Benzocoumarin as a potential scaffold:

A review of its biomedical activities

La benzocumarina como andamio potencial: una revisión de sus actividades biomédicas

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Abstract

Coumarin derivatives have piqued the curiosity of many researchers in the medicine and industry fields due primarily to their chemical diversity and bioactivities. Amongst coumarin derivatives, benzocomarins have garnered significant interest from pharmaceutical chemists in the past few years. Many scientific studies in the literature reported the bioactivities of natural and synthesized benzocoumarin derivatives. The focus of this review was on the general synthetic routes of benzocoumarins, besides the depiction of their biological activities, particularly those pertaining to anticancer, antioxidant, antibacterial, antiviral, and antidiabetic potentials. The authors concluded that the benzocoumarin backbone is an attractive scaffold that sheds light on exploring new drug candidates with novel or improved bioactivities.

Keywords: Benzocoumarin, Antitumor, Antioxidant, Antibacterial, Antifungal, Antidiabetic.

Resumen

Los derivados de la cumarina han despertado la curiosidad de muchos investigadores en los campos de la medicina y la industria debido principalmente a su diversidad química y bioactividades. Entre los derivados de la cumarina, las benzocomarinas han despertado un gran interés entre los químicos farmacéuticos en los últimos años. Muchos estudios científicos en la literatura informaron sobre las bioactividades de los derivados de benzocumarina naturales y sintetizados. El enfoque de esta revisión estuvo en las rutas sintéticas generales de las benzocumarinas, además de la descripción de sus actividades biológicas, particularmente aquellas relacionadas con los potenciales anticancerígenos, antioxidantes, antibacterianos, antivirales y antidiabéticos. Los autores concluyeron que la columna vertebral de la benzocumarina es un andamio atractivo que arroja luz sobre la exploración de nuevos fármacos candidatos con bioactividades novedosas o mejoradas.

Palabras clave: Benzocumarina, Antitumoral, Antioxidante, Antibacteriano, Antifúngico, Antidiabético.

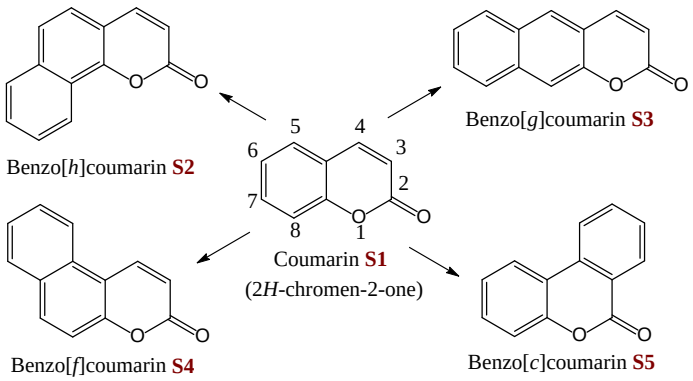
Introduction

Coumarin (also known as 2*H*-chromen-2-one) is an organic compound that belongs to the chemical class known as benzopyrone[1,2]. Coumarin and its derivatives constitute a large group of natural and synthetic compounds with different biological effects such as anticancer[3–8], antioxidant[9–12], antimicrobial[13–17], anticoagulants[18], anti-inflammatory [19–21]. Furthermore, chemists are interested in them because of their variety of applications, such as photosensitizers[22], optical brighteners[23], laser and fluorescent dyes[24], and as additives in cosmetics, perfumes, food, and pharmaceuticals[25]. Numerous molecules based on the coumarin backbone structure were synthesized using novel synthetic techniques[26].

Benzocoumarins (benzochromenones) are benzene-fused coumarins that belong to the π-extended coumarins class. In the parent coumarin backbone **S1**, the position of the fused aromatic ring categorizes benzocoumarin derivatives into four types: benzo[*h*]coumarin **S2** (7,8-benzocoumarin), benzo[*g*]coumarin **S3** (6,7-benzocoumarin), benzo[*f*]coumarin **S4** (5,6-benzocoumarin), and benzo[*c*]coumarin **S5** (3,4-benzocoumarin), as shown in Figure 1[27].

In the past few years, several benzocoumarin-based compounds have been widely synthesized, and their bioactivities prompted efforts to explore new therapeutic agents [28]. These findings provoked the research team to publish a review on the well-known synthetic strategies to prepare benzocoumarins, along with the pharmacological potentials of synthetic and natural benzocoumarins, concentrating on the most significant examples.

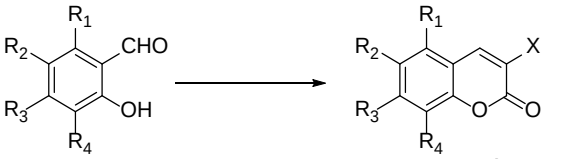
Figure 1. The chemical backbone of coumarin and benzocoumarins.



