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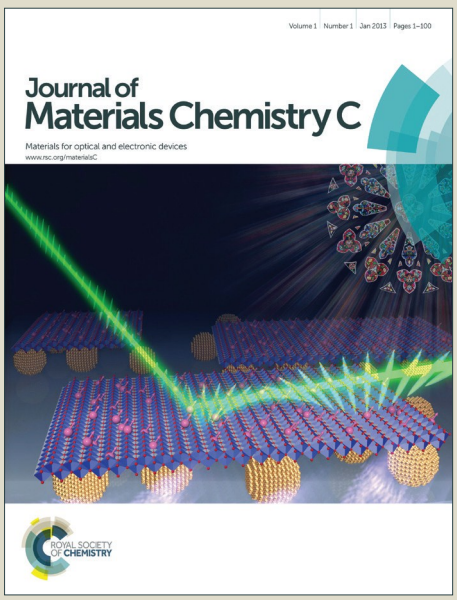

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ARTICLE

π-Expanded Coumarins: Synthesis, Optical Properties and Applications

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Coumarins fused with other aromatic units have recently emerged as a hot topic of research. Their synthesis is partly based on classical methodologies such as Pechmann reaction or Knoevenagel condensation, but it also sparked the discovery of completely new pathways. In very recent years so-called vertically-expanded coumarins were synthesized, effectively expanding the portfolio of existing architectures. A subtle relationship exists between the structure of fused coumarins and their optical properties. Although absorption of UV-radiation and light is unifying theme among these π-expanded coumarins, the fluorescence properties strongly depend on the structure. The mode of fusion, the type of additional ring and the presence of electron-donating and electron-withdrawing substituents all influence the photophysical parameters. Recent advances made it possible to modulate their absorption from 300 nm to 550 nm, resulting in new coumarins emitting orange light. This review serves as a guide through both synthesis strategies and structure-property relationship nuances. Strong intramolecular charge-transfer character made it possible to reach suitable values of two-photon absorption cross-section. Photophysical advantages of π-expanded coumarins have been already utilized in fluorescence probes and two-photon excited fluorescence microscopy.

1. Introduction

Coumarins fascinated humans from the very beginning. From the smell of freshly cut grass through laser dyes to fluorescent probes – we are surrounded by them.[1] More than that, we carry them on our shoulders as optical brighteners. Although π-expanded coumarins, i.e. coumarins possessing additional benzene or heterocyclic rings fused in different ways with chromen-2-one, were synthesized for the first time by Pechmann in 1884,[2] (and some types of them are ubiquitous in nature), it is not until very recently that they make their way towards modern photonic-oriented applications. Even more recently entirely new skeletons possessing one or two coumarin moieties expanded or combined with one another were discovered. Since this topic was never described before, we undertook a systematic journey through these molecules. The review will cover synthetic developments, focusing on the most important examples, with special emphasis given to comparison of old and recent literature. We will also present, compare and analyze linear optical properties of these compounds. Finally, we will describe the current and possible applications. In the following sections we will present representative examples of the linear and angular benzocoumarins (Chapter 2), biscoumarins (Chapter 3), vertically expanded coumarins (Chapter 4), optical properties (Chapter 5) and applications (Chapter 6). Coumarins possessing conjugated C-C double and triple bonds are outside of the scope of this review for space reasons.

2. Coumarins fused with one additional aromatic ring: benzocoumarins and their analogues

2.1 Structure of benzocoumarins

Benzocoumarin derivatives can be classified into four types depending on the position of the fused benzene ring:

benzo[*c*]coumarin, benzo[*f*]coumarin, benzo[*g*]coumarin, and benzo[*h*]coumarin types (Fig. 1).

2.2. Synthesis of benzocoumarins and their analogues

2.2.1. General synthetic routes to benzocoumarins

Synthesis of benzocoumarin derivatives except the benzo[*c*]-coumarin series generally follows the synthetic routes established for coumarin and its derivatives[3] including Knoevenagel condensation, Pechmann reaction, and metal catalyzed cyclization. Therefore, known synthetic routes to benzo[*g*]coumarin, benzo[*h*]coumarin and benzo[*f*]coumarin derivatives are summarized here. Most of these synthetic pathways start from two major classes of compounds, either *o*-hydroxy-naphthaldehyde or naphthols.

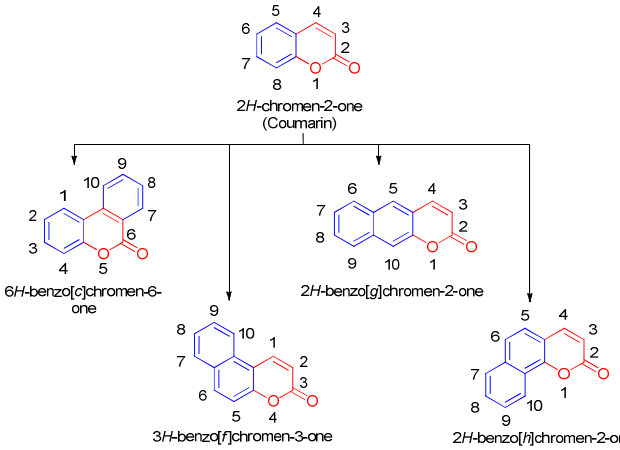
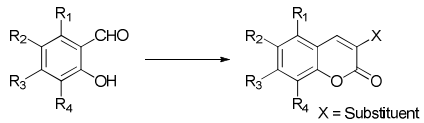


Fig. 1 Structures and numbering of chromen-2-one (coumarin) and benzochromenones (benzocoumarins).

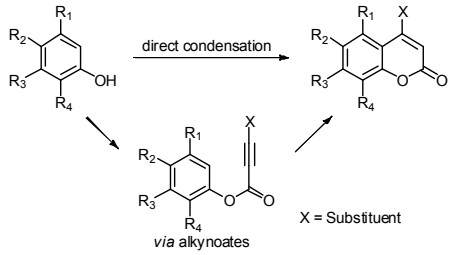
From *o*-hydroxynaphthaldehyde, the synthesis proceeds through initial Knoevenagel condensation with a malonate ester or its analogue followed by intramolecular cyclization with the hydroxyl group to yield the 2*H*-chromen-2-one moiety (Scheme 1). Formation of various types of benzocoumarin derivatives thus depends on the relative positions of formyl and hydroxyl groups on the starting *o*-hydroxynaphthaldehydes (2-hydroxy-3-naphthaldehyde or 2-hydroxy-1-naphthaldehyde or 1-hydroxy-2-naphthaldehyde). Among the *o*-hydroxynaphth-aldehydes, 1-hydroxy-2-naphthaldehyde and 2-hydroxy-1-naphthaldehyde can be readily synthesized from corresponding naphthol derivatives by formylation through the Vilsmeier–Haack or Duff reaction, Reimer–Tiemann reaction, or $MgCl_2$- or $TiCl_4$-mediated reaction. On the other hand, 2-hydroxy-3-naphthaldehyde derivatives can only be obtained by formylation through directed lithiation of methoxy or MOM (methoxymethyl ether) protected 2-naphthol followed by deprotection of the hydroxyl group.[4,5] Although the formylation through the directed lithiation produces one isomer as the major product, a regioisomer that forms in a substantial amount needs to be removed by column chromatography which sometimes causes an isolation problem due to their very similar polarity.



R_1	R_2	R_3	R_4	Product
-H	-CH=CH-CH=CH-		-H	Benzo[*g*]coumarin
-H	-H	-CH=CH-CH=CH-		Benzo[*h*]coumarin
-CH=CH-CH=CH-		-H	-H	Benzo[*f*]coumarin

Scheme 1 General strategy of benzocoumarin synthesis from *o*-hydroxynaphthaldehydes.

Alternatively, benzocoumarin derivatives can be directly synthesized through electrophilic substitution of naphthols with *β*-keto esters followed by cyclization (the upper route in Scheme 2). The reaction occurs with appropriate electrophiles in the presence of strong Brønsted acid or Lewis acid. In a modified way, the metal-catalyzed aryl C-H functionalization of alkynoates is also feasible. Here also the formation of different types of benzocoumarin derivatives depends on the position of hydroxyl group of commercially available starting naphthols (2-naphthol or 1-naphthol). From 2-naphthol, two different isomers also form in substantial amounts, which could be separated in some cases, due to their polarity differences.



R_1	R_2	R_3	R_4	Product
-H	-CH=CH-CH=CH-		-H	Benzo[*g*]coumarin
-H	-H	-CH=CH-CH=CH-		Benzo[*h*]coumarin
-CH=CH-CH=CH-		-H	-H	Benzo[*f*]coumarin

Scheme 2 Direct transformations of phenols into benzocoumarins.

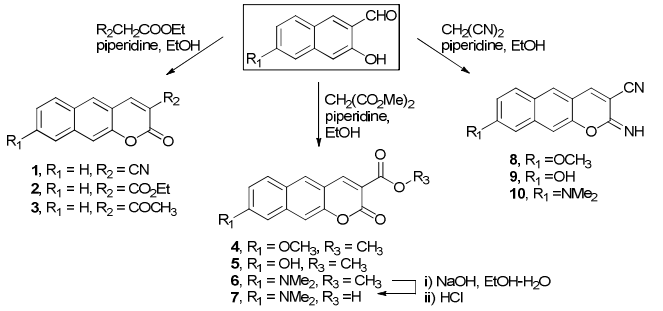
On the basis of above mentioned two main strategies, several synthetic routes have been developed for benzo[*g*], benzo[*h*] and benzo[*f*]coumarins as described in the following. Synthesis of benzo[*c*]coumarins follows rather dissimilar approaches, and accordingly those are mentioned later separately.

Psoralene (furanocoumarin) derivatives as well as pyrrolocoumarins are generally synthesized through different strategies from those used for benzocoumarins. Hence, their synthetic routes are also separately discussed.

2.2.2. Synthesis through the Knoevenagel condensation

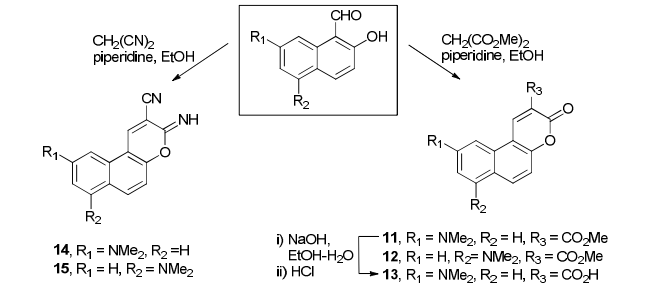
Benzocoumarins can be synthesized from *o*-hydroxynaphth-aldehydes through tandem Knoevenagel condensation and intramolecular cyclization with ethyl cyanoacetate, ethyl acetoacetate and dialkyl malonates that contain an active methylene group in the presence of a catalytic amount of piperidine in dry ethanol or methanol (Scheme 3).[3] This

synthetic strategy is preferred for the formation of a specific type of benzocoumarins, as the regioselectivity of the ring formation depends on the position of the formyl and hydroxyl groups on the naphthalene ring of the starting *o*-hydroxy-naphthaldehydes. As demonstrated, benzo[*g*]coumarins can be synthesized from 2-hydroxy-3-naphthaldehyde (Scheme 3), benzo[*f*]coumarins from 2-hydroxy-1-naphthaldehyde (Scheme 4), and benzo[*h*]coumarins from 1-hydroxy-2-naphthaldehyde (Scheme 5), respectively.

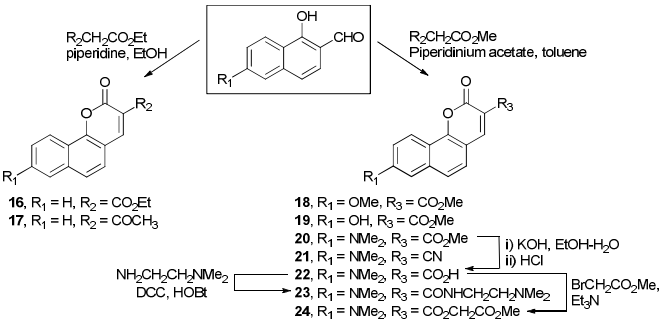


Scheme 3 Synthesis of benzo[*g*]coumarins through the Knoevenagel condensation.

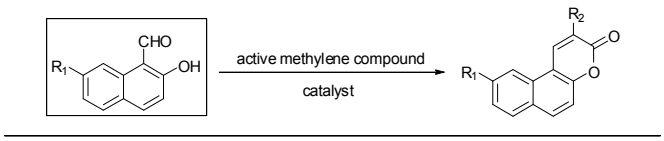
Donor-acceptor containing benzocoumarins (**4**–**7**, **11**–**13**, and **18**–**24**) were synthesized from the *o*-hydroxynaphthaldehydes containing a donor substituent (-OMe, -OH, -NMe_2) on the naphthalene ring at the appropriate position.[5,6] Similarly benzo-iminocoumarins (**8**–**10**, **14**, and **15**) were synthesized using malononitrile as the active methylene component.[5,6]

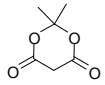
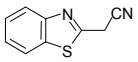
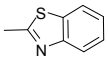
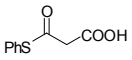


Scheme 4 Synthesis of benzo[*f*]coumarins through the Knoevenagel condensation.



Scheme 5 Synthesis of benzo[*h*]coumarins through the Knoevenagel condensation.



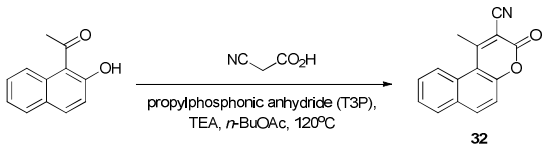
Active methylene compound	Catalyst	Product
$CH_2(CO_2Et)_2$	piperidine	**25**, R_1 = H, R_2 = CO_2Et
$CH_3COCH_2CO_2Et$	piperidine	**26**, R_1 = H, R_2 = $COCH_3$
$CH_2(CN)_2$	pyrrolidine	**27**, R_1 = H, R_2 = CN
	pyridine	**28**, R_1 = H, R_2 = CO_2H
$PhCH_2CO_2H$	NaOAc, Ac_2O	**29**, R_1 = OMe, R_2 = Ph
	piperidine	**30**, R_1 = OMe, R_2 = 
	benzylamine (10 mol%) Et_3N (10 mol%)	**31**, R_1=H, R_2=H

Scheme 6 Various active methylene compounds and catalysts used to synthesize benzo[*f*]coumarins through the Knoevenagel reaction.

Various organic bases or salts other than piperidine are also used as catalyst for the Knoevenagel condensation, including piperidinium acetate,[7-9] pyrrolidine,[10] pyridine,[11] and sodium acetate[12] (Scheme 6). When necessary, the 3-carboxy group can be used for further functionalization (**22**–**24**).[8,9] 3-Carboxy-benzocoumarins were generally produced in two-steps starting from the *o*-hydroxynaphthaldehydes, through Knoevenagel condensation followed by base-mediated hydrolysis of the corresponding esters (as shown for **7**, **13** and **22**). Recently, Yang and coworkers reported a one-step synthesis of 3-carboxy-benzocoumarin (**28**) with good yield (68%) using acetal protected malonic acid as an active methylene precursor.[11]

Phenylacetic acid or (benzothiazolyl)cyanomethylene was also used successfully as the active methylene compound in the Knoevenagel condensation to generate the corresponding 3-phenyl- or benzothiazolyl-benzocoumarins **29** and **30**.[12] Formation of a benzocoumarin with no substituent at C-3 such as benzo[*f*]coumarin **31** was achieved through condensation using a malonic acid monothioester as the active methylene component and benzylamine as the calatyst in 86% yield after 48 h;[13] it was proposed that the reaction involved the Knoevenagel reaction, decarboxylation and lactonization processes.

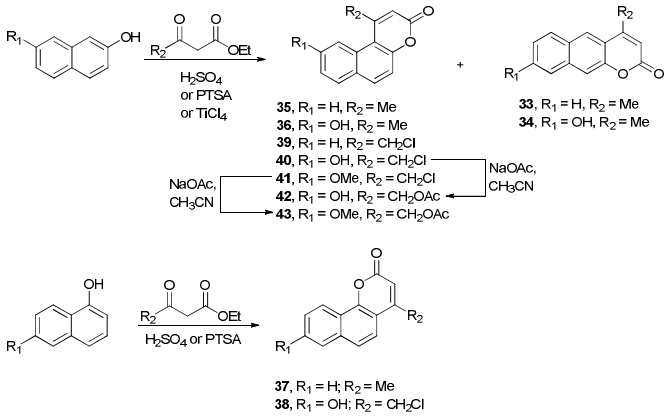
Similarly to the Knoevenagel reaction, the Perkin condensation was also used to synthesize benzocoumarin **32**, starting from 1-acetyl-2-naphthol and cyanoacetic acid in the presence of polyphosphoric anhydride, triethylamine, and *n*-butyl acetate (Scheme 7).[14] But due to the lower nucleophilicity of the acetyl compare to the aldehyde (used for Knoevenagel condensation), a harsh reaction condition was necessary for this Perkin condensation.



