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Review Article

Benzocoumarin Backbone Is a Multifunctional and Affordable Scaffold with a Vast Scope of Biological Activities

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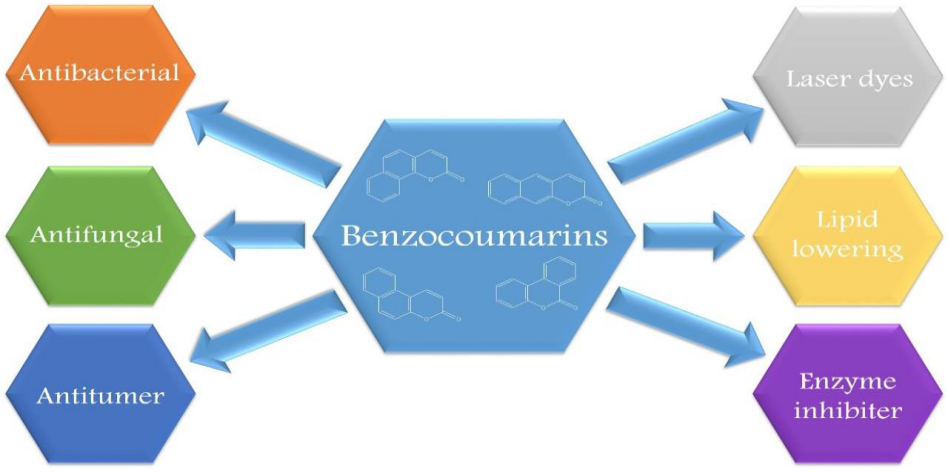
ABSTRACT

Coumarins having an aryl phenol linked to the 3,4-, 5,6-, 6,7-, or 7,8-binding sites are referred to as benzocoumarins. Efforts have been made in recent years to separate new configurations of benzocoumarin analogues with notable biological activities and to devise novel production procedures to create such agents with unique or even improved bioactivities. The separation and characterization of natural benzocoumarin compounds are briefly described in the first section of this study. The innovative synthetic approaches for the production of benzocoumarin-related compounds and also the documented total pathways to synthesize naturally occurring benzocoumarin derivatives are presented in the second portion. The third part contains a comprehensive summary of the attempts conducted to investigate the pharmacological activities of benzocoumarin related compounds, as well as the additional make-up, methods of production, and bioactivity assessment of therapeutically appropriate analogues. The authors' aim is to provide an overview of benzocoumarins, including their natural sources, chemical synthetic methodologies, and bio-medicinal activities that have been investigated over the last few decades.

GRAPHICAL ABSTRACT



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Introduction

Coumarin derivatives are heterocycle compounds that have been linked to a variety of health benefits when used in pharmaceutical, diet, and cosmetic applications. They have a large scale of pharmacological bioactivities, which makes them useful in a variety of medical statements. Laser dyes and fluorescence are examples of their industrial utility [1–9]. As a result of the investigations concerning coumarins and coumarin-related chemicals, there have been a significant number of reviews released in many pharmaceutical sciences, including chemistry of medicinal and natural products, pharmacology, and the pharmaceutical industry [10–17].

Benzocoumarin derivatives are coumarin related compounds which have a phenyl group attached to the 3,4- (class A), 5,6- (class B), 6,7- (class C), or 7,8- (class D) binding sites of the coumarin structure as shown in Figure 1. Alternariol (**BC5**) and its methyl ether (**BC6**), which are mycotoxins produced by *Alternaria* fungus, are the most well-known members of benzocoumarin chemicals [18].

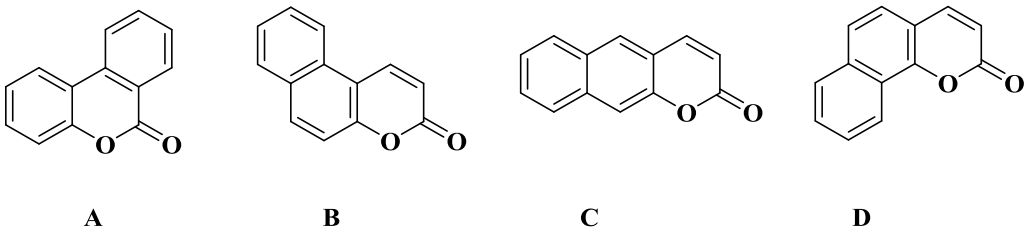


Figure 1: Benzocoumarin class types

Benzocoumarins have antifungal, antimicrobial, and anticancer properties which have been found, prompting medicinal chemistry investigations into benzocoumarins. Many intriguing pharmacological properties (e.g., antidyslipidemic, anti-tumor, antibacterial, and immunomodulating bioactivities) have been discovered as a consequence of the screening of numerous benzocoumarin derivatives in recent years. Benzocoumarins have been evolved into crucial "scaffolds" in the creation of new drugs. However, there has not been a thorough examination of these chemicals. As a result, benzocoumarins were studied in this review in terms of medicinal chemistry [3,6].