Synthetic methods of benzocoumarins

Except for the benzo[*c*]coumarins, benzocoumarin derivatives are synthesized using the same methods as coumarin and its derivatives, such as metal-catalyzed cyclization [29], Pechmann reaction[30], and Knoevenagel condensation [31]. Nearly all of these synthetic routes begin with one of two groups of chemical compounds: naphthols or *o*-hydroxynaphthaldehyde. The 2*H*-chromen-2-one moiety is synthesized from *o*-hydroxynaphthaldehyde through intramolecular cyclization with the hydroxyl group after initial Knoevenagel condensation with a malonate ester or analogs, as indicated in Scheme 1[32]. The positions of hydroxyl and formyl groups on the initial *o*-hydroxynaphthaldehyde compounds determine the creation of different types of benzocoumarin derivatives (1-hydroxy-2-naphthaldehyde or 2-hydroxy-1-naphthaldehyde or 2-hydroxy-3-naphthaldehyde) [33].

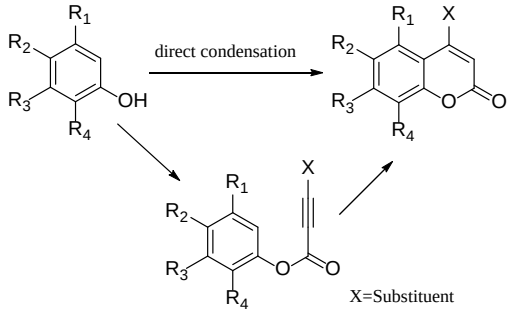
Scheme 1. General strategy of benzocoumarins synthesis from o-hydroxynaphthaldehydes.



Symbol	R_1	R_2	R_3	R_4	Product
S2	-H	-H	-CH=CH-CH=CH-		Benzo[*h*]coumarin
S3	-H	-CH=CH-CH=CH-		-H	Benzo[*g*]coumarin
S4	-CH=CH-CH=CH-		-H	-H	Benzo[*f*]coumarin

On the other hand, by electrophilic substitution of naphthol compounds with *β*-keto esters followed by intramolecular cyclization process, benzocoumarins can be directly synthesized (the upper pathway in **Scheme 2**). In the presence of a strong Lewis acid or Bronsted acid as a catalyst, the reaction occurs with suitable electrophiles. Additionally, functionalization of aryl C–H of alkynoate compounds by using metal as a catalyst is also possible, as illustrated in **Scheme 2**[27]. The position of the hydroxyl group in the initial naphthol compounds (1-naphthol or 2-naphthol) also influences the formation of various types of benzocoumarin-based derivatives. Two isomers form in significant amounts from 2-naphthol, and their polarity differences allow them to be separated[33]. Many synthetic methods for benzo[*f*], benzo[*h*], and benzo[*g*]coumarins have been developed based on the two general strategies mentioned above.

Scheme 2. General strategy of benzocoumarins synthesis from naphthols.



Symbol	R_1	R_2	R_3	R_4	Product
S2	-H	-H	-CH=CH-CH=CH-		Benzo[*h*]coumarin
S3	-H	-CH=CH-CH=CH-		-H	Benzo[*g*]coumarin
S4	-CH=CH-CH=CH-		-H	-H	Benzo[*f*]coumarin

Benzo[*c*]coumarin **S5** synthesis takes a slightly different approach. There are various reactions for synthesizing benzo[*c*] coumarins. These reactions are classified into the following categories: (A) ring-closing reactions: (1) the carbon-carbon bond formation; (2) the carbon-oxygen bond formation; (3) cyclization reactions. (B) ring-transformation reactions: (1) specific oxidation; (2) aromatization; (3) ring enlargement[33].

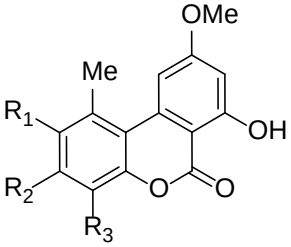
Biomedical activities of benzocoumarin-based compounds

Benzocoumarins have immense interest due to their prominent pharmacological activities, such as antidyslipidemic[34], antioxidant[35], antimicrobial[36], and cytotoxic effects[37]. In laboratory assays, numerous benzocoumarin containing compounds, either from the natural or synthetic origin, were evaluated for their biological actions[28]. This section will cover the bioactivities of many synthesized and natural benzocoumarin-based derivatives, besides the development of structurally-related analogs with novel or enhanced bioactivities, and highlight the most important molecular and structural factors that influence the activities.

Antitumor biomedical activity

Tan and his colleagues have reported the anticancer activity of two novel bezocoumarin-based products, graphislactone H (**S6**) and graphislactone G (**S7**), in addition to previously known products, alternariol monomethyl ether (**S8**) and graphislactone A (**S9**), as shown in Figure 2. These products were isolated from *Cephalosporium acremonium* IFB-E007 and showed a significant inhibitory action versus SW1116 cell lines, with IC_{50} values of 12, 21, 14, and 8.5 µg/ml, respectively [38].

