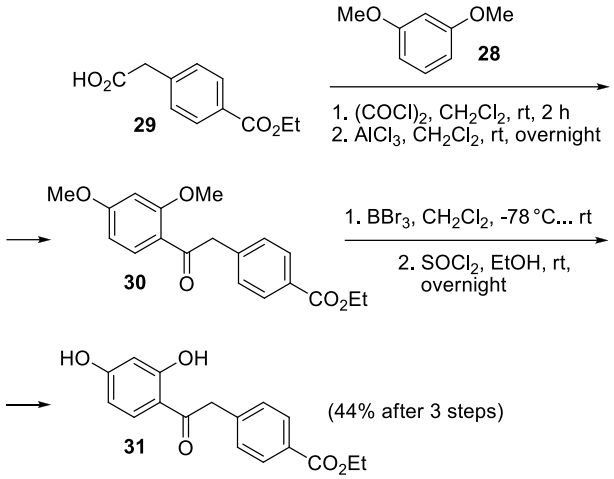
The previously mentioned bioactive isoflavans **14** (Figure 7) were synthesized by a catalytic reduction of corresponding isoflavones [24]. The latter, in turn, were obtained *via* the Houben-Hoesch reaction which was carried out at a rather low temperature. This significantly increased the reaction time but was obviously justified, because the authors successfully obtained a wide series of polyfunctional compounds, including those with a free carboxyl group. The synthetic sequence to these carboxy derivatives is shown in Scheme 4 (on the example of compounds **24** synthesis).

Using a corresponding arylacetic acid **26** instead of a nitrile in the Houben-Hoesch reaction allows to avoid the hydrolysis of the imine fragment and to treat the reaction mixture in milder conditions, which reduces the likelihood of hydrolysis of functional groups present in the main fragment (including ester). If the target product is an isoflavone with a free carboxyl group, the hydrolysis of the ester fragment is expediently carried out after the ring-closure of the pyrone ring. Such sequence of reactions was proposed by the authors of [12], devoted to the synthesis of a large array of bioactive isoflavones with a 4'-carboxyl group, shown in Figure 2. Scheme 5 shows the synthesis of a key compound – methyl 4-(2-(2,4-dihydroxyphenyl)-2-oxoethyl)benzoate (**27**).



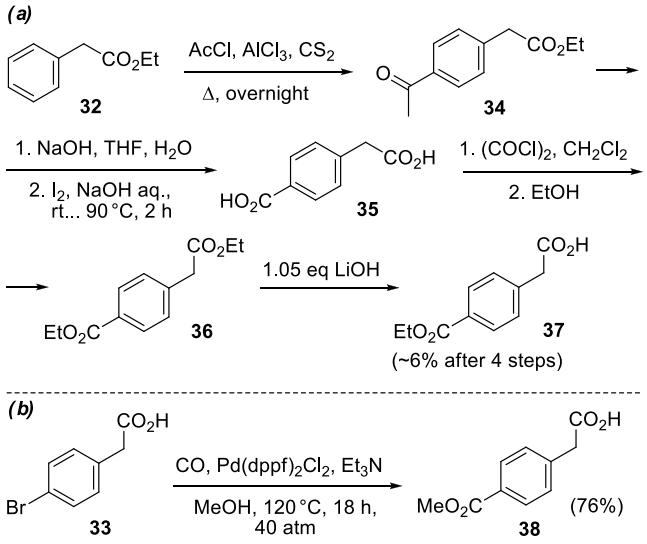
Scheme 5. Synthesis of methyl 4-(2-(2,4-dihydroxyphenyl)-2-oxoethyl)benzoate (**27**).

As an alternative to the Houben-Hoesch reaction between (ethoxycarbonylphenyl)acetic acid **29** and 1,3-dimethoxybenzene **28** in $BF_3 \cdot Et_2O$ medium, the authors of [12] studied in detail the Friedel-Crafts acylation of **28** with (ethoxycarbonylphenyl)acetic acid chlorides in the presence of $AlCl_3$ with subsequent removal of methyl groups of BBr_3. This approach provided higher yields of the target product **31** in comparison to the Houben-Hoesch reaction (Scheme 6).