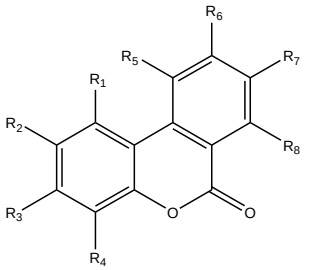
Benzocoumarins' Natural Sources

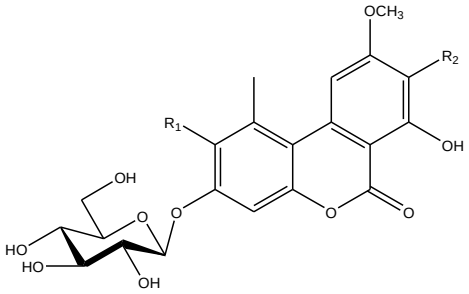
Only 51 benzocoumarin from natural origin have been identified, despite the enormous number of natural coumarins documented. 3,4-Benzocoumarins belong to class A (**BC1-BC30**) are shown in Figure as well as their dimers (**BC49-BC51**) in Figure 3, which constitute the majority of these 51 benzocoumarins, owing to the numerous studies of the lichen mycobiont of *Graphis scripta* and the fungal endophyte *Alternaria* species [18–22]. In addition, many higher plants, such as *Acacia fasciculifera* [23], *Eucomis autumnalis* [24], *Itoa Orientalis* [25], *Eucalyptus Exserta* [26], *Herpetospermum Caudigerum* [27], *Lysimachia Clethroides* [28], *Tamarix Nilotica* [29], *Phyllanthus Niruri* [30] are also been observed to have similar structures.

On the other hand, eight 5,6-benzocoumarins (**BC31-BC38**), as displayed in Figure 4, from class B were discovered. The majority of these compounds have been extracted from the *Juncus acutus* species. The 7,8-benzocoumarins, classified as class D (**BC39-BC48**) and displayed in Figure , make up the majority of the remaining natural benzocoumarins [31]. Unfortunately, no natural sources of 6,7-benzocoumarin (class C) have been discovered. Information about the names of isolated natural benzocoumarins and their sources are summarized in Table 1.