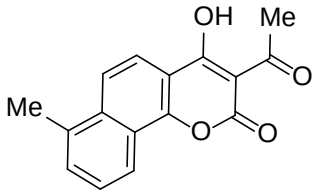
Figure 2. Benzo[c]coumarin-based products with antitumor activity reported by Tan et al.



S6, R_1 = H, R_2 = MeO, R_3 = MeO
S7, R_1 = Cl, R_2 = MeO, R_3 = H
S8, R_1 = H, R_2 = OH, R_3 = H
S9, R_1 = H, R_2 = MeO, R_3 = OH

Tanshinlactone A (**S10**), as illustrated in Figure 3, was extracted from *Salvia miltiorrhiza* root by Don and his colleagues. This natural product exhibited moderate cytotoxicity with IC_{50} values ranging from 6.87 to 8.85 µg/ml versus the test cell lines, which included OVCAR-3 (ovarian adenocarcinoma), HepG2 (hepatocellular carcinoma), and HeLa (cervical epithelioid carcinoma)[39].

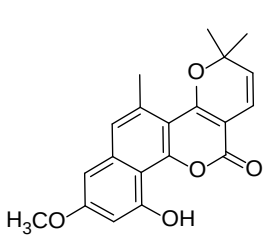
Figure 3. Benzo[h]coumarin-based product with antitumor activity reported by Don et al.



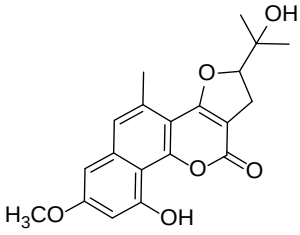
S10

In 2000, bioassay-directed fractionation was used to isolate Vismiaguianins A (**S11**) and B (**S12**) from the **Vismia guianensis** roots, as indicated in Figure 4. Compound **S11**, which had a dimethylpyran ring, was cytotoxic versus KB cells. While compound **S12**, which had a dihydrofuran ring bearing a hydroxyisopropyl group, was inactive. The authors concluded that a dimethylpyran ring in the backbone of **S11** is important for cytotoxicity[40].

Figure 4. Benzo[h]coumarin-based products with antitumor activity as depicted by Seo et al.



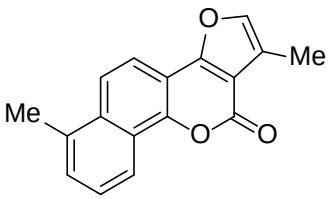
S11



S12

Also, in 2004 Lee and his colleagues isolated **neo**-tanshinlactone (**S13**) from the **Salvia miltiorrhiza** roots, as demonstrated in Figure 5. This natural product exhibited marked suppression versus two estrogen receptor-positive human breast cancer cell lines, which are 20-fold more selective and 10-fold more potent than tamoxifen. Also, the product **S13** was potent in inhibiting human epidermal growth factor receptor 2 overexpression and estrogen receptor-negative breast cancer cell lines. Among the naturally isolated benzocoumarins, **S13** has been identified as a promising lead compound for the development of innovative anti-breast cancer medicines [41].

Figure 5. Benzo[h]coumarin-based product with antitumor activity described by Lee et al.



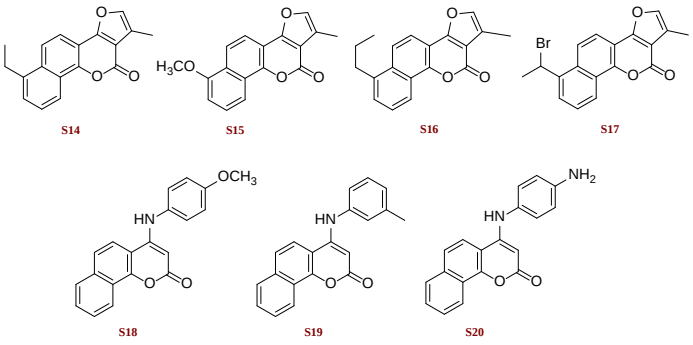
S13

In continuing research, Lee and his colleagues have investigated the structure-activity relationship of a series of synthesized analogs of **S13**, as illustrated in Figure 6. Analogs that contain a methyl-substituted furan ring exhibited greater cytotoxicity than those with hydroxy dihydrofuran or unsubstituted furan rings. However, those without a furan ring did not demonstrate good activity. Compound **S14** showed excellent selectivity and activity versus HS 587-1 (ER-), MDA MB-231, ZR-75-1 (ER+), and MCF-7 cell lines. Moreover, compound **S14** demonstrated high potency versus SK-BR-3 (HER2+, ER-) cell lines [42].