Scheme 6. Synthesis of ethyl 4-(2-(2,4-dihydroxyphenyl)-2-oxoethyl)benzoate (**31**).

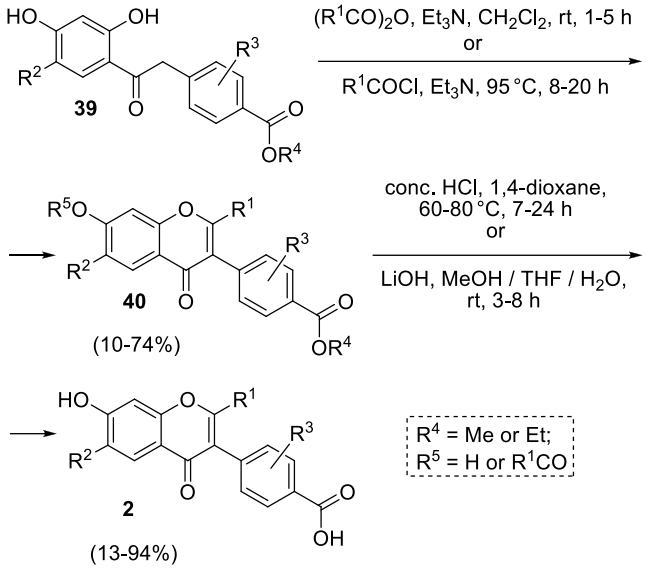
Additionally, two approaches have been successfully used to introduce a carboxyl group in the *p*-position of phenylacetic acid: the Friedel-Crafts acetylation of phenylacetic acid **32** with subsequent oxidation of the acetyl fragment in the iodoform reaction (Scheme **7a**; unfortunately, the total yield of product **37** for four stages was minuscule); or the catalyzed carbonylation of *p*-bromophenylacetic acid **33** with yields of target product **38** of 76% (Scheme **7b**).



Scheme 7. Synthesis of (ethoxycarbonylphenyl)acetic acid **37** and (methoxycarbonylphenyl)acetic acid **38**.

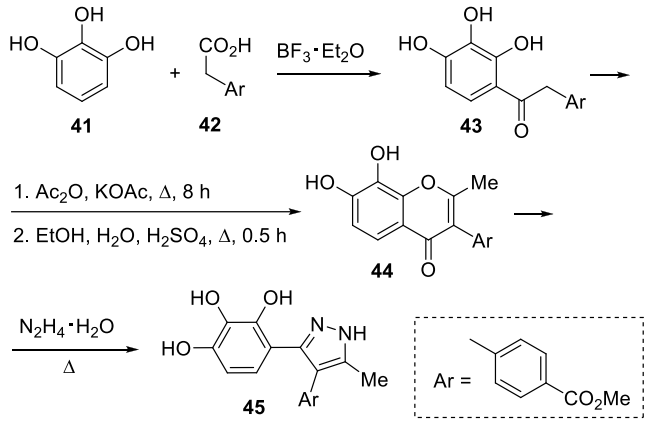
This study is also noteworthy for its use of anhydrides and chloroanhydrides of various carboxylic acids (aliphatic, aromatic, and heteroaromatic, as well as alkoxy and fluorine-substituted) in the cyclization of deoxybenzoins **39** – the products of the Houben-Hoesch reaction. This allowed to obtain isoflavones **40** with various substituents at position 2 of the chromone ring (the list of substituents R^1-R^3 is given in Figure 2 above). Depending on the activity of reagents, the cyclization of deoxybenzoins **39** to flavones **40** took place either with an equivalent amount of Et_3N at

room temperature in a dichloromethane solution or under reflux (Scheme 8). Of course, acylation of the additional hydroxyl group occurred simultaneously with the cyclization. Two methods were also developed for the hydrolysis of the *O*-acyl fragment: heating products **40** in an acidic medium, or treating with LiOH at room temperature, resulting in the formation of corresponding acids **2** with yields of up to 94%.