Scheme 7 Synthesis of benzocoumarin through the Perkin condensation.

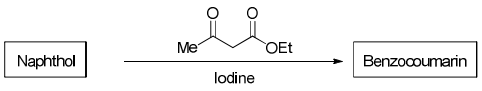
2.2.3 Synthesis through the Pechmann reaction

The Pechmann reaction between a naphthol and a β-keto acid or ester proceeds under acidic conditions to give the corresponding benzocoumarin. The ring formation involves the initial trans-esterification, followed by nucleophilic attack of the naphthol ring at the carbonyl group, and subsequent dehydration.[15] In 1935, Appel first noticed that 1-naphthols react with β-keto esters far more easily than 2-naphthols.[16] This observation was confirmed by proving that the reaction of naphthalene-1,3-diol with ethyl acetoacetate led exclusively to 5-hydroxybenzo[*h*]coumarin.[17] This assignment was subsequently confirmed in the seminal paper by Wolfbeis.[18] 1-naphthol and its derivatives produced benzo[*h*]coumarins selectively in high yields,[19-23] even in the presence of mild catalysts such as sulphamic acid.[24] On the other hand, similar reactions with 2-naphthols required a strong acid (typically 70−80% H_2SO_4) and heating up to 100 °C and always produced a mixture of benzo[*f*]coumarin and benzo[*g*]coumarin (Scheme 8).[25] Fan and co-workers reported the preparation of both regioisomers (i.e. **34** and **36**) from the Pechmann reaction of 2,7-naphtalenediol [26] by adjusting pH value of their aqueous solutions.[27] The authors claimed that benzo[*g*]coumarin **34** and benzo[*f*]coumarin **36** were isolated in 42% and 28% yields, respectively. In contrast, the exclusive formation of benzo[*f*]-coumarin (in 70% yield) was reported by Frechet and co-workers while studying the condensation of 2,7-naphthalene-diol with $CF_3COCH_2CO_2Et$.[28] Also, reactions of 2,6-naphthal-enediol led only to the corresponding benzo[*f*]coumarin in 40% yield.[29] Similarly, 1,7-naphthalenediol provided benzo[*h*]-coumarin exclusively.[30] Analogous observations have been made by Uchiyama and co-workers while studying reaction of 7-methoxy-2-hydroxynaphthalene with ethyl acetoacetate.[31]



Scheme 8 Synthesis of benzocoumarins through the Pechmann reaction.

Several modifications have been successfully done, allowing use of moderate reaction conditions for the Pechmann reaction, including the *p*-toluenesulfonic acid mediated reaction,[32] iodine mediated reaction,[33] and poly(4-vinylpyridinium) perchlorate catalyzed reaction under ultrasonic irradiation.[34]



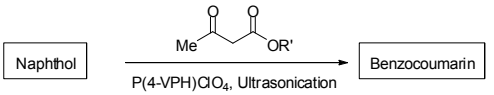
Naphthol	Benzocoumarin	MW reaction		Thermal heating (80 °C)		Room temp[r]	
		Time (min)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)
2-naphthol	**33**	5.0	90	2.1	83	8.0	75
1-naphthol	**35**	5.0	88	2.2	80	8.0	70

Scheme 9 Comparison of the iodine mediated reaction conditions for the synthesis of benzocoumarins through the Pechmann reaction.

The iodine mediated synthesis of benzocoumarins was found to be highly efficient under thermal heating or microwave reaction conditions (Scheme 9).[33] Even at room temperature, the reaction also proceeded with a little longer time to give a comparable yield. Authors, however, did not fully analyzed their products to claim the exclusive formation of benzo[*g*]-coumarin from 2-naphthol, which seemed highly improbable.

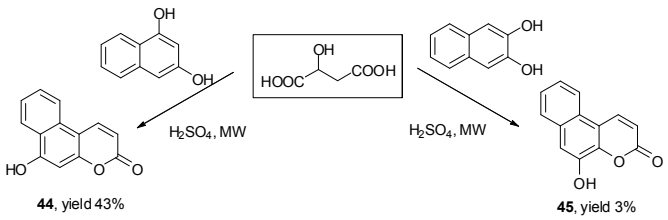
The Pechmann reaction catalyzed by poly(4-vinyl-pyridinium) perchlorate, P(4-VPH)ClO_4, under ultrasonic irradiation at room temperature generated the corresponding benzocoumarin derivatives in high yields (Scheme 10).[34] Also, in this case, authors claimed that the formation of benzo[*g*]-coumarin from 2-naphthol occurred with a high selectivity over benzo[*f*]coumarin. In general, Pechmann reaction conditions generate benzocoumarins with a substituent at 4-position.

Recently, Litinas and co-workers reported that benzocoumarins with no substituent at C-4 could also be synthesized from naphthalene-1,3-diol by treatment with 3-oxopropanoic acid or its ester that was *in situ* generated from malic acid under microwave irradiation (Scheme 11).[35] In this condition, naphthalene-1,3-diol produced corresponding benzocoumarin (**44**) in moderate yield, whereas naphthalene-2,3-diol gave a very low yield of the corresponding benzocoumarin.



Naphthol	Benzocoumarin	Time (min)	Yield (%)
2-naphthol	**33**	24	82
1-naphthol	**35**	22	84
2,7-naphthalenediol	**34** + **36**	25	86 (**34** = 72% and **36** = 14%)

Scheme 10 P(4-VPH)ClO_4 catalyzed Pechmann condensation.



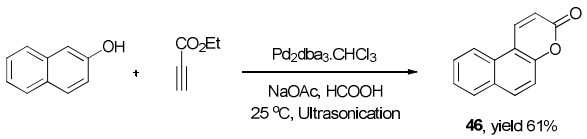
44, yield 43% **45**, yield 3%

Scheme 11 Synthesis of benzocoumarins with no substituent at C-4.

2.2.4. Synthesis through metal catalyzed reactions

Generally, the metal catalyzed cyclization goes through C-H functionalization of aromatic rings to form benzocoumarins. The C-H functionalization occurs at the *ortho*-position of naphthols and their derivatives. Palladium catalysts have been extensively used for this purpose. Other metal species such as platinum, gold, silver, zinc, and nickel are also effective.

The palladium-catalyzed addition of phenols to alkynoates through a net C-H insertion was initially demonstrated by Trost and co-workers. The reaction proceeded at room temperature under sonication to produce unsubstituted benzo[*f*]coumarin **46** in good yields (Scheme 12).[36]

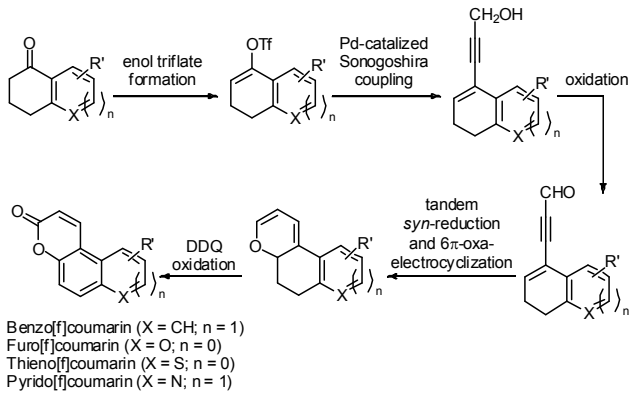


46, yield 61%

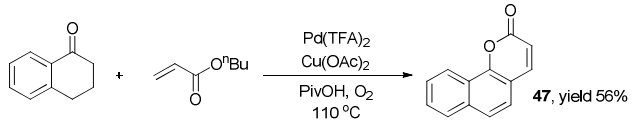
Scheme 12 Synthesis of a benzo[*f*]coumarin through a palladium catalyzed cyclization.

Through palladium-catalyzed Sonogashira coupling reactions benzo-, furo-, thieno-, and pyrido[*f*]coumarins were also synthesized, which involved formation of the 2*H*-pyran-2-one moiety followed by oxidation of the corresponding 2*H*-pyran ring that was formed in situ from an electrocyclization of cis-dienals (Scheme 13).[37]

Recently an one-pot reaction was reported in which 3,4-dihydronaphthalen-1(2*H*)-one was coupled with butyl acrylate to form benzo[*h*]coumarin **47**, which involved tandem palladium-catalyzed dehydrogenation and oxidative Heck reaction, followed by isomerization and then cyclization (Scheme 14).[38]



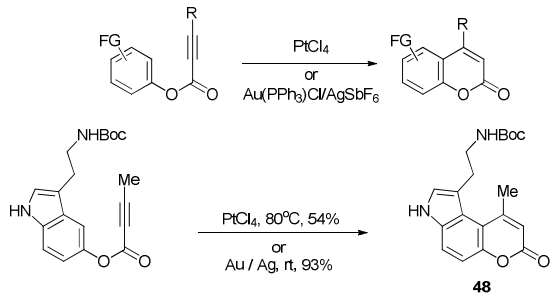
Scheme 13 Pd-catalyzed Sonogashira coupling route to benzocoumarins.



47, yield 56%

Scheme 14 Metal catalyzed route to benzo[*h*]coumarin from 3,4-dihydronaphthalen-1(2H)-one.

Other metal species such as platinum, gold and silver have been also used for the catalytic coupling between aryl C−H bonds and alkynes (6-endo annulation *via* hydroarylation) to form the chromen-2-one ring (Scheme 15).[39] Pyrrolo[*f*]-coumarin **48** was the only product, which was explained by the favorable resonance stabilization of the intermediates. A possible formation of the pyrrolo[*g*]coumarin **48a** seemed to be suppressed due to the less stable reaction intermediates where the pyrrole ring was dearomatized (Scheme 16). According to the suggested mechanism, it is also expected that for other metal-catalyzed cyclization through C-H functionalization benzo[*g*]coumarins or pyrrolo[*g*]coumarins would not be generated.



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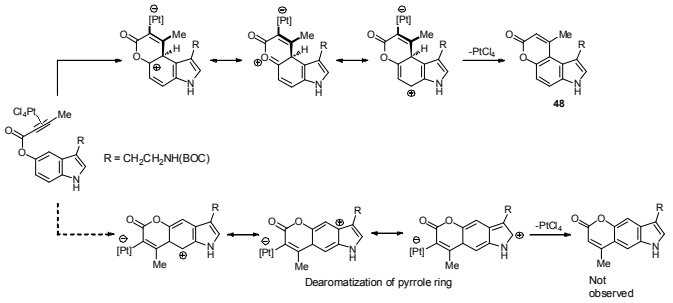
Scheme 15 Nobel metal catalyzed synthesis of benzocoumarin and pyrrolocoumarin derivatives.

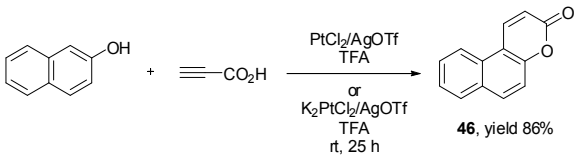


Scheme 16 Mechanism of metal catalyzed aryl C-H functionalization.

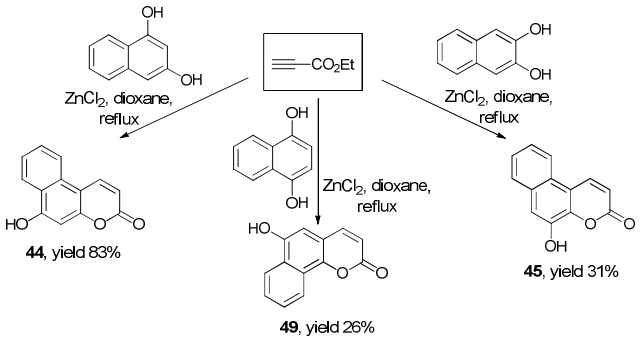
Kitamura and co-workers previously reported several palladium-catalyzed formation of the chromenone ring through C-H functionalization. Recently, they also reported platinum-catalyzed formation of benzocoumarins using propionic acid or its esters and naphthols under similar conditions (Scheme 17).[40] The platinum catalyzed reaction efficiently produced benzo[*f*]coumarin **46** in a high yield.

A similar strategy, namely a $ZnCl_2$-catalyzed synthesis of benzocoumarins using ethyl propiolate, was also demonstrated (Scheme 18).[35] Depending on the starting naphthols, the yield of the corresponding benzocoumarins could vary from poor to high.

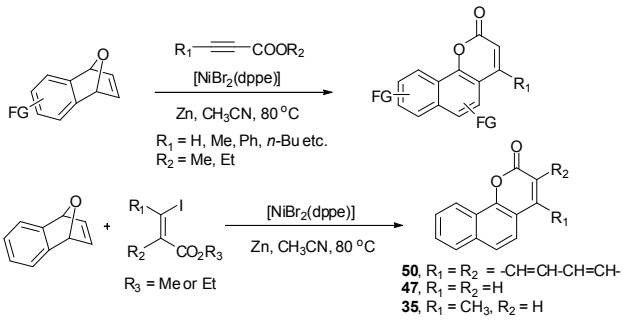
Two types of nickel-catalyzed cyclization were reported in the synthesis of benzo[*h*]coumarins: nickel catalyzed cyclization of an oxanorbornene with alkyl propynoates[41] and nickel-catalyzed cyclization of oxanorbornenes with β-iodo-(Z)-propynoates or an *o*-iodobenzoates[42] (Scheme 19). These routes seem to be useful for the synthesis of highly substituted benzocoumarins. But, according to the proposed mechanism in both cases, only benzo[*h*]coumarin could be formed.



Scheme 17 Synthesis of a benzocoumarin through Pt-catalyzed aryl C-H functionalization.



Scheme 18 Zn-catalyzed synthesis of benzocoumarins.

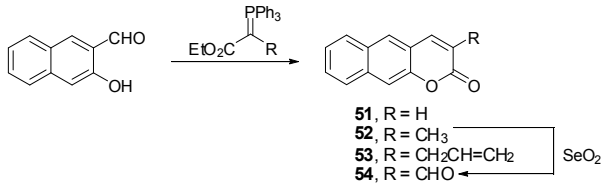


Scheme 19 Ni-catalyzed benzocoumarin synthesis.

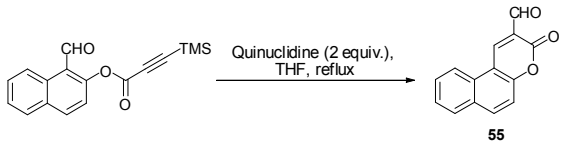
2.2.5. Other synthetic routes

o-Hydroxynaphthaldehydes underwent the Wittig reaction with phosphoranes such as carbethoxymethylene triphenyl-phosphorane or carbethoxyethylidene triphenylphosphorane in aprotic solvents (xylene, diethylaniline or benzene) under heating conditions (Scheme 20). [3,43-45] Introduction of several functionalities at C-3 other than an electron withdrawing substituent could be readily done by this strategy, in comparison with the Knoevenagel condensation route that only generated benzocoumarins with an electron-withdrawing group at C-3.

A base catalyzed intramolecular condensation between propynoate and *o*-formyl groups was used to generate benzocoumarins. Amines were used as base for the activation of the propynoate nucleophile. Formation of 3-formyl-benzo[*f*]coumarin was demonstrated starting from the naphthaldehyde containing trimethylsilyl-protected propynoate and quinuclidine as base (Scheme 21).[46]

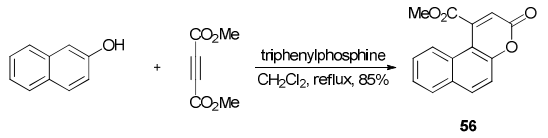


Scheme 20 Synthesis of benzocoumarins through the Wittig reaction.



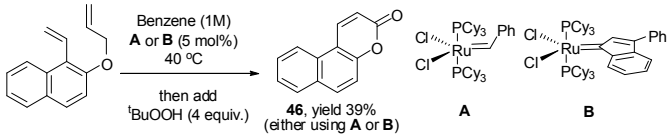
Scheme 21 Synthesis of a benzo[*f*]coumarin through condensation between propynoate and aldehyde groups.