Table 1: Benzocoumarins (BC1-BC51) obtained from natural resources

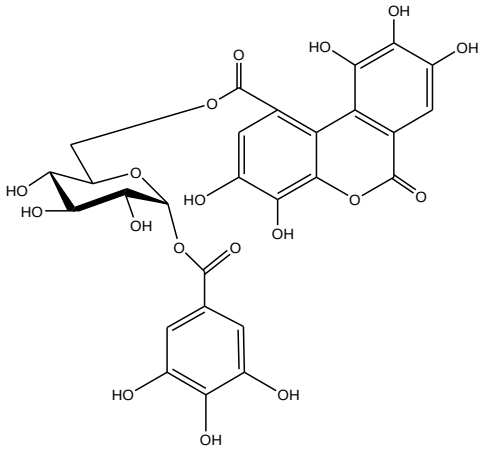
Name of benzocoumarin	Symbol	Sources	Reference
Autumnariol	**BC1**	*E. autumnalis*	[32]
Fasciculiferol	**BC2**	*A. fasciculifera*	[23]
Itolide-A	**BC3**	*I. orientalis*	[25]
No given name in the literatures.	**BC4**	*T. xanthipes*	[33]
Alternariol	**BC5**	*A. tenuis*	[18]
Alternariol methyl ether	**BC6**	*A. tenuis*	[18]
Sabilactone	**BC7**	*S. vulgaris*	[34]
Autumnariniol	**BC8**	*E. autumnalis*	[32]
Alternariol5-*O*-sulfate	**BC9**	*A. tenuis*	[21]
Alternariol5-*O*-methyl ether-4'-*O*-sulfate	**BC10**	*A. tenuis*	[21]
No given name in the literatures.	**BC11**	*E. exserta*	[26]
Altenuisol	**BC12**	*A. tenuis*	[19]
Altertenuol	**BC13**	*A. tenuis*	[19]
Herpetolide-A	**BC14**	*H. caudigerum*	[27]
Herpetolide-B	**BC15**	*H. caudigerum*	[27]
Palmariol-A	**BC16**	*L. palmae*	[35]
Palmariol-B	**BC17**	*L. palmae*	[35]
3-Hydroxy alternariol-5-*O*-methyl ether	**BC18**	*A. tenuis*	[21]
Graphislactone-A	**BC19**	*G. scripta*	[20]
Graphislactone-B	**BC20**	*G. scripta*	[20]
Graphislactone-C	**BC21**	*G. scripta*	[20]
Graphislactone-E	**BC22**	*G. scripta*	[22]
Graphislactone-F	**BC23**	*G. scripta*	[22]
Graphislactone-G	**BC24**	*C. acremonium*	[35]
Graphislactone-H	**BC25**	*C. acremonium*	[35]
No given name in the literatures.	**BC26**	*T. nilotica*	[29]
Lysilactone-A	**BC27**	*L. clethroides*	[28]
Lysilactone-B	**BC28**	*L. clethroides*	[28]
Lysilactone-C	**BC29**	*L. clethroides*	[28]
No given name in the literatures.	**BC30**	*P. niruri*	[30]
No given name in the literatures.	**BC31**	*J. acutus*	[31]
No given name in the literatures.	**BC32**	*J. acutus*	[31]
No given name in the literatures.	**BC33**	*J. acutus*	[31]
No given name in the literatures.	**BC34**	*J. acutus*	[31]
No given name in the literatures.	**BC35**	*J. acutus*	[31]
No given name in the literatures.	**BC36**	*J. acutus*	[31]
No given name in the literatures.	**BC37**	*J. acutus*	[31]
Trigoflavidol-C	**BC38**	*T. flavidus*	[36]
Rubilactone	**BC39**	*R. cordifolia*	[37]
9- Methoxytariacuripyrone	**BC40**	*A. brevipes*	[38]
Tanshinlactone-A	**BC41**	*S. miltiorrhiza*	[39]
7,9-Dimethoxytariacuripyrone	**BC42**	*A. brevipes*	[38]
No given name in the literatures.	**BC43**	*C. proteae*	[40]
No given name in the literatures.	**BC44**	*C. proteae*	[40]
Pannorin	**BC45**	*C. pannorum*	[41]
Vismiaguianin-A	**BC46**	*V. guianensis*	[42]
Vismiaguianin-B	**BC47**	*V. guianensis*	[42]
Neo-tanshinlactone	**BC48**	*S. miltiorrhiza*	[43]
Verrulactone-A	**BC49**	*P. verruculosum*	[44]
Verrulactone-B	**BC50**	*P.verruculosum*	[44]
No given name in the literatures.	**BC51**	*C. lipskyi*	[45]





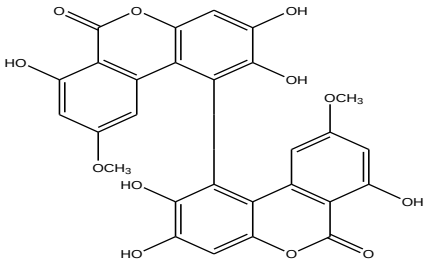
BC27 R1 = H R2 = H
BC28 R1 = H R2 = OCH3
BC29 R1 = OH R2 = H

	R1	R2	R3	R4	R5	R6	R7	R8	
BC1	CH3	H	OH	H	H	H	H	OH	
BC2	H	H	OH	H	OH	OH	H	H	
BC3	H	H	H	OH	OH	H	H	OH	
BC4	H	H	OH	H	OH	H	OH	H	
BC5	CH3	H	OH	H	H	OH	H	OH	
BC6	CH3	H	OH	H	H	OCH3	H	OH	
BC7	H	OCH3	H	CH3	H	OCH3	H	OH	
BC8	CH3	H	OH	OCH3	H	H	H	OH	
BC9	CH3	H	OH	H	H	OSO3H	H	OH	
BC10	CH3	H	OSO3H	H	H	OCH3	H	OH	
BC11	OH	H	OH	H	H	OH	OH	H	
BC12	H	OH	OCH3	H	H	OH	H	OH	OPS
BC12	H	OH	OH	H	H	OCH3	H	OH	RS
BC13	H	OH	OH	H	H	OCH3	H	OH	
BC14	CH2OH	H	OCH3	H	H	OCH3	OH	H	
BC15	CHO	H	OCH3	H	H	OCH3	OH	H	
BC16	CH3	H	OH	Cl	H	OCH3	H	OH	
BC17	CH3	Cl	OH	H	H	OCH3	H	OH	
BC18	CH3	H	OH	OH	H	OCH3	H	OH	
BC19	CH3	H	OCH3	OH	H	OCH3	H	OH	
BC20	CH3	H	OCH3	OH	H	OCH3	H	OCH3	
BC21	CH2OH	H	OCH3	OH	H	OCH3	H	OH	
BC22	OH	H	OCH3	OH	H	OCH3	H	OH	OPS
BC22	OH	OH	OCH3	H	H	OCH3	H	OH	RS
BC23	OH	H	OCH3	OH	H	OH	H	OH	OPS
BC23	OH	OH	OCH3	H	H	OH	H	OH	RS
BC24	CH3	Cl	OCH3	H	H	OCH3	H	OH	
BC25	CH3	H	OCH3	OCH3	H	OCH3	H	OH	
BC26	H	H	OH	OH	OH	OH	OH	H	