Similarly, other analogs as anti-breast cancer drugs were discovered through similar research, including **S15-S19**, as shown in Figure 6. Compound **S15** was more selective versus ZR-75-1 than MCF-7 cells, whereas **S16** demonstrated a selectivity ratio of about 12-fold for SK-BR-3/MCF-7 cells. Compound **S17** exhibited higher potency versus ZR-75-1 and SK-BR-3 cell lines than compound **S13** [43]. Based on the structure of **S13**, compounds **S18** and **S19** were designed as new scaffolds with secondary amine substituents. When compared to **S13**, they both had broader antitumor activities. The structure-activity relationship data showed that the nitrogen substitutions were important for cytotoxic potency [44].

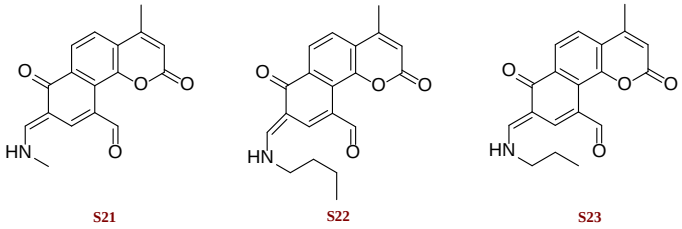
In addition, Lee and his colleagues investigated the amino-substituted analogs that are water-soluble, yielding an active novel benzo[*h*]coumarin-based compound **S20**. Compared with the preceding lead compound **S18**, compound **S20** had a 50-fold increase in water solubility. In mutant mice, the branching of the mammary gland and the total number of mammary cells were reduced by the compounds **S18** and **S20**. Also, one-week therapy with **S20** reduced bromodeoxyuridine-positive cells in mammary glands that are prone to malignancy by 80% [45].

Figure 6. Chemical backbones of neo-tanshinlactone (S13) synthesized analogs described by Lee et al.



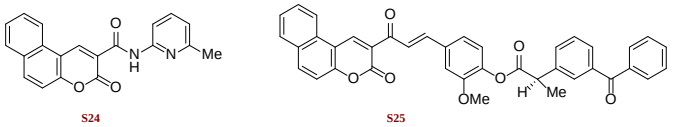
In 2010, Konwar and his colleagues conducted a study inspired by a *neo*-tanshinlactone scaffold. This study included the development of a series of new benzocoumarins (**S21**-**S23**), as demonstrated in Figure 7, on the basis of naturally developed *neo*-tanshinlactone (**S13**) and assessment of their cytotoxicity versus MDA-MB-231 and MCF-7 breast cancer cell lines. The proliferation of MCF-7 cancerous cells line was strongly suppressed by compounds **S21**-**S23** which had IC_{50} values of 3.8, 6.5, and 7.9 μM, respectively. These compounds were able to evoke caspase-dependent death, cell-cycle arrest, and nuclear fragmentation in MCF-7 cells line while being non-cytotoxic to normal osteoblast cells [46].

Figure 7. Benzo[h]coumarin-based compounds with antitumor activity synthesized by Konwar et al.



Recently, Al-Masoudi and his colleagues reported the synthesis of novel benzo[*f*]coumarin-based arylamide analogs and benzo[*f*]coumarin-chalcone with aryl ester derivatives. The antitumor activities of these compounds were evaluated versus human prostate cancer cells line (PC-3). The new compounds **S24** and **S25**, with IC_{50} values of 78.25 and 71.35 μg/mL, respectively, were the most active cytotoxic analogs in the series, as shown in Figure 8[47].

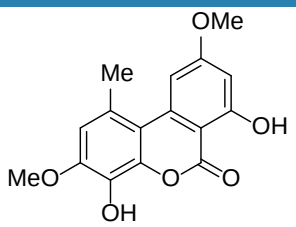
Figure 8. Benzo[f]coumarin-based compounds with antitumor activity prepared by Al-Masoudi et al.



Antioxidant biomedical activity

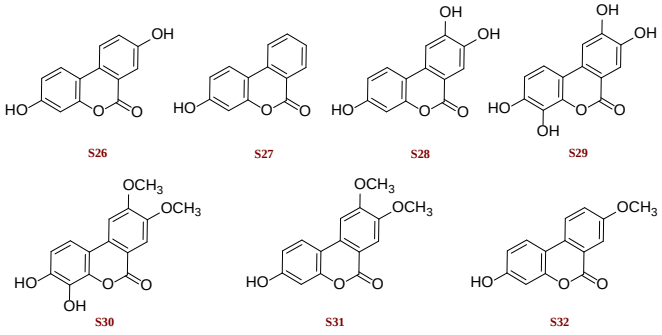
Song and his colleagues have extracted graphislactone A (**S9**) from the cultures of endophytes sheltered in *Trachelospermum jasminoides*, as illustrated in Figure 9. The authors found that the natural product **S9** revealed promising scavenging activities with an IC_{50} of 2.9 μg/mL versus 2,2-diphenyl-1-picrylhydrazyl free radicals. Also, it demonstrated more activities than butylated hydroxytoluene in removing hydroxyl radicals in a dose-related manner. Furthermore, compound **S9** exhibited better antioxidant activities than ascorbic acid in the antioxidant assay, in addition to suppressing reactive substances formation during LDL oxidation using Cu^{+2} as an oxidative inducer[48].