Hekmatshoar and co-workers reported that 2-naphthol reacted with acetylene dicarboxylic acid dimethyl ester, leading to structurally unique benzo[*f*]coumarin **56** with complete regioselectivity (Scheme 22).[47]



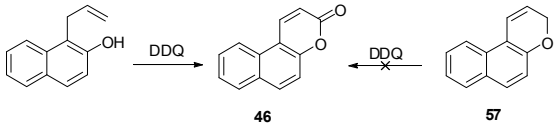
Scheme 22 Synthesis of benzocoumarin through the Wittig condensation.

In 2011, a new synthetic route to benzocoumarins was reported, where tandem ring closing olefin metathesis (RCM) and allylic oxidation sequences (Scheme 23) were used to produce the benzocoumarin **46** in moderate yield.[48]



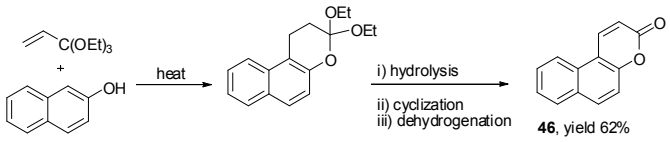
Scheme 23 Synthesis of benzo[*f*]coumarin through ring closing olefin metathesis (RCM).

Also, a simple oxidative cyclization of 1-allyl-2-naphthol was used to generate a benzo[*f*]coumarin: treatment of 1-allyl-2-naphthol with DDQ gave the benzocoumarin as the only product.[49] Interestingly, the direct oxidation of chromene **57** did not produce the benzocoumarin (Scheme 24).



Scheme 24 Synthesis of benzocoumarin through cyclization followed by oxidation.

In yet another method, thermal Claisen rearrangement of 2-naphthol with triethyl orthoacrylate also generated a benzo[*f*]-coumarin precursor, which was further elaborated to the benzocoumarin in good yield.[50] The naphthols that were poor substrates in the Pechmann condensation also gave the benzocoumarins in good yields (Scheme 25).



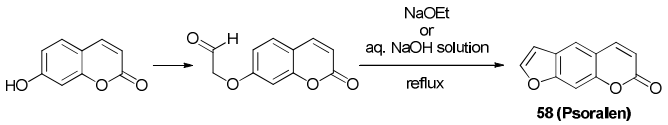
Scheme 25 Synthesizs of benzocoumarin through the Claisen rearrangement.

Rajagopalan and co-workers reported that thermal rearrangement of α-(aryloxy)methylacrylic acid produced benzo[*g*]coumarin in polyethyleneglycol (PEG) medium, which is a facile synthetic route to 3-methyl-benzo[*g*]coumarin.[51]

In spite of tremendous progress in the development of methodology leading to benzocoumarins, the classical Knoevenagel and Pechmann approaches continue to predominate. This chiefly results from availability of both the starting materials and generality of these reactions. One has to emphasize however that unsupported claims related to regioselectivity in Pechmann reaction of 2-naphthol remain to be clarified.[34,35]

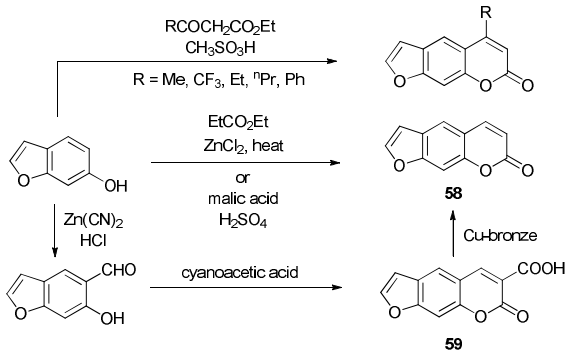
2.2.6. Synthesis of coumarins fused with furan and pyrrole

Psoralene (furo[*g*]coumarin) derivatives can be synthesized either starting from 7-hydroxycoumarins or from 6-hydroxy-benzofuran. Treatment of 2-oxopropyl or 2-oxoethyl ethers of 7-hydroxycoumarin with NaOEt or NaOH under reflux conditions produced the corresponding furo[*g*]coumarins (Scheme 26).[52,53] Also, treatment of a 6-formyl-7-hydroxy-coumarin with ethyl bromoacetate gave the corresponding psoralene, through the Knoevenagel condensation followed by intramolecular cyclization.[53]



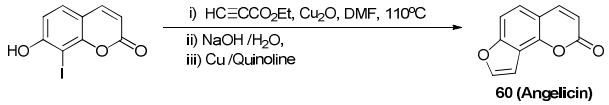
Scheme 26 Synthesis of psoralene derivatives from hydroxycoumarins.

Alternatively, psoralenes were constructed starting from 6-hydroxybenzofuran or its 5-formylated derivative, either through the Pechmann condensation[53,54] or the Knoevenagel condensation[53,55] using appropriate β-ketoesters (Scheme 27). These reactions provide synthetic routes to substituted psoralenes either at C-3 or C-4.



Scheme 27 Synthesis of psoralenes from 6-hydroxybenzofurans.

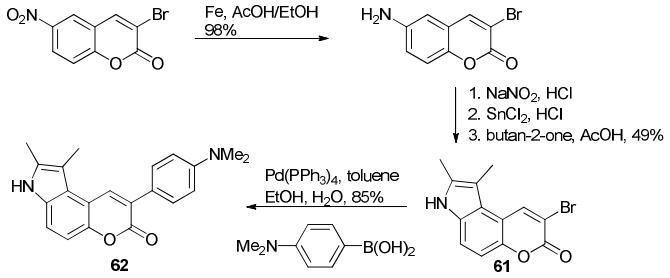
Angelicin, an isopsoralene **60**, was synthesized by a copper catalyzed coupling of 8-iodo-7-hydroxy coumarin with ethyl propynoate followed by base mediated cyclization and decarboxylation (Scheme 28).[56] Similarly, psoralene analogues such as pyrrolocoumarins[57] and thioangelicins[58] were also synthesized starting from the corresponding coumarins.



Scheme 28 Synthesis of angelicin.

Pyrrolo[*f*]coumarin has been prepared from 7-amino-coumarin by following the Sugasawa procedure.[59] The most

comprehensive approach was recently revealed by Yao and co-workers,[60] who reported several strategies towards both pyrrolo[*f*]/[*g*]coumarins. Optical properties of these compounds were also comprehensively investigated (see Chapter 5). Pyrrolo[*f*]coumarin **62** can be obtained from easily available 3-bromo-5-nitrocoumarin through the Fisher indole synthesis followed by Suzuki reaction (Scheme 29).



Scheme 29 Synthesis of a pyrrolo[*f*]coumarin.

2.2.7. Synthesis of benzo[*c*]coumarins and its analogs

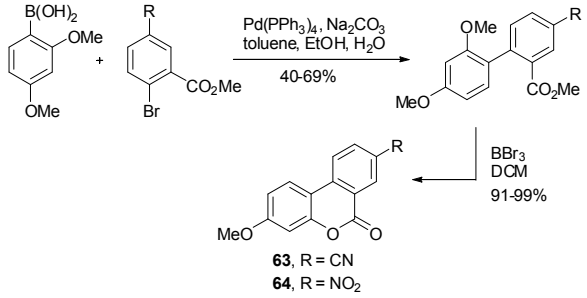
Numerous reactions for synthesis of benzo[*c*]coumarin derivatives are known. According to the mechanism of their formation, these methods are categorized into: (1) reactions of closing new ring: (a) formation of C-O bond in the last step; (b) formation of C-C bond in the last step; (c) cyclizations. (2) transformation of existing ring: (a) ring enlargement; (b) aromatization; (c) specific oxidation.

Recently more attention has been also devoted to the coumarins fused at pyranone ring with furane, pyrrole and thiophene,[61] however for space reason these examples will not be described here.

2.2.7.1. Synthesis of benzo[*c*]coumarins by ring closing reactions

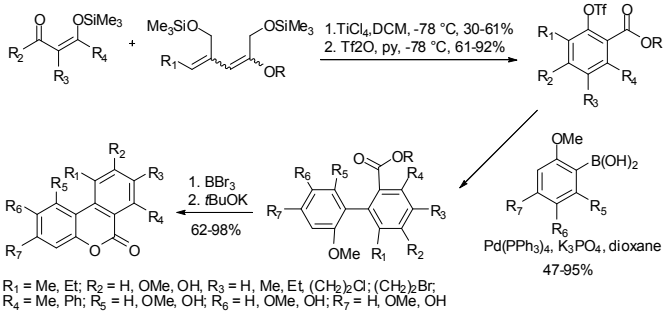
2.2.7.1.1. Formation of C-O bond in last step

Vast majority of methods rely on subsequent reaction on 2,2′-substitued biaryl compunds. Suzuki coupling between substituted *o*-bromobenzoates and 2,4-dimethoxyphenylboronic gave biaryl compound with ester and methoxy group in position 2 and 2′ respectively. Intramolecular BBr_3-mediated lactonization produced desired benzo[*c*]coumarins (Scheme 30). Surprisingly second methoxy group was left unchanged.[62] Analogously biarylamide instead of biarylester can be used for the synthesis of derivatives of benzo[*c*]coumarin.[63]



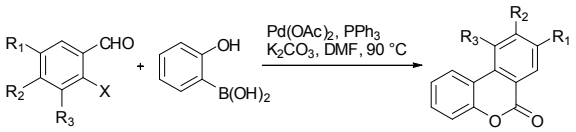
Scheme 30 Synthesis of benzo[*c*]coumarins by BBr_3 promoted lactonization.

Benzo[*c*]coumarins may be also obtained in four-steps based on [3+3] cyclization between 1,3-bis(silyl enol ethers) and 3-silyloxy-2-en-1-ones followed by subsequent Suzuki coupling and BBr_3-mediated lactonization (Scheme 31).[64] This is a suitable method for obtaining derivatives multiply substituted in both benzene rings.



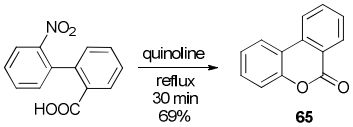
Scheme 31 Synthesis of polysubstituted benzo[*c*]coumarins through [3+3] cyclization followed by lactonization.

Derivatives of benzo[*c*]coumarin were successfully synthesized in reaction between substituted *o*-halobenz-aldehydes and 2-hydroxy-phenylboronic acid. Synthesis involved Suzuki coupling followed by formation of hemiacetal and subsequent aerial oxidation (Scheme 32).[65]



Scheme 32 Synthesis of benzo[*c*]coumarins from *o*-halogenobenzaldehydes and *o*-hydroxybenzeneboronic acids.

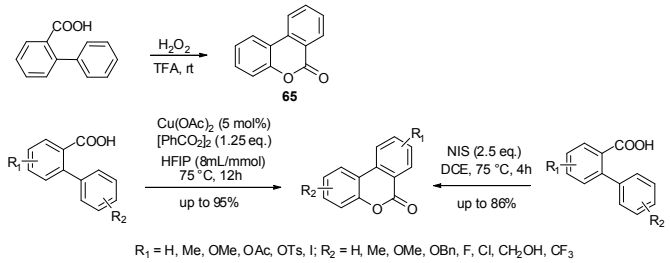
Unsubstituted benzo[*c*]coumarin can be obtained by refluxing 2′-nitrobiphenyl-2-carboxylic acid in quinoline for 30 minutes (Scheme 33). Mechanism of this reaction is an intramolecular nucleophilic substitution, in which carboxylate anion is a nucleophile and nitro substituent is a leaving group. Deng and co-workers established method utilizing this feature to obtain substituted benzo[*c*]coumarins.[66]



Scheme 33 Nucleophilic substitution of nitro group in 2′-nitrobiphenyl-2-carboxylic acids.

The C-O bond formation by oxidative cyclization in the biphenyl-2-carboxylic acid is an interesting example (Scheme 34). Reaction was held in the presence of hydrogen peroxide in TFA at room temperature.[67] The hydrogen peroxide is responsible for generation of carboxyl radical which attacks vicinal benzene ring creating new lactone. Another example of

reaction in which C-O bond was created *via* radical mechanism is Cu-catalyzed lactonization of biaryl 2-carboxylic acid.[68] The main advantages of this method are high yields of obtained products (up to 95%) and wide substrate scope. Very recently, Gao and Wei obtained benzo[*c*]coumarins in similar method, but without use of any catalyst. N-iodosuccinimide (NIS) instead of benzoyl peroxide was used as a radical promotor. Unarguable advantage of this methodology is mild reaction conditions without necessity of addition of any transition metal catalyst.[69] Wang and co-workers found that benzo[*c*]coumarins could be smoothly obtained from biaryl 2-carboxylic acids *via* palladium catalyzed C-O bond formation by carboxyl group directed C-H activation.[70]

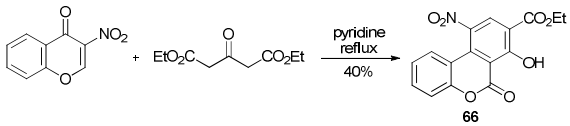


R_1 = H, Me, OMe, OAc, OTs, I; R_2 = H, Me, OMe, OBn, F, Cl, CH_2OH, CF_3

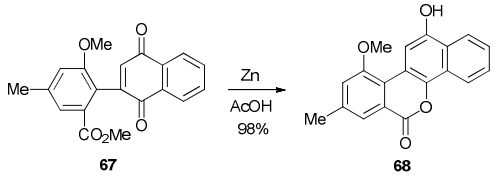
Scheme 34 Oxidative radical cyclization of biphenyl-2-carboxylic acids.

Another interesting example for the synthesis of benzo-[*c*]coumarin core was reported by Winkler and co-workers.[71] Reaction between 4*H*-1-benzopyran-4-one and diethyl acetone-dicarboxylate in refluxing pyridine gave coumarin of an interesting structure in 40% yield (Scheme 35). Mechanism of this reaction is complex and involves Michael addition of carbanion generated from diethyl acetone-dicarboxylate to 3-nitro-4*H*-1-benzopyran-4-one, followed by opening of chromene ring. Then, intramolecular condensation and aromatization of newly made ring takes place, and the last step is lactonization between hydroxyl group attached to one benzene ring and ester group attached to another.

Reductive lactonization of naphthoquinones leads to 6*H*-dibenzo[*d*]naphtho[1,2-*b*]pyran-6-ones, structurally closely related to benzo[*c*]coumarins. Quinone **67** treated with zinc powder in acetic acid provided 6*H*-dibenzo[*d*]naphtho[1,2-*b*]pyran-6-one **68** in excellent yield (Scheme 36).[72]

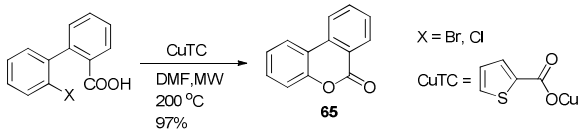


Scheme 35 Condensation between 4*H*-1-benzopyran-4-one and diethyl acetonedicarboxylate.



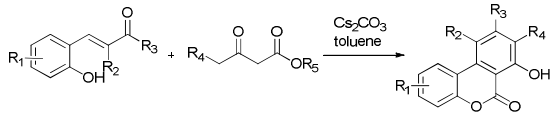
Scheme 36 Reduction of naphthaquinones leading to benzo[*c*]coumarins.

Simple and very efficient reaction of C-O bond coupling in the presence of copper salt assisted by microwave irradiation led to benzo[*c*]coumarin.[73] Reaction conditions were rather harsh (200 °C in DMF) but the yield was excellent, 97% (Scheme 37).



Scheme 37 Copper salt promoted C-O coupling.

Interesting method was reported by Lee and co-workers. Domino reaction between 2-hydroxychalcones with *β*-ketoesters gave smoothly diverse benzo[*c*]coumarins (Scheme 38).[74] Proposed mechanism includes in the first step Cs_2CO_3-mediated Michael addition to afford intermediate which undergoes an intramolecular aldol condensation followed by oxidative aromatization. The last step is lactonization under basic conditions.

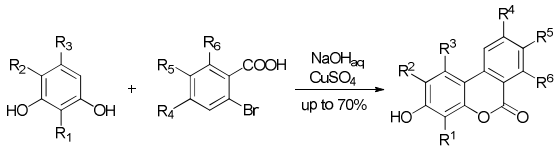


R_1 = H, Me, Br, OMe; R_2 = H, Me, R_3 = Ar, R_4 = H, Me, Ph, CO_2Et; R_5 = Me, Et

Scheme 38 Domino reaction between 2-hydroxychalcones and β-ketoesters.