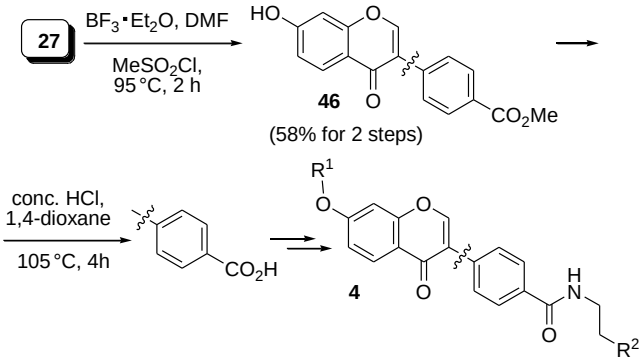
Scheme 8. Synthesis of 4-(7-hydroxy-4-oxo-4*H*-chromen-3-yl)benzoic acids **2**.

Tang et al. demonstrated that the conditions of the Houben-Hoesch reaction should be varied depending on the activity of arylacetic acids or nitriles [23]. Various reagents were used to conduct the cyclization of the chromone ring, allowing for variation of the substituent at position 2 of the system. The data on the synthesis of a derivative with an ester group – compound **44** – is presented in Scheme 9.



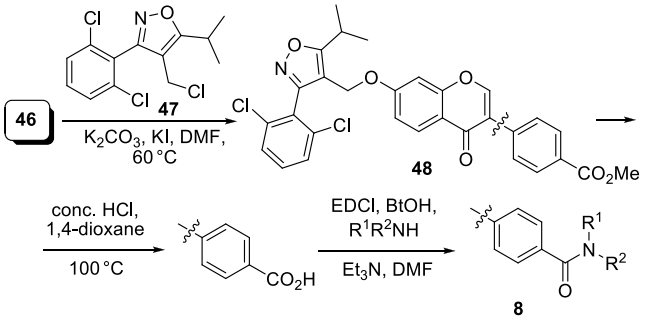
Scheme 9. Synthesis of isoflavone **44** – a precursor of inhibitors of glycogen synthase.

7-Alkoxyisoflavone 4'-carboxylic acid, subsequently converted into various amides **4** (see the list in Figure 3), was synthesized using the Houben-Hoesch reaction as well [14]; the synthesis of 2-(4-(methoxycarbonyl)phenyl)acetic acid required for the reaction was carried out using an approach similar to that shown in Scheme 7a. The authors did not reported a hydrolysis of the ester group neither during the Houben-Hoesch reaction nor during the isolation and subsequent cyclization to isoflavone (Scheme 10).



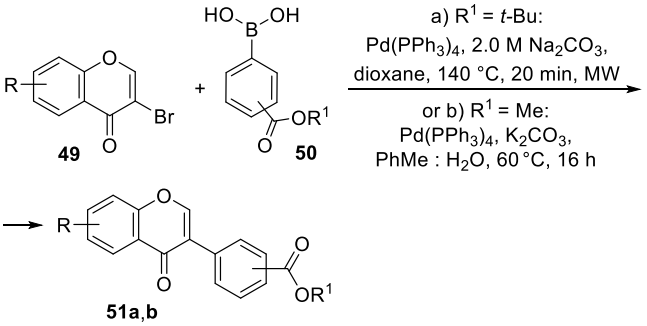
Scheme 10. Synthesis of isoflavone amides **4** – products for the treatment of hyperlipemia, obesity, or type II diabetes.

Isoflavone amides with an isoxazole moiety – compounds **8** – were synthesized in a similar manner; slight differences were related to the temperature regime of the Houben-Hoesch reaction, the conditions of hydrolysis of the ester, and the formation of the amide bond (Scheme 11) [19-20].