Figure 9. Benzo[c]coumarin-based product with antioxidant activity reported by Song et al.



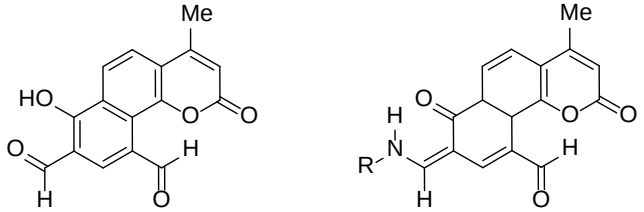
Also, Ferreira and his colleagues evaluated the antioxidant activities of urolithins, which are produced from the metabolism of pomegranate ellagitannins by the gut microbiome. The research team used a cellular assay that permits the detection of antioxidant activity of the test compounds, besides estimation of their bioavailability in the cells. The assay estimated the ability of the tested urolithins to inhibit the oxidation of 2',7'-dichlorodihydrofluorescein by reactive oxygen species[49]. As illustrated in Figure 10, urolithin C (**S28**) and urolithin D (**S29**) showed high antioxidative activities with IC_{50} values of 0.16 and 0.33 μM, respectively, while urolithin A (**S26**) exhibited less antioxidative activities with IC_{50} values of 13.6 μM. On the other hand, urolithin B (**S27**) and all methylated urolithins (**S30**-**S32**) did not have antioxidative activity. The authors concluded that the antioxidant activity of these bezocoumarins was related to the molecule's lipophilicity, as well as to the number of OH groups substituted on the molecule[49].

Figure 10. Chemical structures of benzo[c]coumarin-based urolithins.



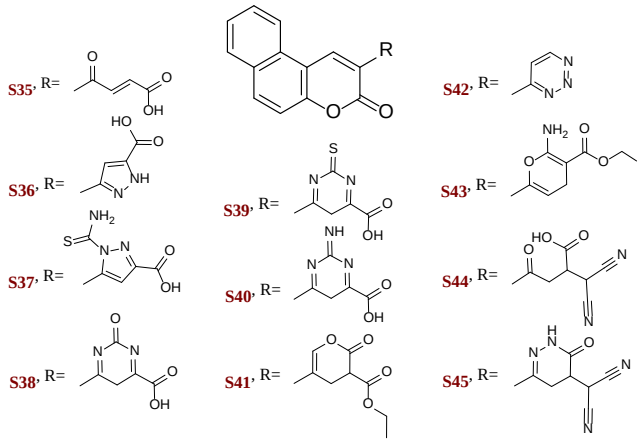
Sashidhara and his colleagues have synthesized a series of Schiff bases using benzo[*h*]coumarin dicarbaldehyde as a building block and evaluated their antioxidant and lipid-lowering activities. As demonstrated in Figure 11, two of these synthesized benzocoumarin derivatives, herein termed **S33** and **S34**, possessed the most promising antioxidant and lipid-lowering activities among the others[50].

Figure 11. Benzo[h]coumarin-based compounds with antioxidant activity synthesized by Sashidhara et al.



In 2016, Salem and his colleagues reported the synthesis of novel series of coumarin- and benzocoumarin-based derivatives. These newly prepared compounds were examined to evaluate their antioxidant potential in tissue homogenates from rat brains and kidneys. As shown in Figure 12, compounds **S37**, **S38**, **S42**, **S36**, and **S40** exhibited a high ability to inhibit oxidation, and the percentage of their inhibitions were 84.6, 84.6, 84.6, 84.4, and 84.4%, respectively. Compounds **S41**, **S35**, and **S44** exhibited high inhibition activities of 75.5, 72.9, and 69.3%, respectively, while compounds **S39**, **S43**, and **S45** showed moderate to weak inhibitions of 56.2, 51.9, and 43.1%, respectively. Furthermore, the authors concluded that the compounds with the benzocoumarin-based scaffold exhibited better antioxidant potential than their coumarin-based scaffold analogs[51].

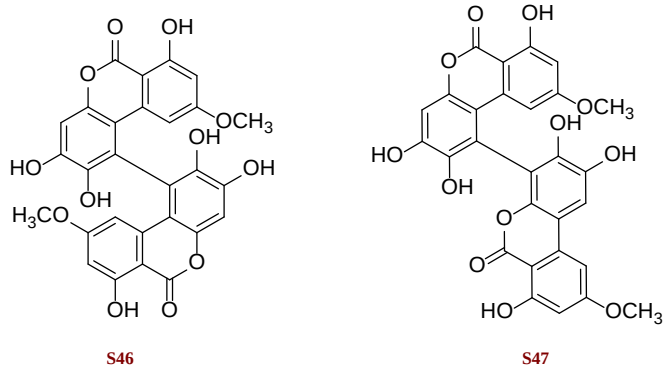
Figure 12. Benzo[f]coumarin-based compounds with antioxidant activity prepared by Salem et al.