2.2.7.1.2. Formation of C-C bond in last step

An alternative approach to the synthesis of benzo[*c*]coumarin derivatives is formation of C-C bond. One of the oldest method for preparation diverse benzo[*c*]coumarins is reaction between *o*-bromobenzoic acids and electron-rich phenols, called Hurtley condensation.[75,76] Reaction is catalyzed by copper salt in aqueous solution of sodium hydroxide (Scheme 39). Despite the fact that this reaction is known for almost a century its mechanism remained unexplored. Recently, it was proved that also electron-rich naphthols undergo this reaction leading to such π-expanded coumarins as 8-hydroxy-dibenzo[*c*,*f*]-chromen-5-one and 2-hydroxy-benzo[*d*]naphtho[1,2-*b*]pyran-6-one.[77]



R_1 = H, Me, OH; R_2 = H, nHex; R_3 = H, OH; R_4 = H, F; R_5 = H, NO_2, CF_3; R_6 = H, F

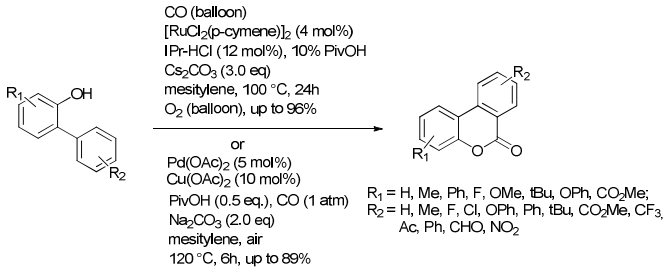
Scheme 39 Synthesis of benzo[*c*]coumarins through the Hurtley condensation.

There are several examples of intramolecular direct arylation, catalyzed by transition metals. Palladium-catalyzed coupling was utilized in total synthesis of antibiotics which were isolated

from *Streptomyces rutgersensis* possessing 6*H*-dibenzo[*d*]-naphtha-[1,2-*b*]pyran-6-one core.[78]

Derivatives of 6*H*-naphtho[2,1-*c*]benzopyran-6-one on the other hand, which are 6*H*-dibenzo[*d*]naphtho[1,2-*b*]pyran-6-ones isomers were synthesized from 1-bromonaphthalene-2-carboxylates in palladium-catalyzed coupling.[79] Scope of this reaction was also expanded to aryl iodides.[80]

Ruthenium-catalyzed carbonylative cyclization of 2-arylphenols to give derivatives of 6*H*-dibenzo[*b*,*d*]pyran-6-one have been recently described.[81] Also, palladium-catalyzed carbonylation of 2-arylphenols can be applied, instead of ruthenium catalyst (Scheme 40).[82]

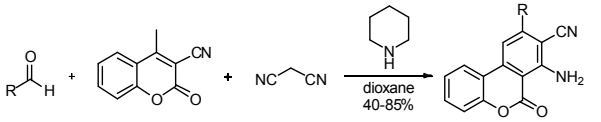


Scheme 40 Synthesis of benzo[*c*]coumarins through transition metal catalysed carbonylation of 2-arylphenols.

2.2.7.1.3. Cyclizations

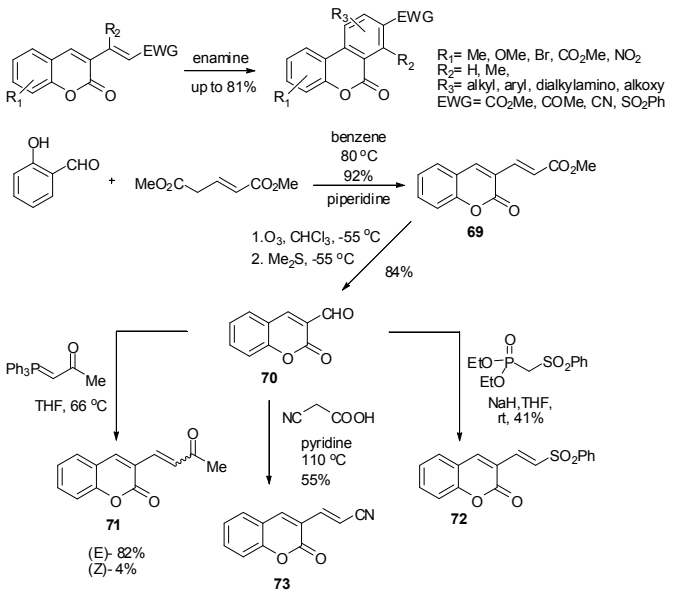
Several multi-component reactions were reported to generate benzo[*c*]coumarin skeleton. Perhaps the most startling is three-component condensation between aromatic aldehyde, 3-cyano-4-methylcoumarin and malononitrile in the presence of catalytic amount of piperidine led to derivatives of benzo[*c*]coumarin substituted with aromatic, cyano- and amino-group in one ring (Scheme 41).[83] Postulated mechanism includes Knoevenagel condensation between aldehyde and malononitrile to give benzylidenemalononitrile. Second step is Michael reaction, carbanion generated in such way, attacks benzylidenemalononitrile with consequent attack on cyano group attached to coumarin moiety and formation of new six-membered ring. Then another cyano group which originated from malononitrile leaves and cyclohexa-2,5-dien-1-imine ring is formed. That species tautomerize to more stable aromatic ring to give desired product.

In normal Diels-Alder reaction dienophiles possessing electron-withdrawing group in their structures and dienes possessing electron donating group undergo cyclization. Notably, in 2011, Bodwell and co-workers developed method of condensation coumarin-derived electron-poor dienes with various electron-rich dienophiles (mostly enamines) to afford diverse benzo[*c*]coumarins through inverse electron demand Diels-Alder reaction (Scheme 42).[84-86]



R = Ph, 4-Tol, 2-MeOC6H4, 4-MeOC6H4, 2-ClC6H4, 3-ClC6H4, 4-ClC6H4, 2-thienyl, 3-pyridyl

Scheme 41 Synthesis of benzo[*c*]coumarins by three components condensation.



Scheme 42 Synthesis of benzo[*c*]coumarins through inverse electron demand Diels-Alder cyclization.

Depending on desired electron-withdrawing group, dienes have been synthesized through different paths starting from 3-formylcoumarin **70**, which have been obtained by ozonolysis of compound **69** which was synthesized from salicylic aldehyde and dimethyl glutaconate. Authors obtained different substituted dienes (**71**–**73**) by applying Wittig reaction, Knoevenagel condensation, and Horner-Wadsworth-Emmons reaction between 3-formylcoumarin (**70**) and corresponding ylide, such as active methylene, 2-cyanoacetic acid, and dialkilphosphonate, respectively (Scheme 42).

Over ninety years of benzo[*c*]coumarins' chemistry resulted in the development of many complementary approaches. It seems that classical Hurtley condensation[75-77] and oxidative cyclization of the biphenyl-2-carboxylic acids[68] are the most general procedures methodologies. From the optical studies point of view both condensation of hydroxychalcones with β-ketoesters[74] and of chemistry recent Bodwell strategies based on inverse-demand Diels-Alder reaction,[84-86] since they lead to densely functionalized compounds possessing both electron-donating and electron-withdrawing groups.

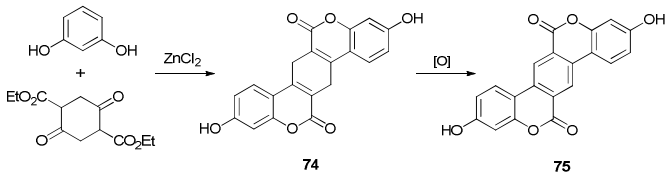
3. Biscoumarins

3.1. Benzobiscoumarins

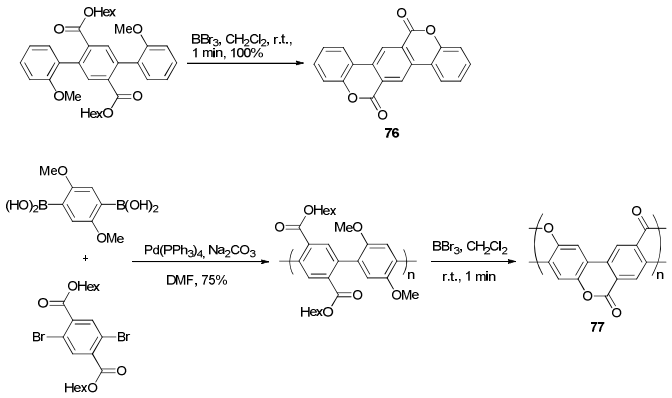
A lot of efforts were put in the design and synthesis of new organic semiconductors, in the attempt to discover manufacturing process of low cost electronic components. Large number of organic molecules was tested for this purpose, including some π-extended coumarins.

Taniguchi and co-workers investigated double Pechmann reaction of electron-rich phenols with diethyl 2,5-dioxocyclo-

hexane-1,4-dicarboxylate.[87] Reaction proceeded easily through intermediacy of partly unsaturated compound **74** leading to highly insoluble biscoumarin **75** (Scheme 43).



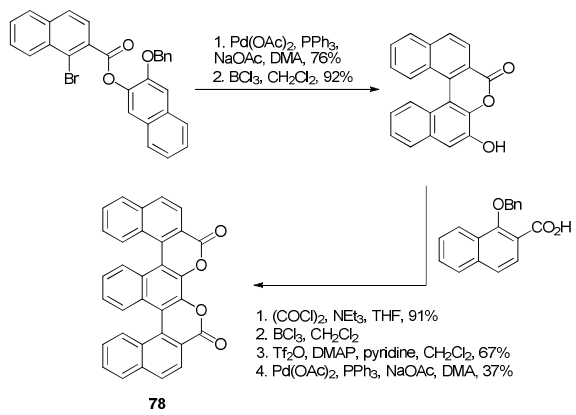
Scheme 43 The synthesis of S-shaped biscoumarins.



Scheme 44 Preparation of ladder-type polymer by BBr_3-promoted lactonization.

Kim and co-workers developed very efficient BBr_3-promoted lactonization of *p*-terphenyldicarboxylic acid derivatives (Scheme 44).[88] Benzobiscoumarin **76** has absorption maxima at slightly longer wavelengths than the non-cyclized precursor (λ_{max} = 328 and 315 nm, respectively), moreover, lactonization resulted in significant hyperchromic effect (over 14-fold increase of extinction coefficient). Large Stokes shift (7400 cm^{-1}) was observed for coumarin **76**, despite its rigid structure. X-ray diffraction analysis confirmed the expected high planarity of **76** and revealed strong π-stacking interaction in the crystals. Encouraged by these results Kim and co-workers extended these studies to a ladder-type polymeric structure **77** (Scheme 44). Cyclization was achieved both in solution and on films, however, prepared polymer was badly soluble in organic solvents, thus its spectroscopic characterization was achieved using film. Once more, lactonization leads to 24 nm bathochromic shift when compared to an opened form. An attempt towards preparation of field-effect transistors using **77** was performed, however, no details were provided in this paper.

Stereochemically interesting two fold lactone-bridged ter-naphthyl **78** is another intriguing example of π-extended biscoumarins (Scheme 45).[89]



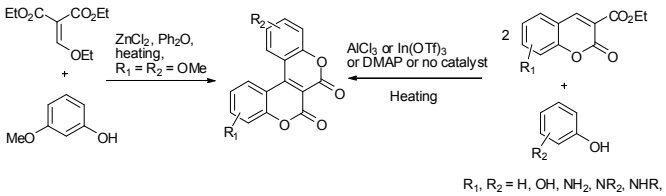
Scheme 45 Preparation of twofold lactone-bridged ternaphthyl.

The crucial steps in its preparation were consecutive palladium catalyzed intramolecular direct naphthalene arylations. Three possible stereo-isomers can be presented for this type of molecule: the two enantiomeric C_2-symmetric *P*,*P*- and *M*,*M*-forms, with two axes homochiral, and achiral *meso*-*M*,*P*-form, with the two axes differently configurated. In general, lactone bridged binaphthyls are configuratively unstable, generating easily interconverting atropo-enantiomers. Opposite to this, **78** seemed to form single species in the NMR experiments, which may be either an enantiomeric mixture of *P*,*P*- and *M*,*M*-**78**, or meso-form M,P-**78**. It was predicted by semiempirical and *ab initio* calculations, that meso-**78** should be energetically favored over the helically distorted *P*,*P*- and *M*,*M*-forms. This hypothesis was consequently confirmed by X-ray diffraction analysis, which proved **78** to exist in remarkably distorted *meso*-form. The prepared coumarin was extensively studied from the point of view of stereochemistry, thus no spectroscopic data is provided in the original paper, however, it has been mentioned that **78** exhibit strong blue-green fluorescence.

3.2. Biscoumarins fused in the pyran-2-one ring.

In the mid 80's, Högberg and co-workers found that heating of 3-methoxyphenol with diethyl ethoxymethylenemalonate in presence of Lewis acid leads to formation of very interesting biscoumarin fused in the pyran-2-one rings (Scheme 46).[90] Despite its intriguing structure, the photophysical properties of these coumarins were not studied. Over 20 years later Kovtun discovered that simple heating of mixture of ethyl 2-oxo-2*H*-chromene-3-carboxylate derivatives with reactive phenols leads to similar product (Scheme 46). It was found that additional equivalent of starting coumarin serves as an oxidant, however, the scope of this reaction was very limited.[91] Very recently Gryko and co-workers further explored this process by applying various catalysts and oxidants, and found that addition of Lewis acid or DMAP significantly enhance the reaction rates. Large group of biscoumarins was prepared and their photophysical properties have been studied in detail.[92] The same group investigated the possibility of applying these coumarins into energy transferring array. Aza-analogs of such biscoumarins are

formed in direct condensation of esters of coumarin-3-carboxylic acids with DBU and DBN.[93]

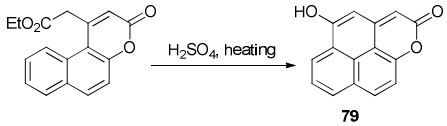


Scheme 46 The synthesis of biscoumarins fused in pyran-2-one ring.

4. Vertically expanded coumarins

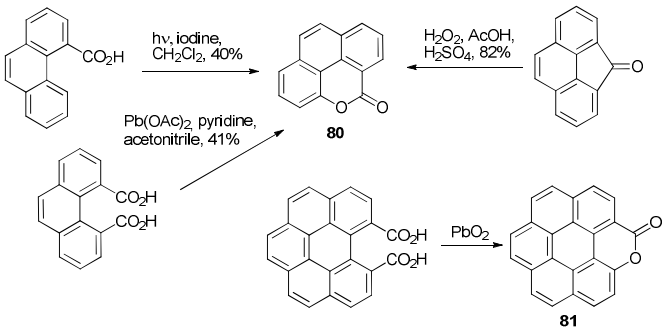
4.1. Oxapyrenone derivatives

In 1915, Dey in his study on the coumarin condensation reported, that heating of ethyl 2-(3-oxo-benzo[*f*]chromen-1-yl)acetate in concentrated sulfuric acid yielded deep yellow precipitate (Scheme 47).[94] The obtained product had intense green fluorescence in alcoholic solution and could be transformed into sodium salt by dissolving in dilute alkalis. Acetyl, benzoyl and methyl ether derivatives were also prepared. On the basis of its chemical behavior and elemental analysis, the structure of this intriguing product has been ascribed as 5-hydroxy-1-oxa-pyren-2-one (**79**), which was the first example of coumarin of this type.



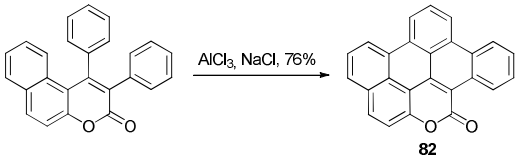
Scheme 47 Preparation of 5-hydroxy-1-oxa-pyren-2-one.

An isomer of such coumarins, formally 4-oxapyren-5-one, can be prepared using many methods, such as well-known oxidation of diphenic acid derivatives with lead tetracetate. Gillis and Porter exploited this method in synthesis of unsubstituted 4-oxapyren-5-one (Scheme 48).[95] The prepared compounds exhibited strong absorption between 275 and 375 nm and have extinction coefficients in the range of 4700–16700 $M^{-1}cm^{-1}$. Ott and Zinke postulated the possible formation of even more complex 1-oxa-coronen-2-one while oxidizing 7,8-dicarboxybenzo[*ghi*]perylene.[96] The same group attempted oxidation of various polycyclic aromatic hydrocarbons, including dibenzoperylene.[97] Minabe and co-workers used Bayer-Villiger oxidation of 4-oxocyclopenta[*def*]phenanthrene for preparation of unsubstituted 4-oxapyren-5-one.[98] Alternatively, well known photolactonization of phenanthrene-4-carboxylic acid in the presence of iodine leads to the same product.[99,100]



Scheme 48 Preparation of 4-oxapyren-5-ons by oxidation of phenanthrene carboxylic acids.