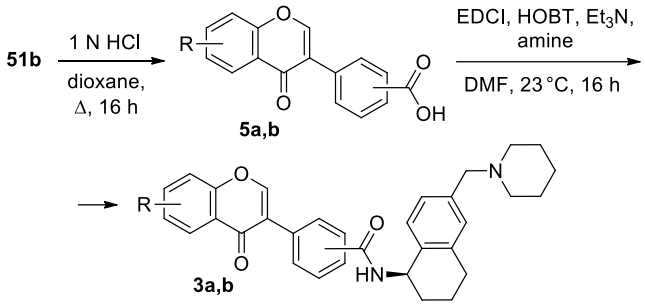
Scheme 11. Synthesis of isoflavone amides **8** – FXR modulators against dyslipidemia.

Another promising modern method for producing isoflavones is the catalytic arylation of 3-halogeno-chromones. One of the undoubted advantages of this approach is the possibility of using reagents with fragments that are unstable under the conditions of "classical" schemes. Using this method, *tert*-butyl esters **51a** of the acids mentioned above (Scheme 1) were obtained by the Suzuki-Miyaura reaction [13]. It should be noted that the ester fragment remained intact, despite the rather high reaction temperature (Scheme 12).



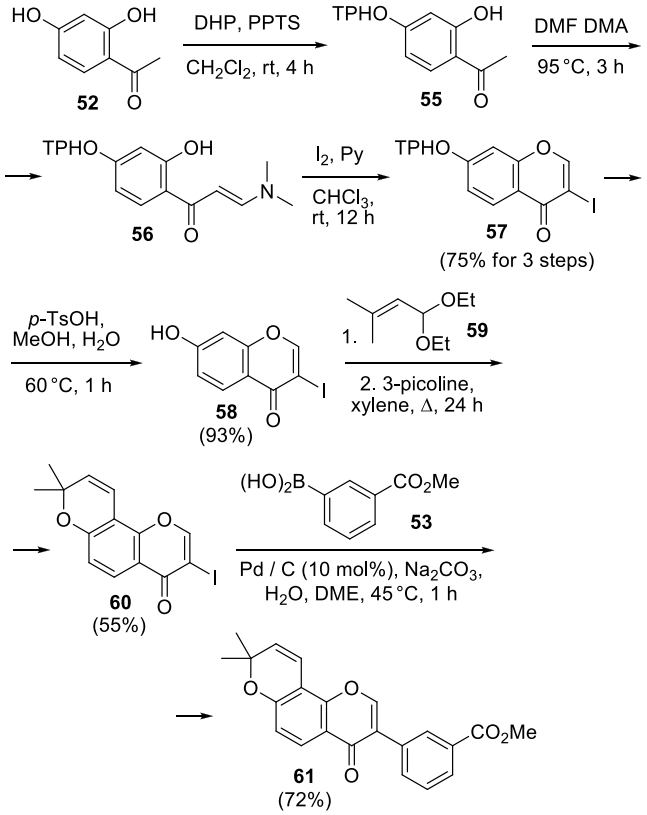
Scheme 12. Synthesis of isoflavones **51a,b** – precursors for antagonists of the bradykinin B1 receptor.

Bioactive isoflavones **3a,b** with amide group (see Table 1 above for a list of substituents) can be easily synthesized from methyl esters **51b** (Scheme 13), as was done in [18].



Scheme 13. Synthesis of amides **3a,b** – antagonists of the bradykinin B1 receptor.