Antibacterial biomedical activity

Kim and his colleagues have extracted and isolated novel benzo[c]coumarin dimers called verrulactones A (**S46**) and B (**S47**) from the culture media of *Penicillium verruculosum* F375 fungus. As shown in Figure 13, the natural products **S46** and **S47** exhibited antibacterial activity versus methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus aureus*. Also, they revealed strong inhibition of the enoyl-ACP reductase of *Staphylococcus aureus* in a concentration-dependent manner[52].

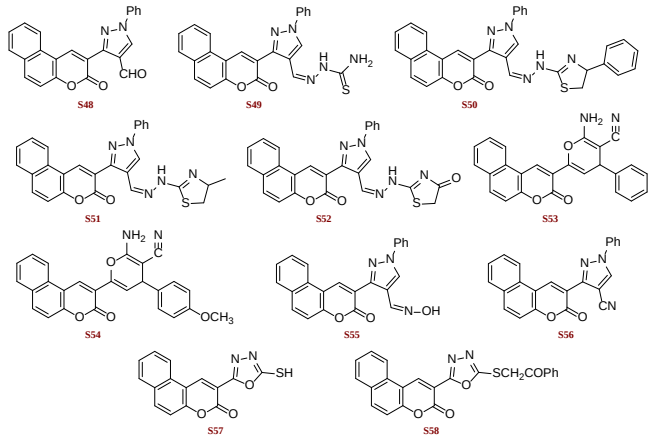
Figure 13. Dimeric benzo[c]coumarin-based products with antibacterial activity reported by Kim et al.



In a separated study, Kamal El-Dean and his colleagues have reported the synthesis of a series of benzocoumarin-

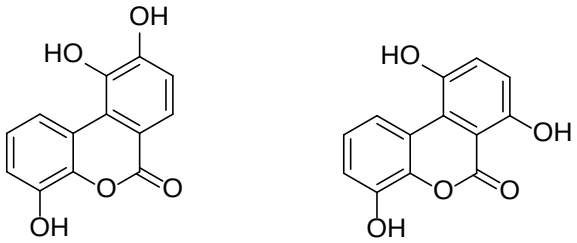
based compounds attached with pyrazolyl, or oxadiazolyl, or thiazolidinyl moieties and evaluated their antibacterial properties. The synthesized compounds revealed intriguing structure-activity relationship. As demonstrated in Figure 14, all compounds numbered **S48**-**S58** exhibited remarkable activity versus all tested bacterial strains, except for compound **S50**, which had no or only weak antibacterial property [53].

Figure 14. Benzo[f]coumarin-based compounds with antibacterial activity prepared by Kamal El-Dean et al.



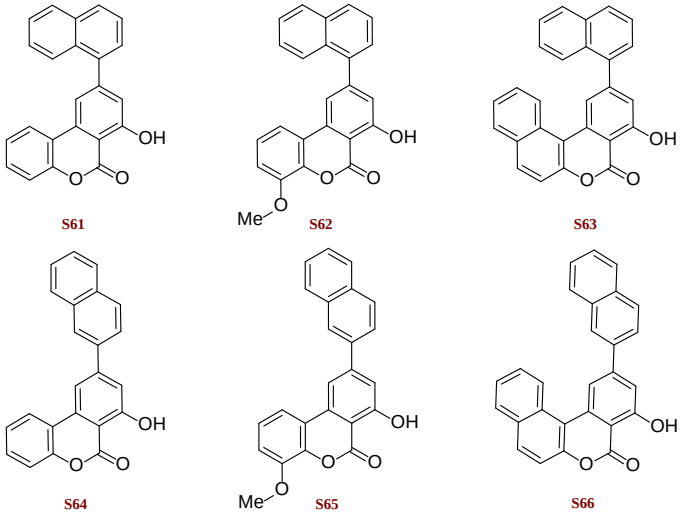
In 2018, Lin and his colleagues reported the antibacterial activity of dendrocoumarin (**S59**), a novel benzocoumarin-based product, and itolide A (**S60**), a previously known benzocoumarin-based product, as shown in Figure 15. These products were isolated from *Dendrobium nobile* stems and exhibited a promising antibacterial potential with broad-spectrum activity versus the test bacteria [54].

Figure 15. Benzo[c]coumarin-based products with antibacterial activity as depicted by Lin et al.