Scholl reaction is also commonly used for preparation of polycyclic aromatic hydrocarbons.[101] Dilthey and Giebert studied dehydrogenative coupling of 3,4-diphenyl substituted benzocoumarin (Scheme 49).[102] The resulting product, possessing six fused benzene rings, formed yellow-brown crystals and had green fluorescence in solution.



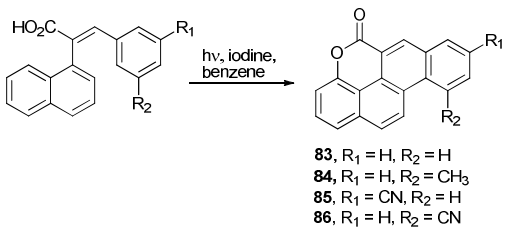
Scheme 49 Preparation of coumarins possessing six fused benzene rings through dehydrogenative Scholl coupling.

Many such polycyclic aromatic hydrocarbons have been studied in the context of their mutagenic activity. While studying structure-activity relationship of chrysene derivatives, Lee-Ruff and Kruk discovered that photocyclization of stilbene carboxylic acids led to secondary photolactonizations (Scheme 50).[100] New method of functionalization of chrysene bay region gives an access to various benzo-4-oxapyren-5-ons, and has been shown to proceed *via* chrysene carboxylic acid. Among the large variety of prepared chrysene derivatives, unsubstituted coumarin **83** exhibited the highest mutagenic activity. The thiophene analogue can be also obtained using this method, however, in much lower yield.[103]

4.2. Oxaperylenone derivatives

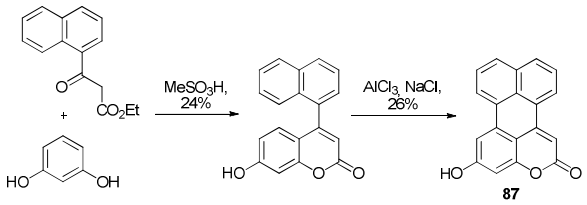
The only example of 1-oxaperylene-2-one was recently published by Gryko and co-workers via the two-step synthesis involved classical Pechmann reaction followed by Scholl coupling (Scheme 51).[104]

The same group developed the synthesis of even more complex chromophores, 1,7-dioxa-perylene-2,8-diones, where two coumarin units are in head-to-tail orientation (Scheme 52).[105]



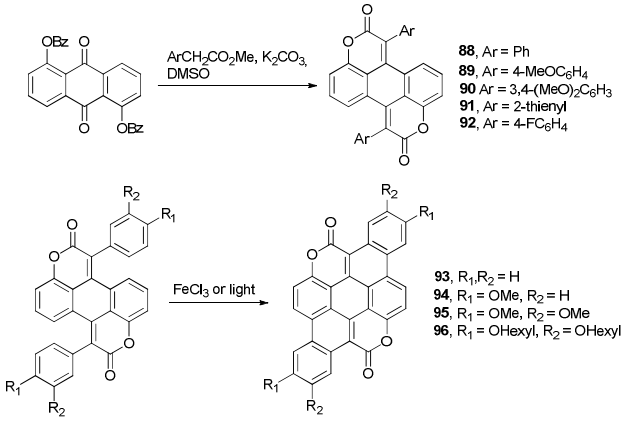
83, R_1 = H, R_2 = H
84, R_1 = H, R_2 = CH_3
85, R_1 = CN, R_2 = H
86, R_1 = H, R_2 = CN

Scheme 50 Preparation of oxapyrenons by photocyclization of stilbene carboxylic acids.



87

Scheme 51 The synthesis of 1-oxaperylene-2-one.

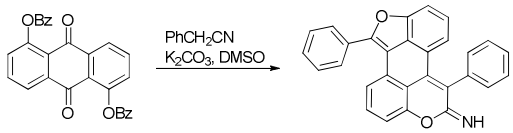


88, Ar = Ph
89, Ar = 4-$MeOC_6H_4$
90 Ar = 3,4-$(MeO)_2C_6H_3$
91, Ar = 2-thienyl
92, Ar = 4-FC_6H_4

93, R_1,R_2 = H
94, R_1 = OMe, R_2 = H
95, R_1 = OMe, R_2 = OMe
96, R_1 = OHexyl, R_2 = OHexyl

Scheme 52 The synthesis of oxaperylenone derivatives.

Their preparation was achieved using 1,5-dihydroxy-anthraquinone as a starting material, which was subjected to esterification, followed by Knoevenagel condensation and transesterification. The π-system of the obtained biscoumarins was further elongated by chemical or light-driven de-hydrogenation, resulting in formation of unprecedented dibenzopentacene derivatives. Already in 1996, Mainagashev and Klimenko noticed that arylacetonitriles react with 1-acetoxyantraquinone to produce π-expanded keto-coumarin.[106] Analogous reaction with phenylacetonitrile led exclusively to π-expanded coumarin **97** (Scheme 53).[107]



97

Scheme 53 The synthesis of π-expanded iminocoumarin.

5. Optical properties

5.1. General comparison of absorption and emission of various benzocoumarins

Molecular origins of optical properties of coumarins were object of intense investigation most prominently by Cole and co-workers.[108] In this chapter, photophysicial properties of benzo[*g*]coumarin, benzo[*h*]coumarin, and benzo[*f*]coumarin and benzo[*c*]coumarin families are critically compared. They show significant variations in the absorption and emission behavior depending on the substituent. The substituent effects can be explained by their resonance contribution with respect to the electron-accepting 2-pyranone moiety. As a result, benzo-coumarins with an electron-donating group at an appropriate position show red-shifts in both the maximum absorption and emission wavelengths.

Coumarin has a conformationally-restricted form of a cis-cinnamic acid ester (Fig. 2), thus it has high photostability, but coumarin itself shows a poor fluorescence quantum yield (Φ_F). With appropriate substitution that enhances intramolecular charge transfer (ICT), coumarin derivatives can emit strong fluorescence in the blue-green region (400–550 nm). For example, substitution of an electron-donating diethylamino group at the 7-position together with an electron-withdrawing ethoxycarbonyl group at the 3-position to coumarin brings a dramatic increase in the quantum yield (from Φ_F = 0.001 to Φ_F = 0.81) along with significant red-shifts in the maximum absorption and emission wavelengths (82 nm and 149 nm, respectively). Such changes can be understood by evoking the enhanced ICT by the substitution. The substituent effects on the photophysical properties of coumarins are listed in Table 1.

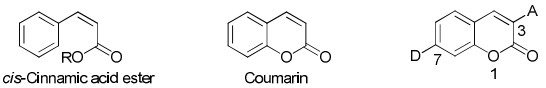


Fig. 2 An effect of coumarin substitution on the spectroscopic properties.

Considering the high photostability and strong fluorescence of coumarin derivatives, π-extended coumarins are expected to provide several advantageous features over the corresponding coumarins. Benzocoumarins with appropriate substituents can be excited at the longer wavelength: This feature becomes a critical issue when the dyes are applied to fluorescence imaging of biological substances of which autofluorescence under excitation at shorter wavelength becomes significant. Also, owing to the extended conjugation, the benzocoumarins may have higher Φ_F.

Table 1 Photophysical properties of coumarin and its derivatives with 3- and 7-substitution.

3-A	7-D	λ_{abs} (nm)	λ_{em} (nm)	Φ_F	Ref.
H	H	330	380	0.002	OMLC[ab]
H	NEt_2	373	440	0.73	OMLC
COOEt	H	334	415	0.12	Ref. 109[c]
COOEt	NEt_2	412	529	0.81	Ref. 109[c]

[a] OMLC: Oregon Medical Laser Center (omlc.ogi.edu). [b] measured in CH_3CN. [c] measured in CH_2Cl_2.

The photophysical properties of benzocoumarin derivatives may be also predicted based on the type and position of electron-donating and/or electron-accepting substituents, as in the case of coumarins. With appropriate substituents, the absorption and emission wavelengths of the parent benzocoumarins can be significantly shifted to the longer wavelength region. Also, the Φ_F can be improved as the conjugation of π-molecular orbitals is elongated. The appropriate position of the donor group can be explained by its resonance contribution to the ICT. For example, benzo[*g*]coumarin derivatives with a donor substituent (D) at C-6 or C-8 can have one additional resonance structure, whereas those with a donor group at C-7 and C-9 do not (Fig. 3). As a result, the 6-D- or 8-D-substitued benzo[*g*]coumarins would show enhanced fluorescence along with red-shifts in the absorption and emission spectra, whereas the 7-D- or 9-D-benzo[*g*]coumarins would not show such changes. Among the 6-D- and 8-D-benzo[*g*]coumarin families, the latter is expected to emit stronger fluorescence with a larger red-shift compared to the former, considering the larger dipole moment expected in the case of the linear π-system over the bent π-system.

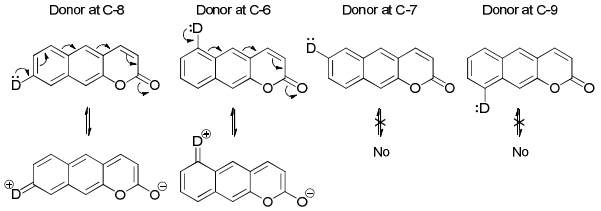


Fig. 3 Resonance stabilization of benzo[*g*]coumarins with a donor substituent at the peripheral benzene ring.

In the same manner, we can analyze which isomers are expected to emit more strongly than the others in the cases of the benzo[*f*]- and benzo[*h*]coumarin derivatives (Fig. 4, Fig. 5).

The benzo[*c*]coumarin derivatives would possess photophysical properties different from the related benzo[*g*]coumarin, benzo[*f*]coumarin, and benzo[*h*]coumarin derivatives. The fused benzene ring in the benzo[*c*]coumarin derivatives has a feature of the "crossed" conjugation and thus its resonance contribution to the absorption and emission wavelengths are predicted to be less efficient than the case of other benzocoumarin families.

The photophysical properties of parent benzocoumarin derivatives show that they have similar or a little shorter maximum absorption wavelengths but have significantly longer maximum emission wavelengths from those of coumarin itself ($\lambda_{abs}/\lambda_{em}$ = 330/380 nm in CH_3CN): benzo[*g*]coumarin, $\lambda_{abs}/\lambda_{em}$ = 321/429 nm in CH_3CN; 3-methyl-benzo[*h*]coumarin, $\lambda_{abs}/\lambda_{em}$ = 274/425 nm in EtOH; 3-methyl-benzo[*f*]coumarin, $\lambda_{abs}/\lambda_{em}$ = 275/425 nm in EtOH). Benzocoumarins with donor and acceptor substituents at appropriate positions would show further red-shifts in the maximum absorption and emission wavelengths (Fig. 6). This is the case indeed. Photophysical properties of various benzocoumarin compounds are tabulated in the next sections.

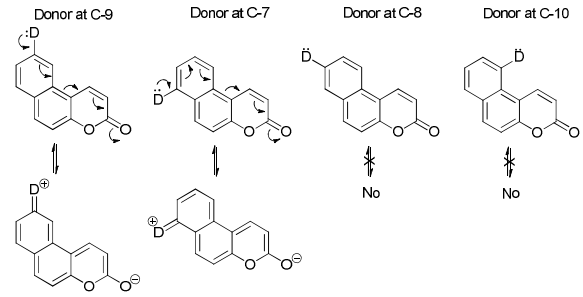


Fig. 4 Resonance stabilization of benzo[*f*]coumarins with a donor substituent at the peripheral benzene ring.

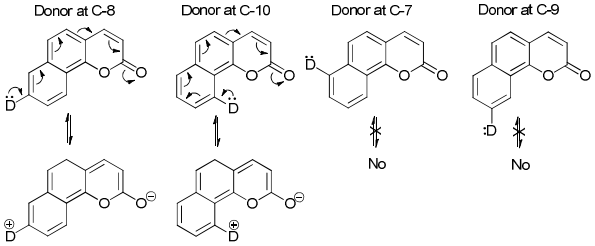


Fig. 5 Resonance stabilization of benzo[*h*]coumarins with a donor substituent at the peripheral benzene ring.

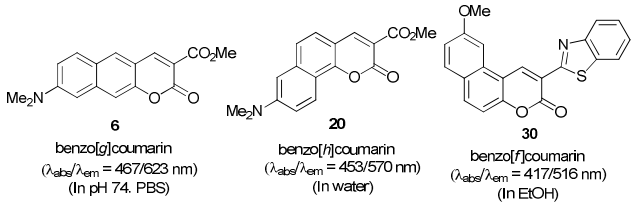


Fig. 6 Comparison of the absorption and emission maxima among benzocoumarins substituted with donor and acceptor groups.

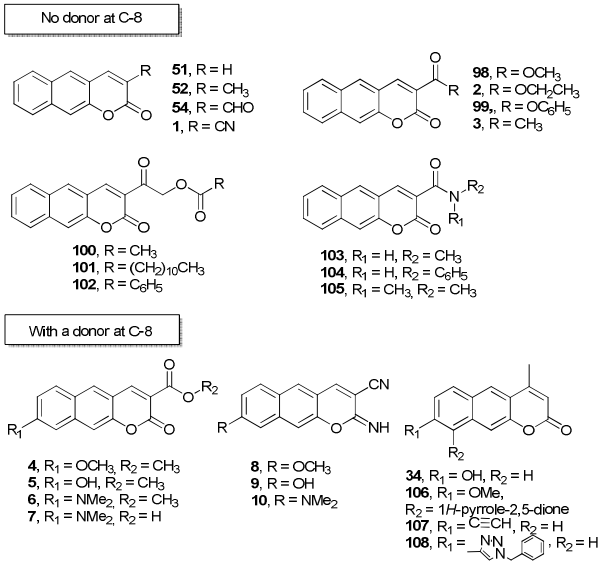


Fig. 7 Reported benzo[*g*]coumarin derivatives.

5.2. Benzo[*g*]coumarins

As discussed in the previous section, the benzo[*g*]coumarin family, which has the linearly extended conjugation, is predicted to have larger transition dipole moments compared to the other families. Benzo[*g*]coumarins can be categorized into two types whether they have an electron donor (D) group at C-8 or not: i) the parent type and ii) 8-D-substituted type (Fig. 7). The maximum absorption wavelength (λ_{abs}) and the maximum emission wavelength (λ_{em}) of parent compound **51** are 321 nm and 429 nm, respectively. Other analogues that have a substituent at C-3, mostly an electron-withdrawing substituent, show small changes in the absorption and emission spectra from the parent compound depending on the substituent: λ_{abs} = 322−346 nm; and λ_{em} = 465−549 nm (Table 2). The parent type compounds show the maximum absorption and emission wavelengths in the comparable range: λ_{abs} = 321−346 nm; and λ_{em} = 429−549 nm).

Table 2 Photophysical properties of benzo[*g*]coumarin derivatives without a donor substituent.[a]

Compd	λ_{abs} (nm)	λ_{em} (nm)	RFI[b]	Ref.[c]
51	321	429	100	Ref. 3
52	322	465	82	Ref. 3
54	345	547	126	Ref. 3
1	335	533	67	Ref. 3
98	332	534	60	Ref. 3
2	331	534	345	Ref. 3
99	337	539	115	Ref. 3
3	337	549	375	Ref. 3
100	345	544	131	Ref. 3
101	345	544	125	Ref. 3
102	346	544	136	Ref. 3
103	334	515	270	Ref. 3
104	343	n.d	n.d	Ref. 3
105	326	510	31	Ref. 3

[a] n.d.: not detected, n.r.: not reported. [b] relative fluorescence intensity (RFI) under the same experiment conditions. [c] measured in CH_3CN.