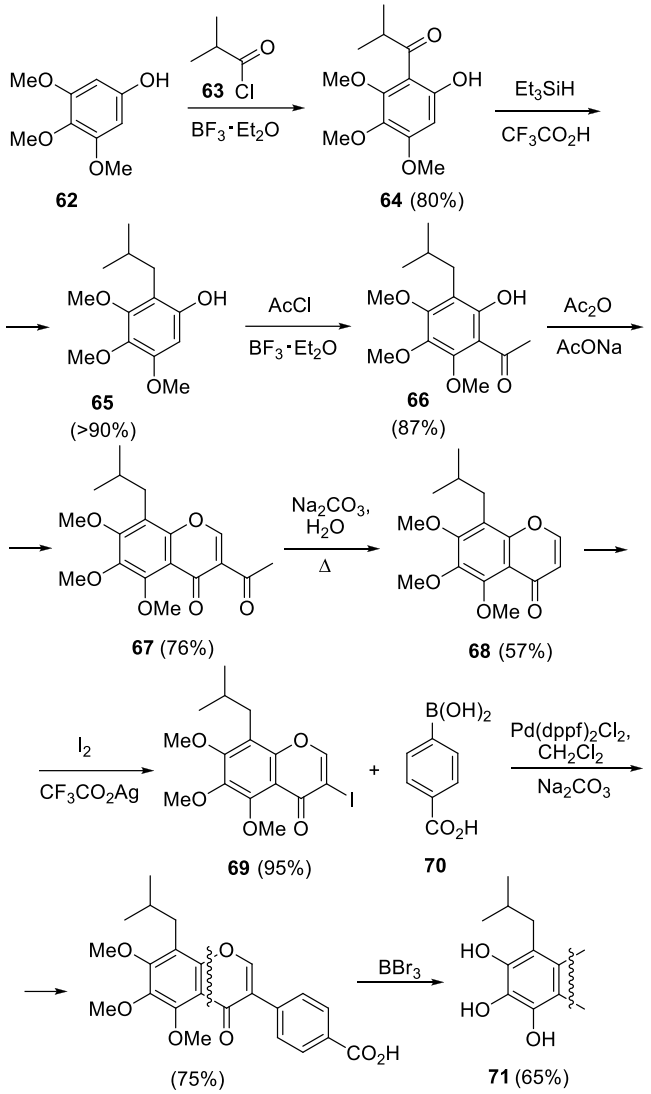
In the preparation of pyranoisoflavones, the pyran ring was first annealed to 7-hydroxy-3-iodochromone **58**, and only then was it combined with boronic acids [22]. At the coupling stage, standard conditions were used – palladium catalyst with triphenylphosphine ligands, aqueous organic medium, sodium carbonate as a base. In this way, an extensive list of 3-substituted pyranoisoflavones was synthesized, mainly with hydroxy and alkoxy groups in the B ring, as well as some 3-pyridylisoflavones. The yield of compound **61** with the ester group is shown in Scheme 14.



Scheme 14. Synthesis of pyranoisoflavone **61**.

The literature contains plenty of examples of the Suzuki reaction's preparative possibilities for the synthesis of isoflavones that are functionalized, among other things, with a carboxyl group. In fact, the main difficulties in this method are associated not so much with the implementation of the combination itself, but with the synthesis of the starting 3-halochromones.

For example, the authors of [28] carried out coupling of 3-iodochromone **69** and arylboronic acid **70** with a free carboxyl group with a yield of 75%, but the synthesis of the starting 3-iodochromone **69** from 3,4,5-trimethoxyphenol **62** required 6 stages (Scheme 15).

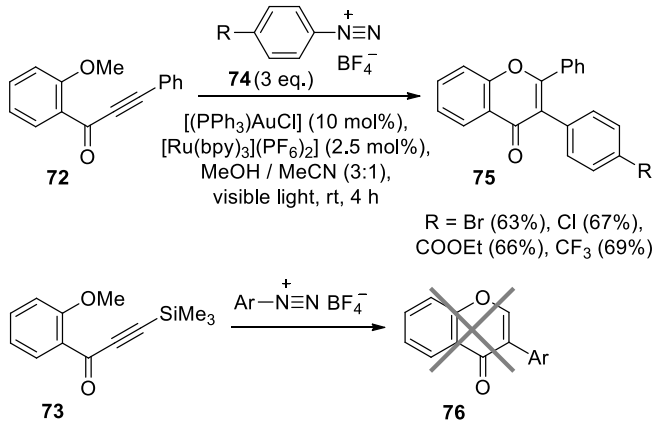


Scheme 15. Synthesis of isoflavone **71** *via* coupling of 3-iodochromone **69** and arylboronic acid **70**.