Recently, Patel and Patel synthesized and evaluated the antibacterial property of new naphthalene substituted benzocoumarin-based compounds. As illustrated in Figure 16, all the synthesized compounds **S61**-**S66** exhibited significant activity versus the test bacteria. Also, the authors concluded that compounds **S62** and **S65** that have OCH_3 group on the 8th position of the coumarin ring revealed the most promising antibacterial activity among the others[55].

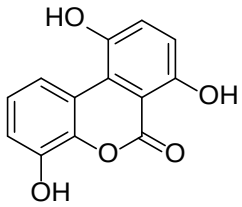
Figure 16. Benzo[c]coumarin-based compounds with antibacterial activity prepared by Patel and Patel.



Antifungal biomedical activity

Zeng and his colleagues have isolated Itolide A (**S60**), a benzocoumarin-based product, for the first time from *Itoa orientalis* seeds. As shown in Figure 17, the natural product **S60** revealed weak antifungal activity versus the test fungi with IC_{50} values of 132.25 µM towards *Rhizoctonia solani* and 240.00 µM towards *Sclerotium rolfsi* [56].

Figure 17. Benzo[c]coumarin-based product with antifungal activity reported by Zeng et al.

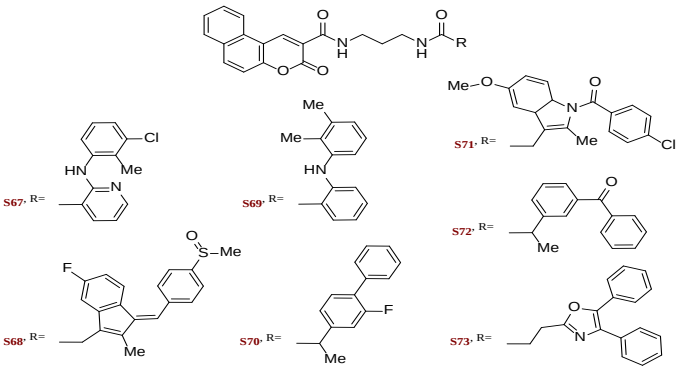


In addition, Kamal El-Dean and his colleagues have evaluated the antifungal property of the synthesized series of benzocoumarin-based compounds (**S48**-**S58**), which are attached with pyrazolyl, or oxadiazolyl, or thiazolidinyl moieties, as illustrated in Figure 14. Some of these compounds exhibited remarkable activity towards the test fungi strains. For example, compound **S49** revealed significant activity versus all the test fungal strains, while compound **S48** had activity only versus *Fusarium oxysporum* fungi. Also, the best antifungal activity were attributed to compound **S55**, which had oxime moiety in its chemical backbone [53].

In 2020, Jaber and his colleagues reported the synthesis of novel series of benzocoumarin-based compounds attached with anti-inflammatory drugs through an alkyl amide linker, as shown in Figure 18. These newly prepared compounds (**S67**-**S73**) were screened to evaluate their antifungal property. The outcomes revealed that all these compounds

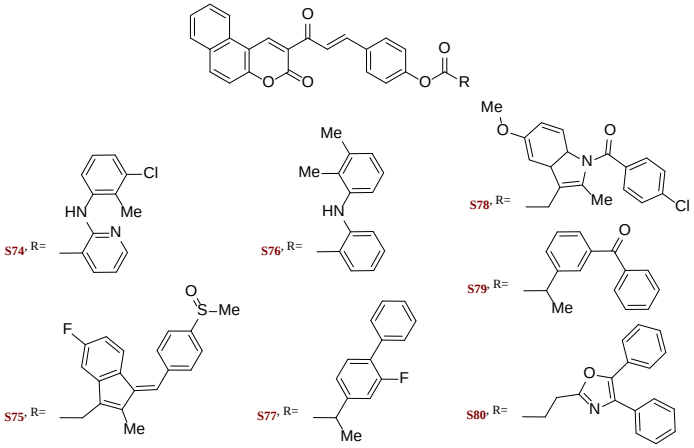
possessed significant activity versus the test fungal strains, but compounds **S67**, **S69**, and **S73** were the best [57].

Figure 18. Benzo[f]coumarin-based compounds with antifungal activity synthesized by Jaber et al.



In a continuing study, Jaber and his colleagues have synthesized and evaluated the antifungal potential of new series of benzocoumarin-chalcone connected with anti-inflammatory drug moieties via an ester linker (**S74**-**S80**), as shown in Figure 19. Compounds **S74**, **S75**, S76, and **S78** revealed good antifungal activity towards the test fungi. The authors deduced that the NH, F, Cl, and methoxy groups play a specific role in this activity[37].

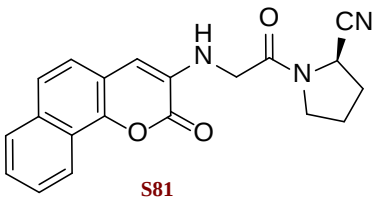
Figure 19. Benzo[f]coumarin-chalcone-based compounds with antifungal activity prepared by Jaber et al.