In contrast to the parent type benzo[*g*]coumarins, the 8-donor substituted compounds show significant red-shifts depending on the donor substituent (Table 3). A more electron-donating substituent at C-8 causes larger ICT and hence more red-shifts in both the absorption and emission maxima. Accordingly, values of λ_{abs} and λ_{em} increase in the order: compound **4** (8-OMe) < compound **5** (-OH) < compound **6** (-NMe_2). In analogy to 7-methoxycoumarin, compound **34** is an environment-sensitive fluorophore:[31] It is almost non-fluorescent in aprotic solvents whereas it strongly fluoresces in protic solvents (Table 3). The substituent effect is maximized in the case of a dialkylamino donor substituent, and compound **6** that has 8-dimethylamino donor and 3-methoxycarbonyl acceptor showed a large bathochromic shift ($\Delta\lambda_{em}$ = 146 nm) from that of the parent benzo[*g*]coumarin **51** and emitted in the red region (λ_{em} = 623 nm). It should be noted that the benzo[*g*]coumarin derivatives with an amino donor group at C-8, such as **6** and **10**, can be excited at the much longer wavelength (λ_{abs} = 444−467 nm) and have high quantum yields (Φ_F = 0.61−0.67). These are important features when such dyes are applied to two-photon bioimaging; they could be excited at the NIR wavelength (900 nm) under two-photon excitation conditions, which would reduce the auto-fluorescence from biological samples that becomes a significant issue when excited at the shorter wavelength as in the case of the conventional coumarin compounds. Further comments on these aspects are discussed in the application section.

Table 3. Photophysical properties of benzo[*g*]coumarin derivatives with a donor substituent.[a]

Compd	λ_{abs} (nm)	λ_{em} (nm)	Φ_F	Ref.
4	355	539	0.12	Ref. 6[b]
5	450	603	0.07	Ref. 6[b]
6	467	623	0.61	Ref. 5[c]
7	413	599	0.01	Ref. 6[b]
8	357	522	0.26	Ref. 6[b]
9	435	582	0.20	Ref. 6[b]
10	444	607	0.67	Ref. 5[c]
34	357	466	0.35	Ref. 21[d]
106	344	443	0.01	Ref. 12[d,e]
107	334	437	0.01	Ref. 21[d]
108	339	445	0.02	Ref. 21[d]

[a] n.d.: not detected, n.r.: not reported. [b] measured in H_2O. [c] measured in EtOH. [d] Measured in $CHCl_3$. [e] In CF_3CH_2OH Φ_F = 0.33.

5.3. Benzo[*h*]coumarin and benzo[*f*]coumarin families

Both benzo[*h*]coumarin and benzo[*f*]coumarin families are bent-shaped molecules (Fig. 4–6). The shorter conjugation length may result in a decrease in the transition dipole moment. Hence these benzocoumarins seem to have the absorption and emission maxima in the shorter wavelength region compared to the linear benzo[*g*]coumarin family. The $\lambda_{abs}/\lambda_{em}$ values for the representative compounds below (Fig. 8) are in accordance with the argument.

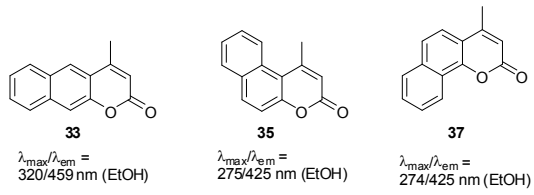


Fig. 8 Comparison of the absorption and emission maxima among benzo[*f*]-, benzo[*g*]- and benzo[*h*]- coumarins family.

Again, introduction of an electron donor group at C-8 of benzo[*h*]coumarin causes a significant red-shift in both the absorption and emission maxima, and the effect becomes notable in the case of amino substituent. If we compare the maximum absorption and emission wavelengths of compound **16** (Fig. 9, Table 4) ($\lambda_{abs}/\lambda_{em}$ = 379/470 nm, in CH_3CN) with those of compound **20** ($\lambda_{abs}/\lambda_{em}$ = 453/570 nm, in H_2O), there seems to be significant red-shifts in the latter amino-substituted one even though we count a portion of shift by the solvent effect. However, the red-shifts are less dramatic compared to the case of the corresponding linear benzo[*g*]coumarin **6** ($\lambda_{abs}/\lambda_{em}$ = 467/623 nm) (Fig. 7, Table 2). It is notable that compounds, **22** and **23** (Fig. 9, Table 4) showed two-photon absorbing properties and used to two-photon bioimaging of magnesium ions, details of which will be covered in the application section.

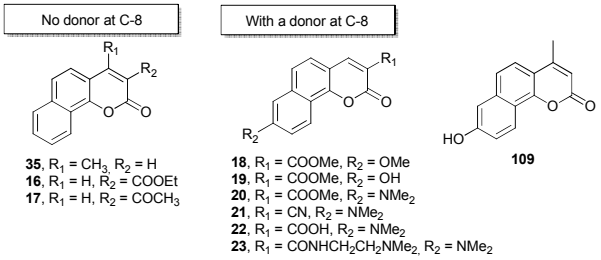


Fig. 9 Reported benzo[*h*]coumarin derivatives.

Table 4 Photophysical properties of benzo[*h*]coumarin derivatives.[a]

Compd	λ_{abs} (nm)	λ_{em} (nm)	Φ_F	Ref.
35	274	425	0.078	Ref. 20[b]
16	379	470	n.r	Ref. 3[c]
17	390	491	n.r	Ref. 3[c]
18	391	481	0.82	Ref. 7[d]
19	397	482	0.48	Ref. 7[d]
20	453	570	0.19	Ref. 7[d]
21	457	590	0.05	Ref. 7[d]
22	413	556	0.29	Ref. 8[e]
109	357	432	n.d.	Ref. 18[g]
23	446	549	0.20	Ref. 9[f]

[a] n.d.: not detected, n.r.: not reported. [b] measured in EtOH. [c] measured in CH_3CN. [d] measured in H_2O. [e] 10 mM Tris, 100 mM KCl, pH 7.05 buffer. [f] universal buffer (pH 7.0). [g] In EtOH/DMF 1:1.

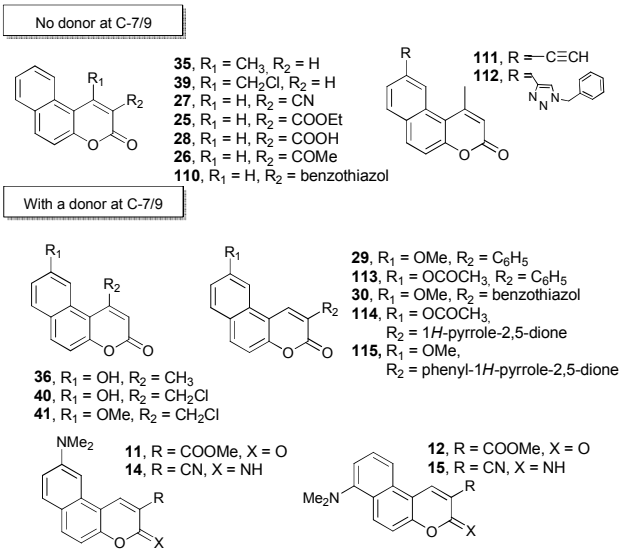


Fig. 10 Reported benzo[*f*]coumarin derivatives.

Benzo[*f*]coumarins without an electron-donating group at C-9, the parent type, show similar absorption and emission behaviors compared to the related benzo[*h*]coumarin derivatives. However, introduction of an electron-donating group at C-9 of the benzo[*f*]coumarins results in significant red-shifts in both the maximum absorption and emission wavelengths (Fig. 10, Table 5). For example, introduction of a hydroxyl to compound **35** ($\lambda_{abs}/\lambda_{em}$ = 275/425 nm, in EtOH) at C-9 resulted in compound **36** ($\lambda_{abs}/\lambda_{em}$ = 361/462 nm, in EtOH), which caused significant red-shifts in both the maximum absorption and emission wavelengths. The corresponding benzo[*f*]coumarin with dimethylamino substituent at C-9, compound **11**, also showed a significant red-shift in the maximum absorption wavelength (462 nm in DMSO), but it emitted very weakly in polar media such as DMSO and H_2O compared with the corresponding benzo[*g*]coumarin **6**.[6] When the benzo[*f*]coumarins with a dimethylamino group at C-9, compounds **11** and **14**, were compared with those with the same donor group at C-7, the C-7 analogues, compounds **12** and **15** respectively, gave very weak fluorescence in polar solvents such as CH_3CN and H_2O.

Table 5 Photophysical properties of benzo[*f*]coumarin derivatives.[a]

Compd	λ_{abs} (nm)	λ_{em} (nm)	Φ_F	Ref.
35	348	415	0.16	Ref. 20[b]
39	352	418	0.08	Ref. 23[b]
27	380	456	n.r	Ref. 10[c]
25	371	445	n.r	Ref. 3[d]
28	370	450	0.21	Ref. 11[e]
26	390	491	n.r	Ref. 3[d]
110	406	476	0.87	Ref. 110[d]
111	362	403	0.23	Ref. 21[b]
112	352	420	0.35	Ref. 21[b]
36	361	462	0.02	Ref. 21[b]
40	361	462	0.02	Ref. 23[b]
41	354	472	0.03	Ref. 23[b]
29	365	458	0.86	Ref. 12[b]
113	362	438	0.73	Ref. 12[b]
30	417	516	0.99	Ref. 12[b]
114	358	430	0.023	Ref. 12[b]
115	376	501	0.061	Ref. 12[b]
11	450	n.d	n.d	Ref. 6[g]
14	484	n.d	n.d	Ref. 6[g]
12	396	n.d	n.d	Ref. 6[g]
15	400	n.d	n.d	Ref. 6[g]

[a] n.d.: not detected, n.r.: not reported. [b] measured in EtOH. [c] measured in DMF/HEPES 1:1 v/v. pH 7.4. [d] measured in CH_3CN. [e] measured in MeOH. [f] measured in DMSO. [g] measured in H_2O.

5.4. Heterocycle-fused coumarin derivatives

Coumarin core can be fused by a heterocyclic ring such as furan, pyrrole, and thiophene. Psoralene, a furan fused coumarin, thus represents a family of natural products known as furocoumarins. Psoralene and its isomer angelicin, and related compounds are widely used for the treatment of psoriasis, eczema, vitiligo, and cutaneous T-cell lymphoma (Fig. 11). Psoralene and its analogues constitute an important class of photosensitizers. Its derivatives have the absorption and emission maxima in the range of 303−335 nm and 500−524 nm (Table 6). The furan- and thiophene-fused compounds **121**−**125** show photophysical properties not much different from those of coumarin itself: λ_{abs} = 306−351 nm, λ_{em} = 395−422 nm (Φ_F <0.1). Interestingly, pyrrole-fused coumarin derivatives show little fluorescence.

5.5. Benzo[*c*]coumarins

The replacement of the C-C double bond in 7-hydroxycoumarin with the benzene unit (i.e. dye **126**) bathochromically shifts both absorption and emission only 10–25 nm (Table 7, Fig. 12). At the same time, Φ_F increases from 0.08 to 0.21 and the Stokes shift remains almost the same. Systematic optical studies of

substituted benzo[*c*]coumarins proved that most of these compounds are characterized with large Stokes shifts. For amino-substituted benzo[*c*]coumarins, there is also a strong dependence of optical properties on the position of the amino group. When compared to compound **126**, the presence of tertiary amino group at ring C typically shifts absorption hypsochromically (**130**, Fig 12, Table 7). Hypsochromic shift is most probably caused by decreased accepting ability of the ring C imparted by an amino group, which leads to a weaker intramolecular charge transfer (ICT). The presence of an additional amino group at position 6 or 8 in coumarin directly triggers a non-emissive state. Interestingly, dye **131** bearing NH_2 in position 4 (ring A) does not display any measurable fluorescence while compounds bearing a tertiary amino group at position 9 (**130**, ring C) shows fluorescence (Φ_F = 0.05). Still, their λ_{em} (410–450 nm) is far from the value reported for analogous 7-hydroxybenzo[*c*]coumarin (**128**) by Langer and co-workers[113] (490 nm) which implies excited-state intra-molecular proton transfer (ESIPT) in the latter case as the most probable explanation. A bathochromic shift of absorption is also appeared when the benzo[*c*]coumarin chromophore is fused with an additional benzene ring (Fig. 12, compound **132**). The highest fluorescence quantum yield (Φ_F = 0.36) was measured for 7,9-dihydroxy-thieno[2,3-*c*]coumarin (**129**), which at the same time possesses relatively large Stokes shift (5800 cm^{-1}).

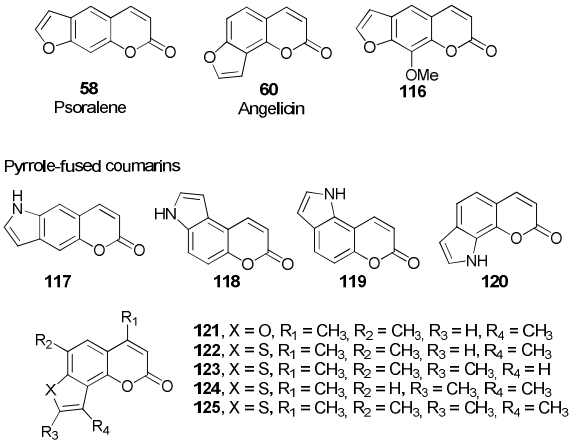


Figure 11. Reported Heterocycle-fused coumarin derivatives.

Table 6 Photophysical properties of coumarins fused with heterocycles.[a]

Compd	λ_{abs} (nm)	λ_{em} (nm)	Φ_F	Ref.
116	303	500	n.r	Ref. 111
117	335	524	0.08	Ref. 57
121	330	395	0.0023	Ref. 112
122	348	414	0.018	Ref. 112
123	306	415	0.013	Ref. 112
124	347	417	0.017	Ref. 112
125	351	422	0.017	Ref. 112
62	410	523	0.55	Ref. 60[e]

[a] n.d.: not detected, n.r.: not reported. [b] measured in EtOH/H_2O (5/95). [c] measured in EtOH. [d] measured in dioxane. [e] Measured in CH_2Cl_2.

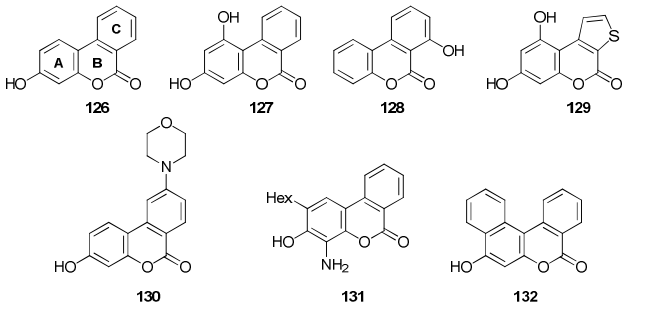


Fig. 12 Reported benzo[*c*]coumarin derivatives.

Table 7 Photophysical properties of benzo[*c*]coumarin derivatives.[a]

Compd	λ_{abs} (nm)	λ_{em} (nm)	Φ_F	Ref.
126	334	427	0.21	Ref. 77[c]
127	341	438	0.16	Ref. 77[c]
128	357	489	n.r.	Ref. 113[d]
129	341	425	0.36	Ref. 77[c]
130	304	408	0.05	Ref. 77[c]
131	330	n.d.	n.d.	Ref. 77[c]
132	399	460	0.04	Ref. 77[c]

[a] n.d.: not detected, n.r.: not reported. [b] measured in EtOH. [c] measured in DMF. [d] measured in CH_3CN.

5.6. Other π-expanded coumarins and bis-coumarins

Vertically-expanded coumarins and bis-coumarins typically have strongly bathochromically shifted absorption and emission versus 7-hydroxycoumarin (Table 8, Figs. 13–14). For example, dye **97** displays 100 nm red-shift. Vertical π-expansion allowed coumarin to gradually decrease HOMO-LUMO gap (λ_{max} **97**<**134**<**90**) reaching 450 nm for head-to-tail bis-coumarin **90** (Table 8, Fig. 14). On the other hand, bis-coumarin **75**, which is formally an analog of benzo[*c*]-coumarins shares with them similar optical properties. In analogy progressive shift of emission can be observed while moving from coumarins, through bis-coumarins. Emission maxima stretch as far as 565 nm for compound **90**, and 571 nm for pentacene-expanded coumarin **96**. Presence of strongly electron-donating group in suitable position ensures strong ICT, which in turn results in significant Stokes shifts. Interestingly, head-to-tail biscoumarins possess rather small Φ_F, which increases significantly once two phenyl rings are fused (**90** versus **96**). The modifications of structure enable full control over optical properties. Fluorescence quantum yield can be modulated from negligible to 0.9 and emission can be shifted over 560 nm (compounds **90**, and **96**). In contrast for 1,7-dioxaperylene-2,8-diones fluorescence quantum yield is virtually independent on substituent orientation in benzene ring.[105] The electronic spectra of these fused coumarins differ in the shape. Due to a more rigid structure, compound **96** is characterized by a well resolved structure, while compound **90** show unstructured absorption bands. Fluorescence quantum yields determined for compound **90** are moderate (Φ_F = 10–30%) and the Stokes shifts are rather large (5000–7000 cm^{-1}). It is reasonable, therefore, to assume that aryl substituents in compound **90** do not overlap with π-system of the main

chromophore in the ground state, due to steric hindrance with hydrogens at bay position, but their geometry alters in the excited state. The π-expanded coumarin **79** represents an interesting case (Table 8). Very small Stokes shift indicates lack of ICT, while compound is strongly fluorescent.