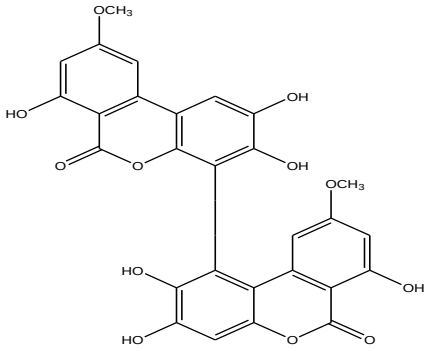


BC30

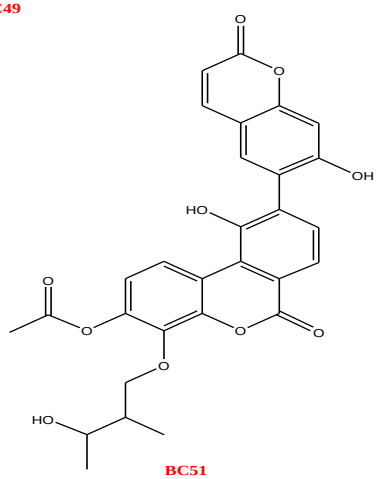
Figure 2: Chemical structures of class A natural benzocoumarins



BC49

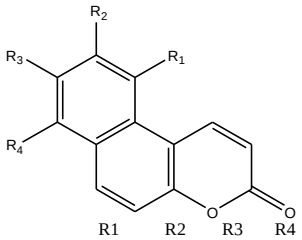


BC50

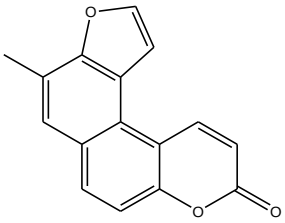


BC51

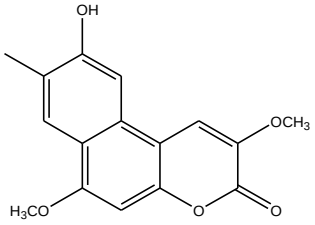
Figure 3: Chemical structures of class A benzocoumarins dimers



	R1	R2	R3	R4
BC31	CH2	H	CH3	H
BC32	CCH2	CH2OH	H	H
BC33	H	OH	CH3	H
BC34	CHC H2	CH3	OH	H
BC35	CH H2	H	OH	CH3
BC36	CH2OH	OH	CH3	H

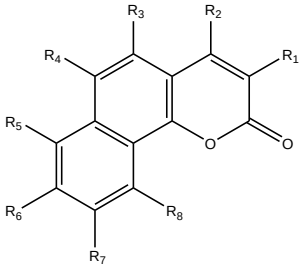


BC37

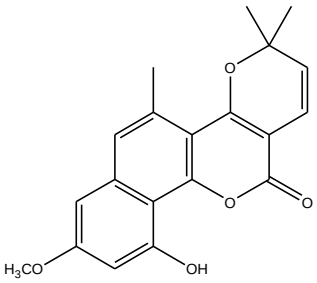


BC38

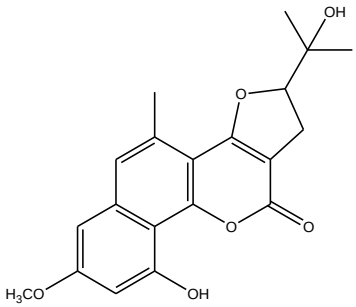
Figure 4: Chemical structures of class B natural benzocoumarins



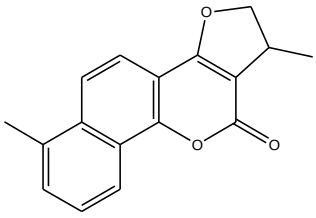
	R1	R2	R3	R4	R5	R6	R7	R8
BC39	H	H	COOCH3	OH	H	H	H	H
BC40	H	H	NO2	H	H	H	OCH3	H
BC41	COCH3	OH	H	H	CH3	H	H	H
BC42	H	H	NO2	H	OCH3	H	OCH3	H
BC43	CH3	H	H	OH	OCH3	H	H	H
BC44	CH3	H	H	OCH3	OCH3	H	H	H
BC45	H	OH	CH3	H	H	OH	H	OH



BC46



BC47



BC48

Figure 5: Chemical structures of class D natural benzocoumarins

Benzocoumarin's Derivatives Synthesis

Traditional Approaches to Synthesize Benzocoumarins

Benzocoumarins are members of the coumarin family, and a number of benzocoumarin related compounds were synthesized by traditional coumarin's production techniques, like Pechmann, Wittig, Perkin reactions, and other [46–48]. By employing the ortho- disseminated

naphthalene derivatives as initial material for the generation of benzocoumarins [49–53].