In the same manner, the same group obtained isoflavone-3'(4')-carboxylic acids with alkyl substituents at positions 2 and 8 and hydroxy groups at positions 5-7, which were used for the synthesis of a large group of amides – potential inhibitors of Bcl-2 (Figure 5) [21].

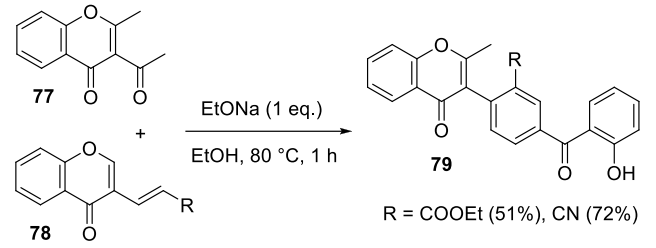
A more recent approach to catalytic heterocyclization of various systems (2*H*-benzo-[*e*][1,2]-thiazine 1,1-dioxides (benzosultams), benzoselenophenes, benzothiophenes, 4*H*-chromen-4-ones (flavones), 3*H*-indoles, 1*H*-isochromen-1-ones (isocoumarins), and 4*H*-thiochromen-4-ones (thioflavones)) was a photopromoted gold-catalyzed arylative heterocyclization of alkynes [29]. This method was tolerant towards many functional groups, including

esters functional groups, and the yield of corresponding 3-aryl-2-phenylchromone **75** with a 4-CO_2Et substituent did not differ significantly from the yield of Cl-, Br-, CF_3-derivatives (Scheme 16). Unfortunately, this technique has so far been developed only for 2,3-diarylchromones, and attempts to obtain 2-unsubstituted isoflavones by introducing silyl derivatives into the reaction have not been successful.



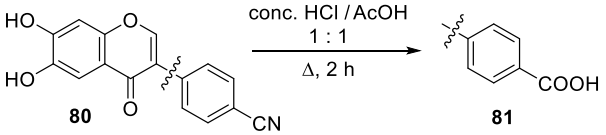
Scheme 16. Synthesis of 3-aryl-2-phenylchromone **75**.

Unusual polycyclic structures – condensed benzo-γ-pyrones – were obtained by a domino reaction between 3-acetyl-2-methylchromone **77** and various 3-(2-*R*-vinyl)-chromones (R = EWG) **78** [30]. In this specific method of constructing isoflavones **79**, the diene fragment of 3-vinylchromone **78** and the acetal group of acethyl-chromone **77** participated in the formation of the benzene ring (Scheme 17).



Scheme 17. Synthesis of isoflavone **79** *via* domino reaction.

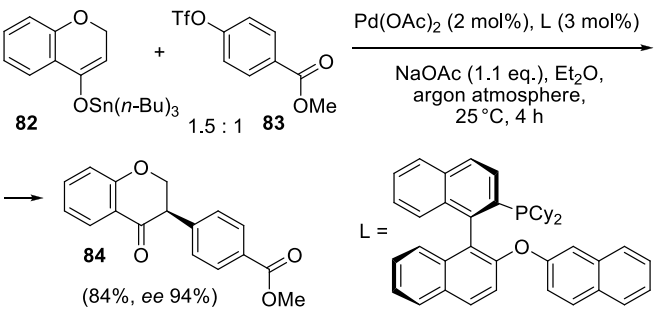
The patent [24] mentioned the possibility of obtaining 4'-carboxyisoflavone **81** by the hydrolysis of the corresponding nitrile in an acidic medium (Scheme 18).