Table 8 Photophysical properties of other π-expanded coumarins.[a]

Compd	λ_{abs} (nm)	λ_{em} (nm)	Φ_F	Ref.
75	322	410	0.11	Ref. 107[b]
76	328	433	n.r.	Ref. 88[b]
79	470	480	0.66	Ref. 94,107[c]
87	418	466	0.19	Ref. 104[d]
89	367 (460)	595	0.25	Ref. 105[e]
90	450	565	0.10	Ref. 105[e]
96	520	571, 615	0.90	Ref. 105[e]
133	374	455	0.18	Ref. 92[c]
134	439	530	0.91	Ref. 92[c]
135	447	533	0.29	Ref. 92[c]

[a] n.d.: not detected, n.r.: not reported. [b] measured in DMF. [c] measured in CH_2Cl_2. [d] measured in CH_3CN. [e] measured in $CHCl_3$.

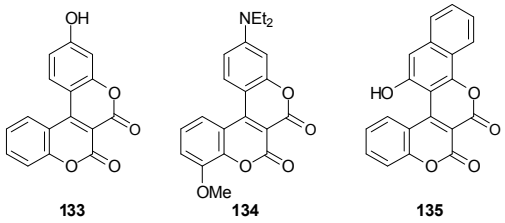


Fig. 13 Structures of chromeno[3,4-*c*]chromene-6,7-diones **133**-**135**.

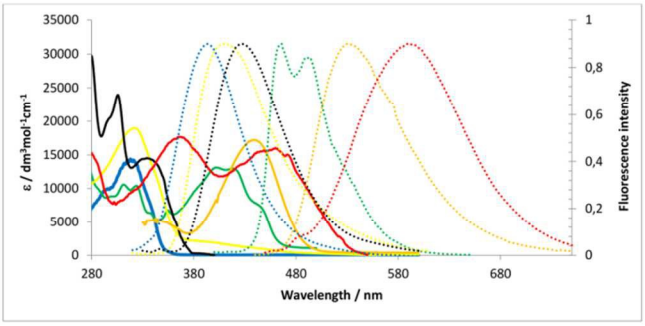


Fig. 14 Absorption (solid) and emission (dotted) spectra of 7-hydroxycoumarin (blue), 3-hydroxybenzo[*c*]coumarin (black), compound **75** (yellow), compound **87** (green), bis-coumarin **89** (red) and compound **134** (orange).

6. Applications

Benzocoumarins and heterocycle-fused coumarin derivatives have been used in various research areas due to the unique photophysical and biological properties. They are used in the development of (1) fluorescent probes and tags, (2) photo-labile materials, and (3) bioactive materials. These applications are overviewed in this chapter.

6.1. Fluorescent probes and dyes

Fluorescent probes based on common fluorophores are essential for the investigation of molecular interactions, which have been widely used as analytical tools in biological, medical, and environmental sciences.[114] Coumarins have been widely used as the fluorophores in fluorescent probes and also fluorescent tags for biological molecules. The conventional coumarin dyes have the maximum absorption wavelength in the UV-Vis region. Excitation in the short wavelength region may cause problems in tissue imaging such as autofluorescence, shallow penetration depth and photo-damage. Therefore, benzo-coumarins due to their π-extended feature are expected to lessen those problems met with the fluorescence imaging of tissues. Benzocoumarins with desirable photophysical properties would have higher photostability than the π-extended coumarins elongated by carbon-carbon double bonds.

Coumarins with an electron-donating group at the appropriate position behave as dipolar dyes. As dipolar dyes constitute an important class of two-photon absorption dyes owing to their intramolecular charge-transfer nature in the excited state, coumarin fluorophores have potential as two-photon absorbing materials. Two-photon microscopy (TPM) based on the two-photon (TP) excitation combined with the laser scanning technology has emerged as a powerful bioimaging tool in recent years. A big advantage of TP excitation is the "localization of excitation", which alleviates photo-damage outside the focal point and also enables to obtain 3D images with very high resolution. Furthermore, TP excitation at the NIR (near-infrared wavelength) region of 700−1100 nm (the biological optical window) reduces the autofluorescence from biological samples as well as enables deep-tissue imaging (down to <1 mm). In this regards, benzocoumarin derivatives that can be excited at the longer wavelength region (450 nm or longer; 900 nm or longer under TP excitation) are promising for the development of TP fluorescent probes for biological systems.[115]

In this chapter, we will cover selected examples of fluorescent probes that are based on benzocoumarin compounds, categorized by the probe excitation method: one-photon (OP) probes and two-photon probes.

6.1.1. One-photon probes based on benzocoumarins and their analogues

LeCompte and co-workers reported benzo[*g*]coumarin **136** and **137** containing a maleimide group as fluorescent thiol probes (Fig. 15).[12] The sulfhydryl group of biothiols underwent 1,4-addition to the maleimide moiety,[116] which caused turn-on fluorescence change. In the case of the linear type probe **136**, the conjugate addition of glutathione (GSH) caused 6-fold fluorescence enhancement ($\lambda_{abs}/\lambda_{em}$ = 365/536 nm in aqueous phosphate buffer at pH 7.2; $\Delta\Phi_F$ = from 0.02 to 0.12). Under the same conditions, the bent type probe **137** caused 8-fold fluorescence enhancement ($\lambda_{max}/\lambda_{em}$ = 358/430 nm).

Wang and co-workers reported a fluorescent fluoride probe **138**, a bis(silyl ether) of 1,1′-binaphthol containing *o*-(1,1-bis-(ethoxycarbonyl)vinyl) substituent. Desilylation of probe **138** on treatment with fluoride results in the corresponding naphthol which rapidly underwent an intramolecular condensation with one of the ester groups to produce the benzo[*g*]coumarin

compound that is fluorescent ($\lambda_{abs}/\lambda_{em}$ = 360/460 nm in THF; $\Delta\Phi_F$ = from 0.009 to 0.01). This sensing scheme was originally reported by Swager and co-workers.[109]

The product benzo[*g*]coumarin was further utilized for sensing cyanide; the conjugate addition of cyanide resulted in the addition product (within 2 h at 25 °C), which further underwent *β*-hydride elimination to produce the cyano-substituted benzocoumarin (within 30 min at 25 °C). This conversion caused a red-shift in the emission intensity and an increase in the quantum yield ($\Delta\lambda_{em}$ = from 360 to 460 nm; $\Delta\Phi_F$ = from 0.01 to 0.055).[117]

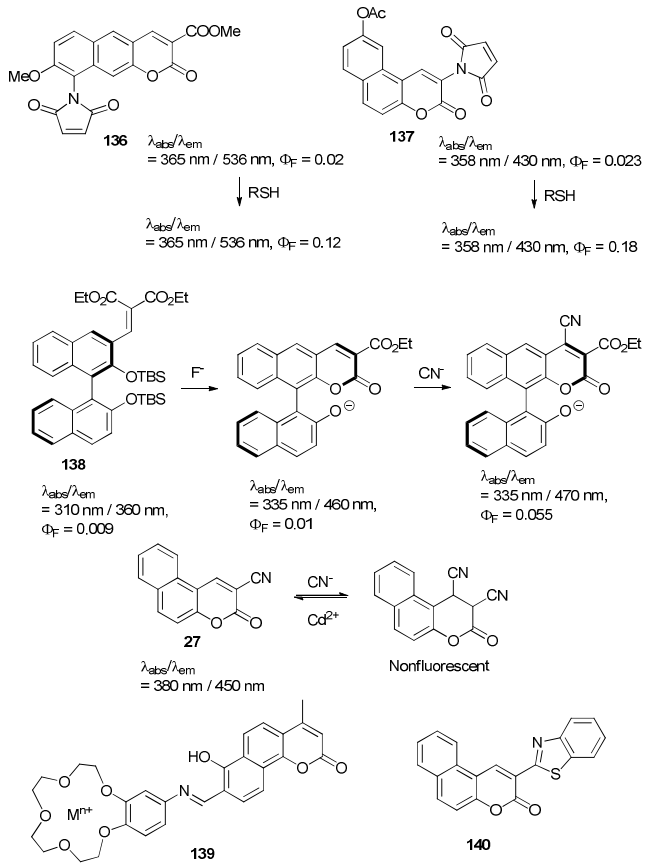


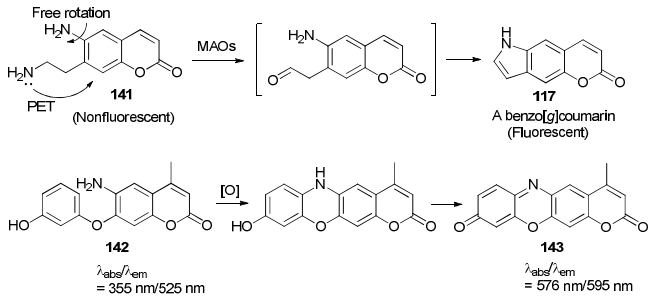
Figure 15 Benzocoumarin based one-photon fluorescent probes for thiol (**136** and **137**), fluoride and cyanide ions (**138**), cyanide ions (**27**), metal species (**139**) and viscosity (**140**).

Kim and co-workers reported 3-cyano-benzo[*f*]coumarin **27** as a fluorescent cyanide probe. Probe **27** emitted blue fluorescence at 450 nm when excited at 380 nm. The 1,4-addtion of cyanide ions to probe **27** resulted in fluorescence quenching. When the cyanide adduct was treated with cadmium ions, the quenched fluorescence was recovered, as the cyanide was removed as $Cd(CN)_2$ complex. The conjugate addition and elimination processes were carried out in aqueous media (1:1 DMF-HEPES buffer).[10]

Minkin and co-workers reported a benzo[*h*]coumarin based Schiff base **139** that contained a benzocrown ether, which acted as a dual sensing system for metal ions.[118] Strong fluorescence of probe **139** itself ($\lambda_{abs}/\lambda_{em}$ = 480/530 nm) was quenched upon addition of both copper(II) and cobalt(II) ions in DMSO. The fluorescence response, however, was dependent on media; probe **139** selectively responded to Mg(II) and Ba(II) in acetonitrile or toluene, which behavior was ascribed to the different tautomer ratio (benzenoid versus quinoid) depending on media (the quinoid fraction was 19.8 in toluene or acetonitrile, but was changed to be 33.5 in DMSO). Bizzarri and co-workers reported a benzo[*f*]coumarin containing 2-benzothiazole at C-3 (**140**) and its derivative as polarity-sensitive dyes for cell imaging. Solvatochromic dyes have been extensively employed in selective staining of various cellular domains. Dipolar dyes, which contain electron-donor (D) and acceptor (A) groups conjugated through an aromatic core, show polarity-sensitive optical properties as they can produce the intramolecular charge-transfer (ICT) excited states. The formation of ICT states are indicated by red-shift in the maximum emission wavelength as the solvent polarity increases. Dye **140** showed emission shift in the range from 476 to 486 nm (Φ_F = 0.92−0.04), with absorption shift from 403.5 to 413.5 nm depending solvents.[110]

Sames and co-workers reported aminoethyl-coumarin **141** as a fluorescent probe for monoamine oxidases (MAOs) (Scheme 55).[57] MAOs, MAO-A and MAO-B, catalyze the aerobic oxidation of amine substrates. Dysfunction of MAOs is associated with disorders in some cental and peripheral nervous systems. Abnormal activity of MAOs can cause neuronal diseases involving AD (Alzheimer's disease), PD (Parkinson's disease), and psychiatric disorders.[119] MAOs oxidized the aminoethyl group of probe **141** to aldehyde intermediate, which subsequently reacted with the nearby amine to form the pyrrolocoumarin **117**; the conversion accompanied with turn-on fluorescence change. Probe **141** showed different K_m values toward MAO-A and MAO-B (31 ± 2 μM and 510 ± 40 μM, respectively). The linear type pyrrolocoumarin **117** showed strong fluorescence response but the other bent type pyrrolocoumainrins (pyrrolo[*h*]coumarin and pyrrolo[*f*]-coumarin, see Fig. 11) did not.

Yang and co-workers reported a coumarin based fluorescent probe **142** for peroxynitrite (Scheme 54). Peroxynitrite ($OONO^-$), an endogenous oxidant, is generated through the nearly diffusion-controlled combination of nitric oxide (NO) and superoxide radical anion. Peroxynitrite can cause protein malfunction by nitration of the tyrosine phenol residue, and oxidizes amino acids such as tryptophan, histidine, and cysteine. Upon reaction with peroxynitrite, probe **142**, which was green-fluorescent ($\lambda_{abs}/\lambda_{em}$ = 355/525 nm), produced a red-fluorescent extended coumarin product **143** ($\lambda_{abs}/\lambda_{em}$ = 576/595 nm) via an orange-fluorescent intermediate ($\lambda_{abs}/\lambda_{em}$ = 475/585 nm). This three-channel probe was applied for live-cell imaging of peroxynitrite in human glioma cells.[120]



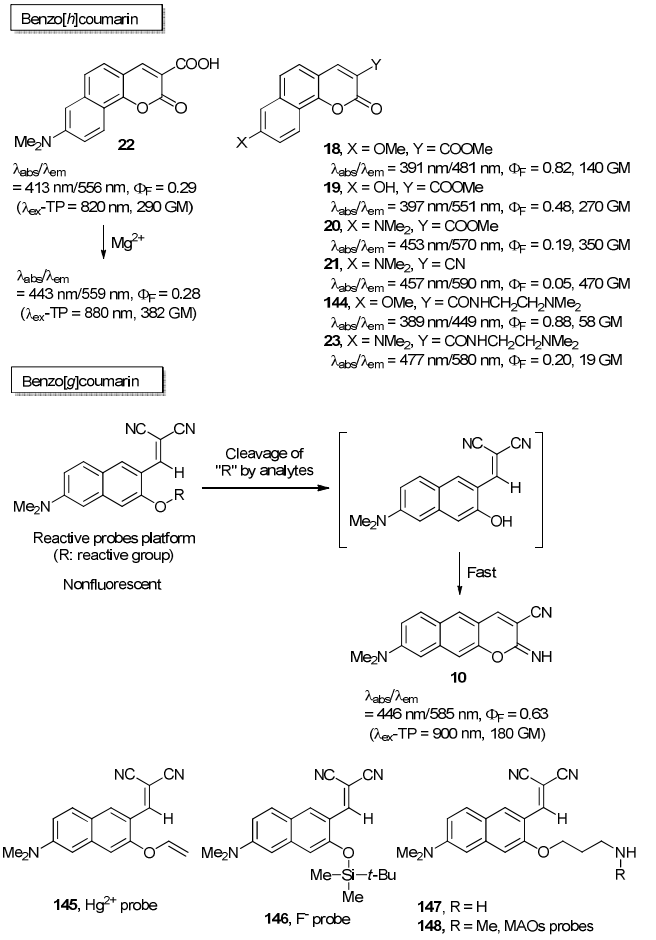
Scheme 54 Fluorescent probes **141** and **142**, which are based on coumarins fused with heteroaromatic rings.

6.1.2. Two-photon (TP) probes based on benzocoumarins and their analogues

Molecular structures of π-extended benzocoumarins are expected to provide larger two-photon absorbing ability with longer excitation and emission wavelengths, compared with the corresponding coumarins. As two-photon dyes, benzo-coumarins are of particular interest for their photo- and chemical-stability expected, in addition to other advantageous features mentioned above. Indeed, a few recent examples demonstrate potential of benzocoumarin dyes as two-photon absorbing materials for bioimaging applications.