In 2020, Ansary and his colleague addressed a variety of one-pot benzocoumarin's derivatives synthesis techniques, as well as their benefits and drawbacks when compared to the other techniques. They concluded that the Kostanecki reaction procedure provides a significant enhancement in benzocoumarin's production reaction environment, as well as the benefit of its synthetic capabilities with a wide structural variety [54].

Novel Approaches to Synthesize Benzocoumarins

Organic chemists have been paying attention to the growing importance of benzocoumarins in the latest years. As a result, a number of extremely good synthetic approaches for these substances have been developed, some of which would be discussed below in detail.

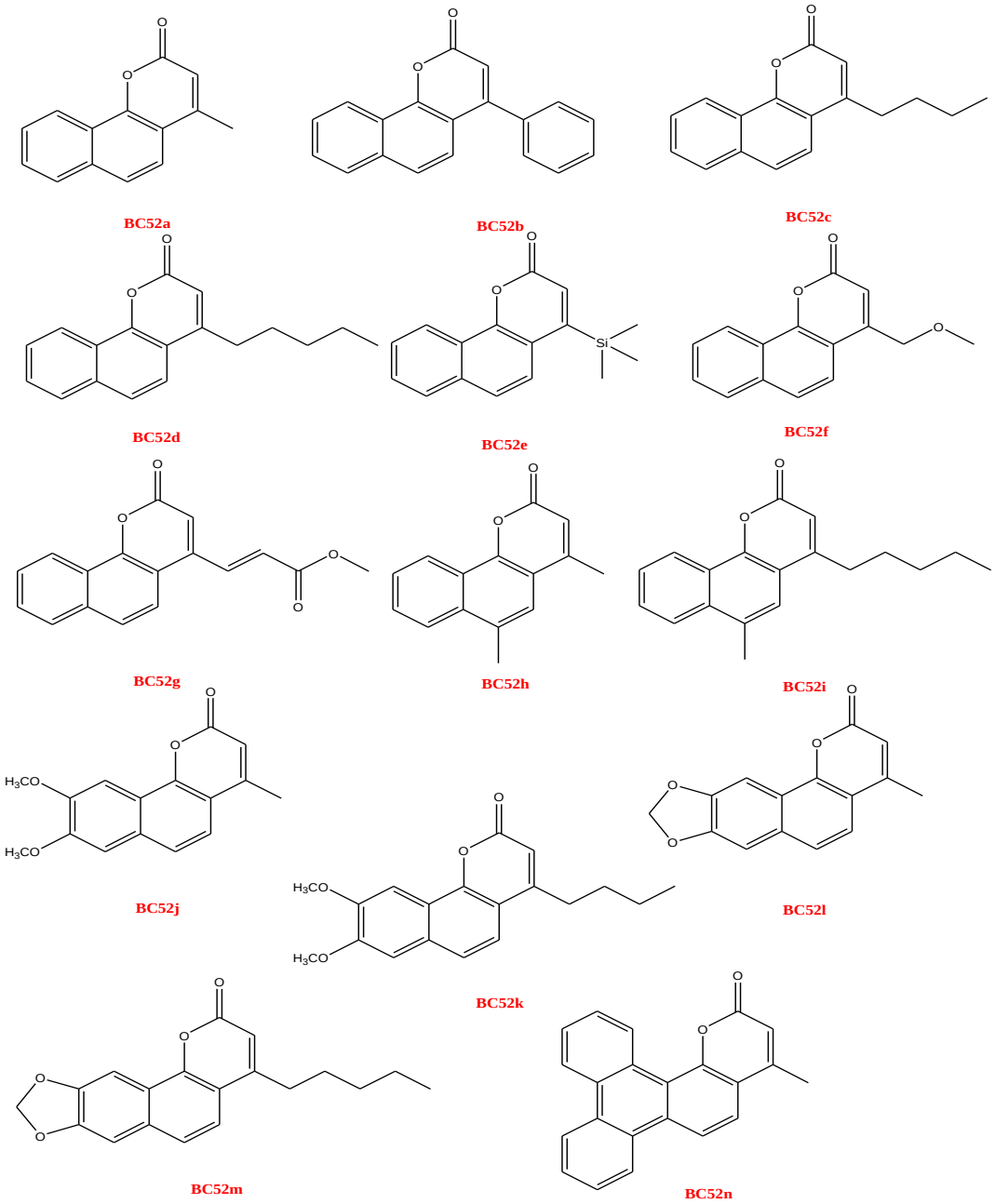


Figure 6: Chemical structures of the benzocoumarins symbolized as BC52a-n

Cheng and his colleagues proposed a relatively convenient one-pot technique for the synthesis of benzocoumarin derivatives in 2001, utilizing new Ni-catalyzed cyclization of propiolates with tricyclic alkenes [55]. In reasonable yields, this reaction can produce benzocoumarin derivatives, symbolized as **BC52a-n** and is depicted in Figure , with impressive stereoselectivity and regioselectivity.