Scheme 18. Synthesis of isoflavone **81**.

Synthesis of 3-(carboxyphenyl)chromone derivatives

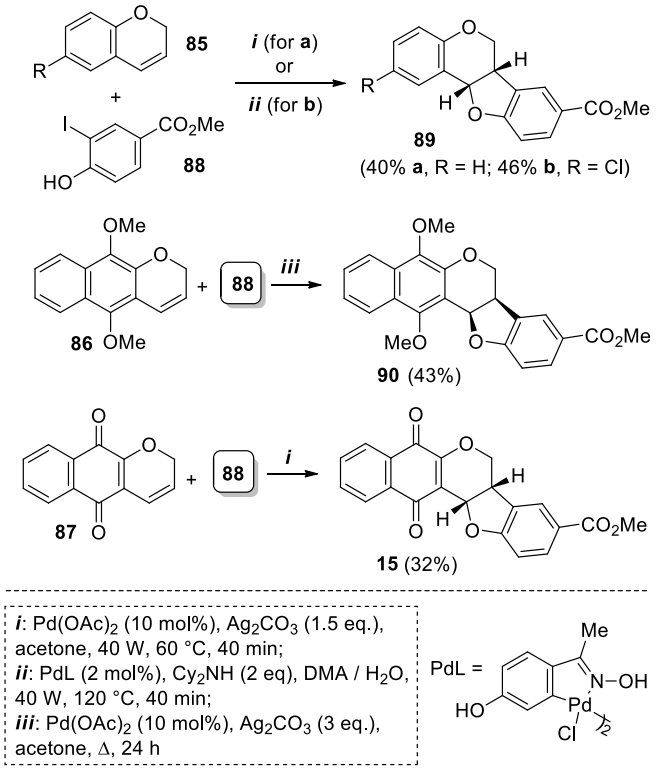
Compound **84** – isoflavanone with an ester group – was obtained by the catalytic arylation of the α-position of chromanone [31]; the high enantioselectivity of this reaction is remarkable (Scheme 19).



Scheme 19. Synthesis of isoflavanone **84**.

As it was mentioned earlier (Figure 7), the adducts that were obtained during a palladium-catalyzed oxyarylation of the multiple bonds of chromanes contained the structural fragment of isoflavane [25, 32-33]. Although such pterocarpans maintain interest as biologically active substances [25], the synthetic method was not very effective because the reaction yield never reached above 65% even under microwave irradiation for 40 min.

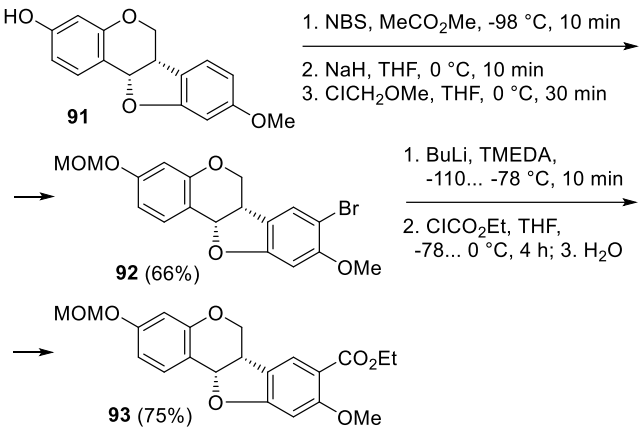
Nevertheless, the ability to use of a wide variety of substituents, as well as the successful use of electron-deficient quinone **87**, are worth mentioning as the reaction's advantages. Not only compounds with ester groups but their analogues with chloro-, nitro- and methoxy- groups were obtained as well (Scheme 20) [33]. The latter reaction led to the formation of biologically active derivatives (Figure 7). The quinone cyclic system also was obtained by the oxidation of dimethoxy derivatives [25].



Scheme 20. Synthesis of pterocarpans **15, 89-90**.