Cho and co-workers reported several benzo[*h*]coumarin compounds as two-photon probes for Mg^{2+} (Scheme 55).[8] These benzo[*h*]coumarin probes showed larger two-photon absorption cross-sections (TPACS) than the previously known magnesium probes such as Mag-fura-2, MgG (Magnesium Green), and OG (Oregon Green 488 BATPA-1) of which TPACSs were less than 50 GM. For example, Mg^{2+}-bound probe **22** showed a TPACS of 382 GM in an aqueous medium when excited at 880 nm (under TP excitation, λ_{abs} = 443 nm, λ_{em} = 559 nm). Probe **22** was used to image free Mg^{2+} in the endogenous stores at the depth of 100–300 μm in live tissues by TPM. In a further study, they synthesized other benzo[*h*]-coumarin derivatives **18**–**21**, **23** and **144** as two-photon *in vivo* imaging probes for Mg^{2+}.[7] The emission wavelength of the benzo[*h*]coumarin probes increased as the electron-donor group became stronger (-OMe (**18**, 481 nm) < -OH (**19**, 551 nm) < -NMe_2 (**20**, 570 nm)) and the electron-acceptor group became stronger (COOMe (**20**, 481 nm) < CN (**21**, 590 nm)). A large Stokes shift was observed in the case of probe **19**, plausibly because the hydroxyl group existed as the alkoxy form at the excited state where it became much more acidic. The benzo[*h*]coumarins **18**–**21** showed TPACS of 140–470 GM after binding with Mg^{2+}, high photostability, appreciable water-solubility, cell permeability, and low cytotoxicity. Probes **144** and **23**, which had ethylenediamine moiety, were able to sense Mg^{2+} in lysosomes. Probes **144** ($\lambda_{abs}/\lambda_{em}$ = 389/449 nm) and **23** ($\lambda_{abs}/\lambda_{em}$ = 477/580 nm) were used to visualize Mg^{2+} in the lysosome in live cells and tissues at the depth of 80–170 μm by TPM.[9]

Ahn and co-workers developed two-photon probes based on analyte-promoted chemical conversions of benzo[*g*]coumarin precursors to the corresponding benzo[*g*]coumarin analogues. Probe **145** underwent Hg^{2+}-promoted hydrolysis of the vinyl ether moiety, followed by an intramolecular cyclization to produce the benzo[*g*]coumarin analogue (IminoPOS, **10** in Scheme 55) that emitted strong fluorescence ($\lambda_{abs}/\lambda_{em}$ = 446/585 nm).[5] IminoPOS was found to be highly fluorescent (Φ_F = 0.63) and showed TPACS of 180 GM under two-photon excitation at 900 nm. It is notable that IminoPOS has the larger TPACS (180 GM), the higher fluorescence quantum yield (Φ_F = 0.63), and the longer maximum absorption wavelength (λ_{max} = 448 nm), compared with acedan (2-acetyl-6-dimethylamino-naphthalene) that has been widely used in two-photon probes. Probe **145** selectively responded to Hg^{2+} among various competing metal species, as already demonstrated by the original one-photon probe based on the vinyl ether hydrolysis.[121]



Scheme 55 Benzo[*h*]coumarin based a two-photon fluorescent probe for Mg^{2+} (probe **22**) and an organ specific staining dyes (**18-21, 23, 144**). Benzo[*g*]coumarin based two-photon absorbing dye (**10**) and fluorescent probes for Hg^{2+} (**145**), F^- (**146**), and MAOs (**147, 148**).

Applying the sensing scheme, Ahn and co-workers further developed silyl enol ether **146** as the first two-photon fluoride probe.[122] Thus, desilyation of probe **146** by fluoride, followed by the intramolecular cyclization produced the two-photon excitable IminoPOS. This sensing scheme showed faster

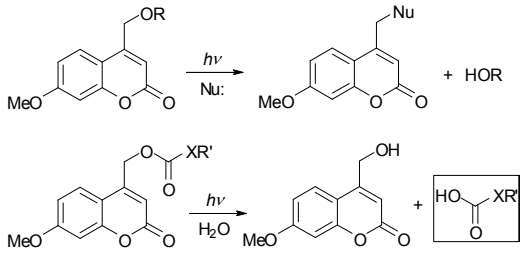
response to fluoride over the known desilyation-based fluoride sensing probes that responded rather slowly at room temperature. Probe **146** was used to image fluoride ions in cells and in a live vertebrate, zebrafish, by TPM for the first time.

Ahn and co-workers also developed benzo[*g*]coumarin precursors **147** and **148** as two-photon probes for MAOs.[123] The enzymatic oxidation of the aminopropyl group, followed by β-elimination and subsequent an intramolecular condensation produced IminoPOS, fulfilling turn-on fluorescent sensing of MAO-A and MAO-B ($\lambda_{abs}/\lambda_{em}$ = 448/585 nm) in pH 7.4 HEPES buffer. Probe **147** (R = H) was further used to image highly expressed MAOs in live chromaffin cells by TPM (λ_{ex}-TP = 900 nm, 10 mW laser power) for the first time.

6.2. Photo-caging benzocoumarins

One of interesting applications of benzocoumarin derivatives is their use as the photo-caging system. A molecule of biological interest is "caged" by the covalent attachment of a photo-labile protecting group onto a functional group of the molecule. This caged molecule is inactive until light irradiation but becomes active upon light irradiation in the biological environment, enabling spatial distribution and temporal release. This photo-caging strategy has been used to cage various biomolecules including amino acids, peptides, proteins, nucleic acids, and others.[124,125]

Coumarins, particularly those of 4-hydroxymethyl derivatives are known to undergo photolysis (Scheme 56).[126] On the basis of this discovery various biomolecules of interest have been introduced, mostly as the acyl derivatives, which can be released in biological systems under UV irradiation.[127]



Scheme 56 Photo-caging systems based on 4-hydroxymethyl derivatives.

In 1999, Tsien demonstrated the photolysis under two-photon irradiation in the NIR region, rather than in the UV region under single photon irradiation. Thus the brominated 7-hydroxycoumarin-4-glutamates **149** and **150** efficiently released glutamate on photolysis under both OP and TP irradiation conditions (Fig. 16).[124] Recently, several benzo-coumarin analogues that have the same structural feature of the coumarins have been studied as photo-caging systems.

Gonçalves and Costa have reported several photo-caged benzo[*f*]coumarins systems (compounds **151**–**155**). First, they reported GABA-caged benzo[*g*]coumarin **151** ($\lambda_{abs}/\lambda_{em}$ = 345/503 nm, Φ_F = 0.21 in EtOH) and benzo[*f*]coumarin **152** ($\lambda_{abs}/\lambda_{em}$ = 345/472 nm, Φ_F = 0.76 in EtOH). Photolysis of both compounds to release GABA required less irradiation times (t_{irrad}) than that of the coumarin-based caging system, and photochemical quantum yields (Φ_{photo}) were higher at shorter wavelength (Compound **151**: t_{irrad} = 479 min at 254 nm, Φ_{photo} = 0.037; t_{irrad} = 790 min at 350 nm, Φ_{photo} = 0.007. Compound **152**: t_{irrad} = 169 min at 254 nm, Φ_{photo} = 0.095; t_{irrad} = 84 min at 350 nm, Φ_{photo} = 0.062).[128,129] In a further study, Costa and co-workers also reported amino acids-caged benzo[*f*]coumarins **153** ($\lambda_{abs}/\lambda_{em}$ = 347−349/463−469 nm, Φ_F = 0.14−0.75 in EtOH). Photolysis of these compounds in MeOH/HEPES buffer (80/20) released the amino acids within 44−513 min with rate constants in the range of k = 0.59−6.70 × 10^{-2} min^{-1}.[130]

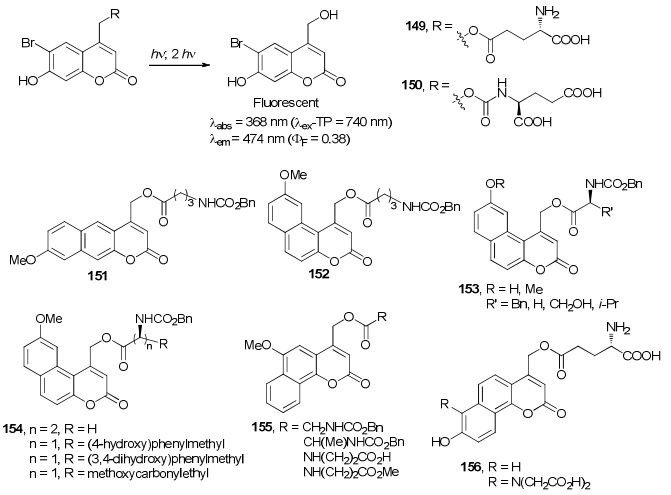


Fig. 16 Photo-caging systems based on coumarin (**149**) and benzocoumarin derivatives (**150**–**156**).

Gonçalves and co-workers later examined photolysis of the same amino acids-caged benzo[*f*]coumarins **154** in different solvents (EtOH, MeOH/HEPES (80:20), and CH_3CN/HEPES (80:20)) at different irradiation wavelengths (254, 300, and 350 nm). The results gave rate constants in the range of k = 0.26−0.50 × 10^{-2} h^{-1} and photochemical quantum yields in the range of Φ_{photo} = 0.001−0.039.[131]

Costa and Gonçalves also reported benzo[*h*]coumarin based amino acids-caged molecules **155** ($\lambda_{abs}/\lambda_{em}$ = 371−374/470−473 nm, Φ_F = 0.31−0.71, in EtOH),[132] which have a methoxy substituent at C-6. Photolysis of the compounds in MeOH/HEPES buffer (80/20) released the amino acids within 30−469 min with rate constants in the range of k = 0.62−9.94 × 10^{-2} min^{-1}.

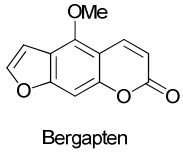
Abe and co-workers also reported glutamate-caged benzo[*h*]-coumarins **156** and their photolysis reactions under OP and TP excitation conditions.[22] Larger TPACSs were computed at the TD-B3LYP/6-31+G(d) level of theory in vacuum: 15 GM was calculated for the first TPA maximum at 680 nm. Coumarin-derived compounds showed TPACSs of less than <1 GM by experiments. Photochemical release of glutamate from **156** was monitored by NMR analysis under irradiation with a high-pressure Hg lamp (>290 nm). The photochemical quantum yield was determined to be Φ_{photo} = 0.006 at 355 nm.

6.3. Electron- and energy-transfer

A large variety of coumarins have been used for construction of artificial light harvesting antennas. Recently Gryko and co-workers decorated corrole, one carbon short analogue of porphyrin, with ethynyl-biscoumarins.[133,134] The synthesis of corrole-coumarin dyads consisted in condensation of dipyrromethane and aldehyde bearing protected acetylene function, followed by oxidation with DDQ. Excitation of the dyad in the UV region led to complete quenching of the coumarin luminescence, whereas the corrole luminescence remained identical to that of optically matched reference corrole solution. This suggested efficient (ca. 100%) energy transfer from coumarin to corrole subunit, which was confirmed by time-resolved luminescence studies. Energy transfer was ascribed to a dipole-dipole mechanism (Förster)[135], and its rate was measured as $k_q = 1.3\times10^{11}$ s^{-1}. Photoinduced electron transfer was not observed for this type of dyads, due to the insufficient reduction potential of the coumarin moiety.

6.4. Bio-active materials

Natural and synthetic coumarin derivatives have been found to exhibit a variety of biological activities such as antioxidant, anticoagulant, antibacterial, anti-inflammatory, antifungal activity, and antimicrobial acitivity.[56,136,137] Psoralene, a representative furocoumarin compound, had been used in sunscreens as tanning activator, but its use was banned in 1996 due to a high risk of melanoma (Figs. 11 and 17).[138] Angelicin showed antifungal activity and was considered as a lead structure in this research area.[56] Furanocoumarins comprise a family of plant-derived chemicals that are well known to possess mutagenic and carconogenic properties.[139] The intercalation of furocoumarins into DNA under UV irradiation (320–400 nm) can cause intrastrand cross-links between the 4′,5′-furan or the 3,4-pyrone side of the furanocoumarin and the 5,6-double bond of a pyrimidine base, mostly on the thymine. Furocoumarins are thus used for treatment of several skin diseases such as psoriasis, vitiligo, mycosis fungoides, and chromic leukaemia.[111] The activity of furocoumarins has been mainly attributed to the covalent photo-binding to DNA, resulting in an antiproliferative effect.[138]



Bergapten

Fig. 17 Furocoumarin derivative - Bergapten.

Growing interest of benzo[*c*]coumarin derivatives is dictated mostly by their wide spectrum of biological activity. There are numerous naturally occurring compounds both plant and animal origin which possess structure of 6*H*-dibenzo[*b*,*d*]pyran-6-one including fasciculiferol **157** separated from Acacia fasciculifera tree,[140] herpetolide[141] **158** occuring in Herpetospermum caudigerum seed, alternariol[142] **159**, metabolite of Alternaria fungi, urolithin[143,144] **160**, microflora human gut metabolite and ellagic acid[145] **161**, which can be found in bile, inhibitor of Vascular Endothelial Growth Factor receptor, possessing potential antitumor activity (Fig. 18).[146] Naturally occurring compounds which possess analogous structure of 6*H*-dibenzo[*d*]naphtho[1,2-*b*]pyran-6-one, such as Gilvocarcin[147] **162** and Arnottin[148-150] **163** display biological action such as antibacterial and antitumor. Structure of benzo[*c*]coumarin serves as a core for many active compounds including: selective oestrogen agonist or antagonist for treatment of breast cancer or osteoporosis[151-153] caseine kinase inhibitor as potential drug in treatment of kidney diseases,[154] nonsteroid androgen receptor antagonist as drug in treatment of prostate cancer[155] and acetylcholinesterase inhibitor as a drug slowing development of Alzheimer disease.[156] Furthermore benzo[*c*]-coumarins can serve as the intermediates in cannabinoids synthesis, which are utilizing as painkillers, appetite stimulants and drugs with antiemetic action.[157,158] In addition to biological activity, benzo[*c*]coumarins possess other important feature-fluorescence. They are exploited as laser dyes[159] and optical brightener.[160] Recently, technologies utilizing two-photon absorption phenomena[161,162] including: bio-imaging, three-dimensional polymerization or photodynamic therapy has been developed. The variety of purposes enforces tight cooperation between researchers from different field of science such as physics, biology, medicine and chemistry. The challenge of chemists is to continue to seek new scaffolds with improved properties for new, more specialized applications.

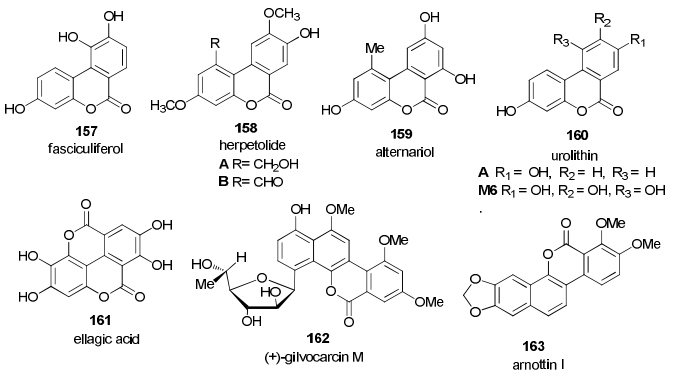


Fig. 18. Benzo[*c*]coumarin derivatives in nature.

7. Summary and Outlook

Since the first synthesis of benzocoumarins by von Pechmann 130 years ago, the tremendous knowledge has been accumulated regarding coumarins with π-expanded chromophores. These compounds initially attracted attention due to the natural occurrence of various derivatives especially possessing the skeleton of benzo[*c*]coumarin. The interest has shifted in last years towards cutting-edge optoelectronic applications. The thorough analysis of compounds known for a century and those discovered in last decade, has allowed us to state the hypothesis that some of these architectures are better in terms of optoelectronic properties than parent coumarins. Among the benzocoumarin families, the substituent effects are

maximized in the case of the linear-shaped benzo[*g*]coumarin family over the other bent-shaped ones. As some of the benzocoumarins showed promising two-photon absorbing properties, the benzo[*g*]coumarin derivatives hold a great promise in the development of two-photon probes for bioimaging applications. Needless to say a great deal of additional effort is needed to explore possibilities of some of these molecules. We hope that this Review in addition to organizing knowledge on this topic, will serve as catalyst to spark further studies. The future targets can be extended to more densely substituted benzo[*g*]coumarins and head-to-tail biscoumarins. For practical applications, it is important to seek balance between high Φ_F, large Skokes' shift and photostability. We believe that many new compounds, such as head-to-head biscoumarins–yet unknown, can be discovered with the help of this Review and that some of them will find the way towards practical applications.

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Notes and references

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Graphical abstract

Synthesis, optical properties, applications of various types of benzocoumarin compounds are overviewed.