Antidiabetic biomedical activity

In 2015, Soman and Sharma reported the designing, synthesizing, and evaluating 3-aminocoumarin-based compounds as dipeptidyl peptidase-IV (DPP-IV) inhibitors to treat type II diabetes. Among all the synthesized compounds, the benzocoumarin-based compound **S81**, as illustrated in Figure 20, had the highest potency to inhibit DPP-IV enzyme activity with an IC_{50} value of 3.16 µM. Furthermore, the docking studies revealed that the **S81** compound had the best affinity for binding to the enzyme than the other prepared compounds [58].

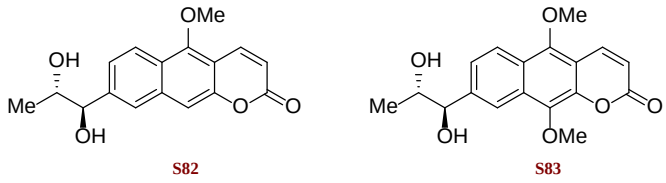
Figure 20. Benzo[h]coumarin-based compound with antidiabetic potential prepared by Soman and Sharma.



S81

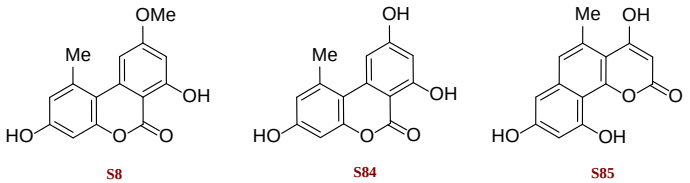
In a specific study, Naveed and his colleagues have isolated two novel benzocoumarin-based products, longipetalasin A (**S82**) and B (**S83**), from *Tribulus longipetalus*, as shown in Figure 21. The authors found that the natural products **S82** and **S83** possessed an excellent inhibition of α-glucosidase enzyme activity with IC_{50} values of 94.17 and 85.65 µM, respectively. Consequently, the authors proposed that these products are promising drug candidates for the management of diabetes mellitus [59].

Figure 21. Benzo[g]coumarin-based products with antidiabetic potential described by Naveed et al.



In 2016, Imhoff and his colleagues have isolated three benzocoumarin-based compounds, alternariol-9-methyl ether (**S8**), alternariol (**S84**), and pannorin (**S85**), from *Aspergillus* and *Botryotinia fuckeliana* marine fungi, as illustrated in Figure 22. For the first time, these natural products showed efficient inhibition of the glycogen-synthase-kinase-3β with IC_{50} values in a sub-µM range. Nowadays, inhibitors of this enzyme are considered as attractive targets to evolve antidiabetic agents[60,61].

Figure 22. Benzocoumarin-based products with antidiabetic potential as depicted by Imhoff et al.



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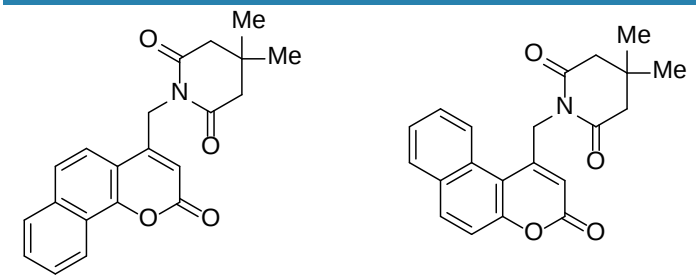
Recently, Kumar and his colleagues have synthesized and evaluated the antidiabetic potential of a new series of coumarin-cycloimide derivatives. Two of these derivatives, **S86** and **S87**, were based on a benzocoumarin moiety, as demonstrated in Figure 23. Both compounds revealed a moderate percentage of glucose-uptake activity via insulin-resistant cell model (HepG2) in values of 71.00 and 65.80%, respectively, at 50 nM, besides possessing a good safety profile[62].

Figure 23. Benzocoumarin-based compounds with antidiabetic potential synthesized by Kumar et al.



S86 S87

Conclusion

Over the past decades, there has been a rising interest for benzocoumarins in medicinal chemistry, due primarily to their extended π-conjugation system compared to coumarins. This property has piqued experts' attention in investigating their biologically active aspects. Consequently, many natural and synthesized benzocoumarin derivatives were discovered to have a variety of bioactivities, such as antidiabetic, antimicrobial, anti-dyslipidemia, antitumor, and antioxidant effects. This review concluded that the benzocoumarin derivatives are potential scaffolds for drug candidates due to their characteristic pharmacological attributes. Thus, the research communities should put more effort into designing and synthesizing new benzocoumarins with novel or improved activities, besides learning more about these compounds' binding and mechanism of action with their targets.

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Conflict of interest

The authors have no conflicts of interest to disclose.

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