The carboxylation of the heterocyclic system itself as a method for modifying an isoflavonoid with a carboxyl group was carried out only for pterocarpans [34]. The bromination of the (+)-medicarpin **91** under free-radical

conditions with NBS (*N*-bromosuccinimide) in methyl acetate led to the formation of the 8-bromoderivative **92** (Scheme 21). The protected 8-bromo derivative **92** was treated with butyllithium and TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) at low temperature (-110 °C) followed by quenching of the lithio derivative with ethyl chloroformate to give the ethyl ester **93**. This approach, however, is not applicable to isoflavones.



Scheme 21. Synthesis of pterocarpan **93**.

Conclusions

The literature data reveals numerous practical applications for 3-(carboxyphenyl)chromones and their derivatives. A carboxyl group modifications were the main synthetic routs to chromones' derivatives. Although the number of compounds of this class is still relatively small, most of them appeared in many biological studies where they demonstrated a fairly high level of biological activity. The existing data allows us to consider 3-(carboxyphenyl)-chromones as synthetically available compounds. In some cases the presence of the carboxyl group in the molecules necessitated adjustments to the "classical" synthetic protocols. Most of these derivatives were obtained using popular approaches in the synthesis of isoflavones – the Houben-Hoesch reaction or catalytic arylation of 3-halogenochromones. It should be noted that the number of publications on this topic has been steadily increasing since 2000. Moreover, the reports on the preparative synthesis of new 3-(carboxyphenyl)chromones facilitated studies of their biological activity, which undoubtedly will significantly improve the prospects of creating new drugs and other practically useful substances based on this class of compounds.

Notes

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The authors declare no conflict of interest.

Author contributions. The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

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Особливості синтезу та біологічної активності 3-(карбоксифеніл)хромонів

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Резюме: Флавоноїди та їх похідні історично були джерелами терапевтичних засобів. З кожним роком публікується все більше даних про нові флавоноїдні сполуки (як виділені з природних джерел, так і синтезовані) та їх різноманітну фізіологічну та фармакологічну активність. У цьому огляді представлена інформація щодо синтезу 3-(карбоксифеніл)хромонів та їх біологічної активності, опублікована як у періодичних виданнях, так і в патентній літературі. Наш інтерес до 3-(карбоксифеніл)хромонів, було викликано насамперед тим, що є багато літературних даних про методи синтезу та біологічну активність 2(3)-заміщених та 2,3-дизаміщених хромонів, але дані про ізофлавони, що містять карбоксильну, естерну або амідну групу в кільці В обмежені та фрагментарні. Тим не менше, інтенсивність роботи над цією темою в 2000 рр. почала зростати, в першу чергу, завдяки виявленню цікавих біологічних властивостей карбоксиізофлавонів та їх похідних; і це, в свою чергу активізувало розробки оригінальних методів синтезу таких сполук. Представлений огляд літератури дозволяє вважати 3-(карбоксифеніл)хромони та їх похідні синтетично доступними сполуками, хоча в деяких випадках присутність карбоксильної групи в субстраті вимагає певних удосконалень "класичних" методів. Більшість із представлених у огляді 3-(карбоксифеніл)хромонів були отримані з використанням підходів, популярних у синтезі ізофлавонів – реакції Губена-Хеша з наступною циклізацією або каталітичного арилювання 3-галогенохромонів. Структура 3-(карбоксифеніл)хромону має також багато можливостей для модифікації, зокрема: синтез амідів за карбоксильною функцією, анелювання додаткових гетероциклічних фрагментів, одержання частково насичених за кільцем С похідних та продуктів рециклізації хромонової системи. Перелічені перетворення були реалізовані на практиці і привели до створення нових біологічно активних сполук, що беззаперечно підтверджує потенціал подальшого розвитку хімії 3-(карбоксифеніл)хромонів.

Ключові слова: хромони; ізофлавони; біологічна активність; синтез.