Cheng and colleagues then refined the previously stated process by incorporating a novel Ni-catalysed cyclization of oxabicyclic alkenes with either 2-iodobenzoate or β-iodo-(*Z*)-propenoates to obtain annulated coumarins, symbolized here as **BC53a-l** and displayed in Figure 7, in excellent yield. Under the modest reaction conditions, this technique provided a facile and efficient one-pot production of a range of complex coumarin structures as **BC53a-l** [56].

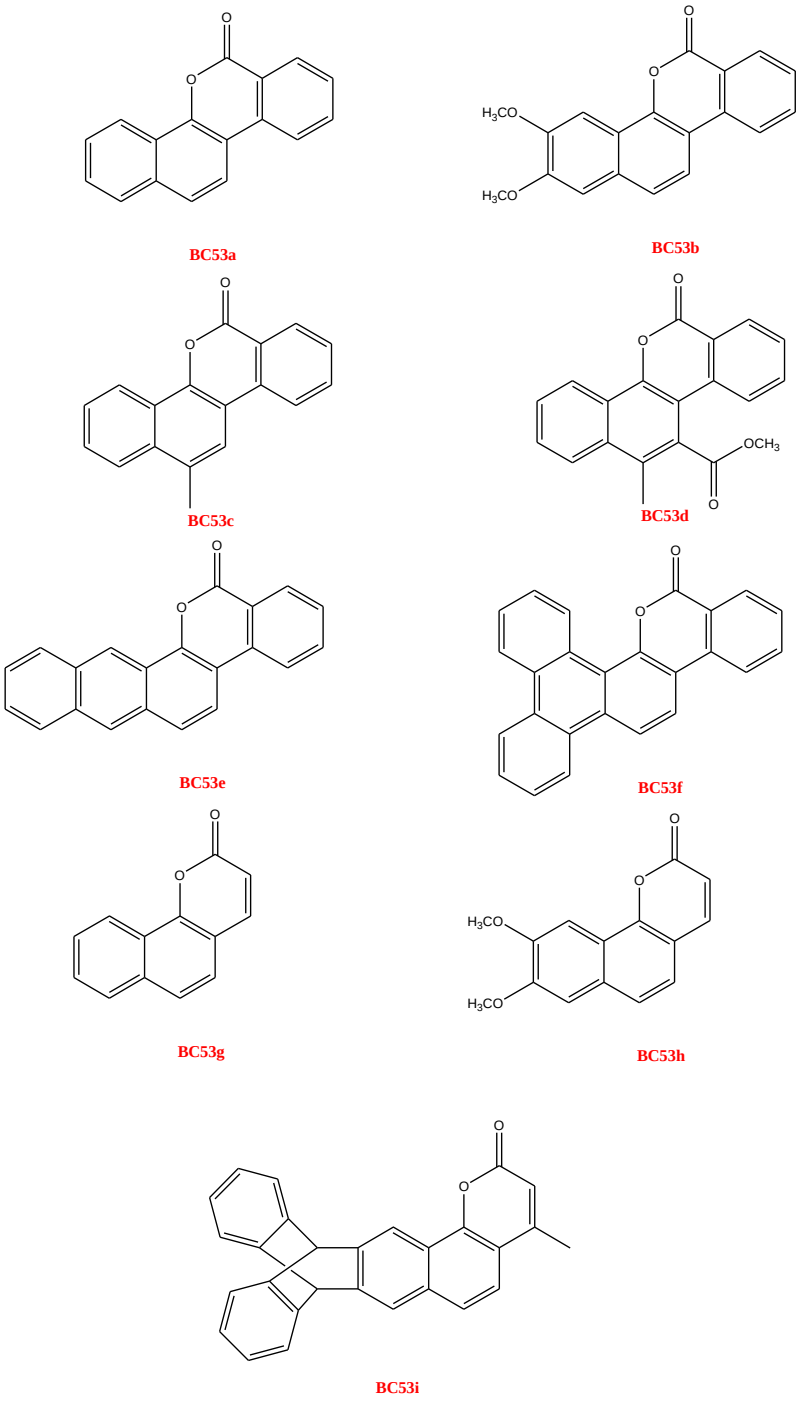


Figure 7: Chemical backbones of the benzocoumarin symbolized as BC53a-i (BC53j=BC52a,BC53k=BC52j,BC53l=BC52n)

Nevertheless, the precise pathway of this synthesis is not perfectly understood, and the process for benzocoumarin generation is only explored in light of the previous findings and known Ni chemistry. Hon and colleagues in 2009 devised a novel and practical approach to produce benzocoumarin structures, symbolized as **BC55a-e,** via oxidizing the relative 2*H*-pyran ring derivative **BC54** which was produced *in situ* by the *cis*-denials electrocyclization. 1-Tetralone

used as a precursor for creating the aromatic rings of the benzocoumarins [57].

In 2010, Coelho and colleagues reported that the Reformatskii reaction of naphtha[2,1-b]pyran-1-one and bromoacetic acid ethyl ester resulted in the unexpected synthesis of the new benzocoumarin symbolised as **BC56** [58].

The alcohol was produced by the Reformatskii reaction of the ethyl bromoacetate with a ketone in the presence of iodine and zinc. The conjugated ester (produced via removal of water) with the unpredicted new photochromic **BC56** were obtained by refluxing alcohol and HOAc. Due to its fascinating photophysics, the photochromic properties of **BC56** under continual irradiation by UV light were examined, too. According to the findings, the continual irradiation via UV rays at 20°C of the colorless **BC56** and toluene solution resulted in the formation of lemon colouring with λ_{max} spectrum at 432 nm. UV irradiation of **BC56** leading mainly to the creation of photoproduct **BC57** that is a heat-stable product, as well as a little amount of **BC58**, based on further investigation of ^{1}H NMR spectra. Goel and colleagues published a novel generic approach to synthesize a variety of functional oxygen heterocycles, involving benzocoumarin **BC59** & **BC60**, which are displayed in Figure 8 [59].

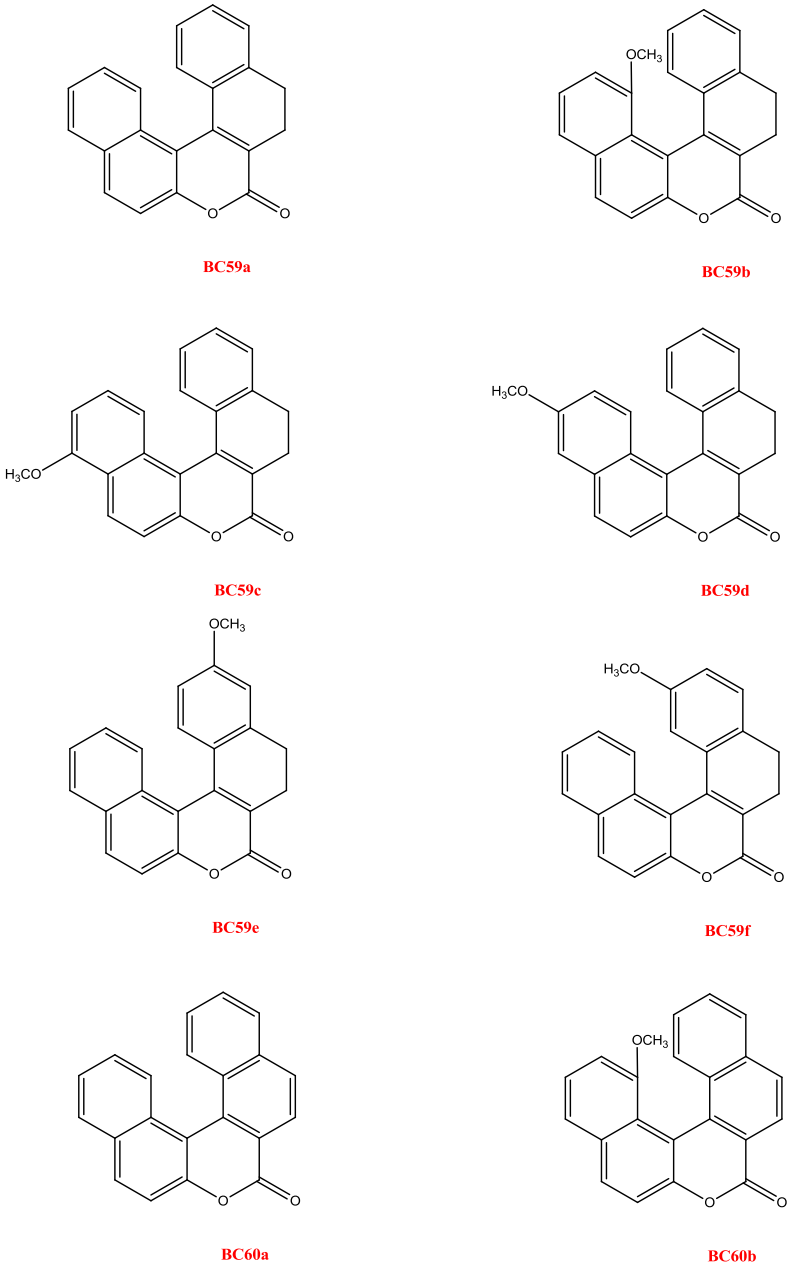


Figure 8: Chemical backbones of the benzocoumarins symbolized as BC59a-f and BC60a-b

Ray and colleagues reported a new efficient one-pot production method of class-A benzocoumarin derivatives and their improved models, symbolized as **BC61a-h** and depicted in Figure , by Suzuki-Miyaura cross-coupling of 2-bromonaphthalene carboxaldehyde derivatives or 2-bromobenzaldehyde with 2-hydroxyphenyl boronic acid, the subsequent oxidative lactonization of hydroxyl- and aldehyde-moiety was coming later [60].

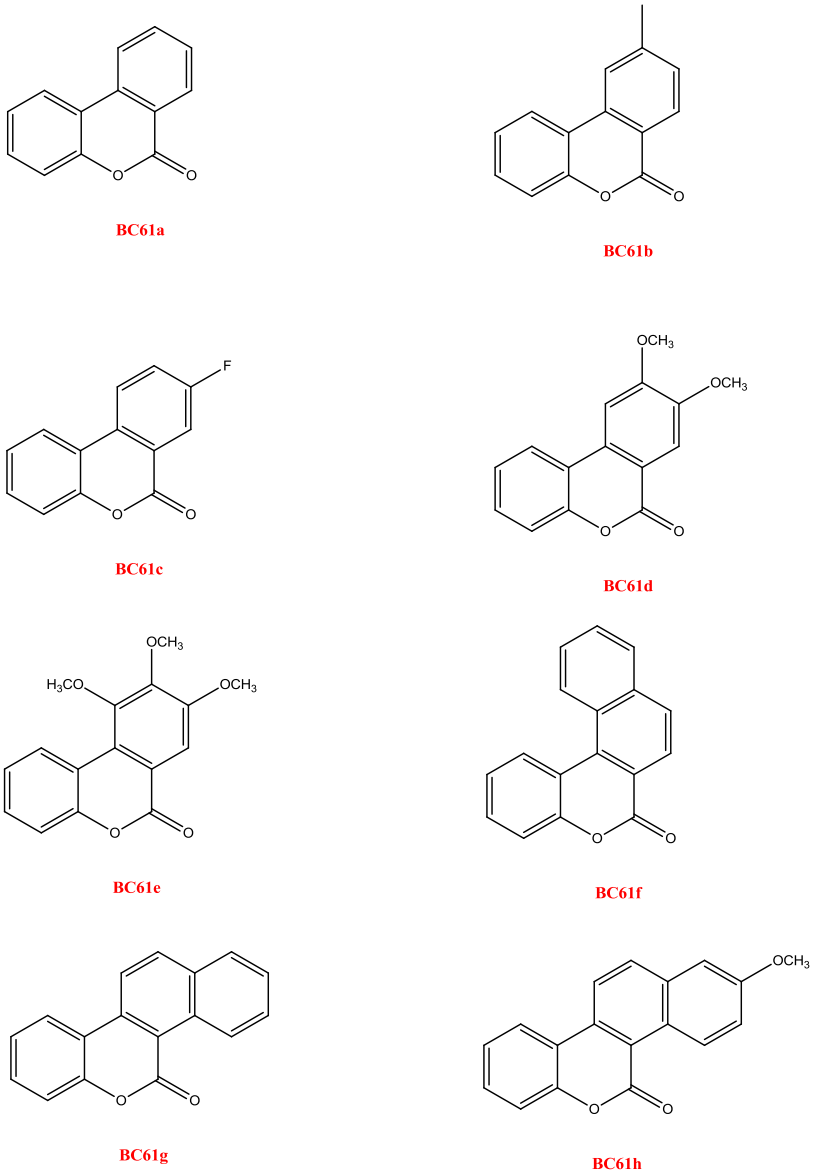


Figure 9: The chemical backbones of benzocoumarins BC61a-h

To create the benzocoumarin structure's biaryl lactones, Wang and colleagues devised a new and feasible C-H activation/C-O cyclization directed by carboxyl and was catalysed by Pd(II)/Pd(IV). Benzocoumarins, symbolized as **BC62a-ab** and displayed in Figure 10, were produced by the respective 2-aryl carboxylic acids cyclization in relatively high yields (more than 96%) under optimal operating conditions [61].

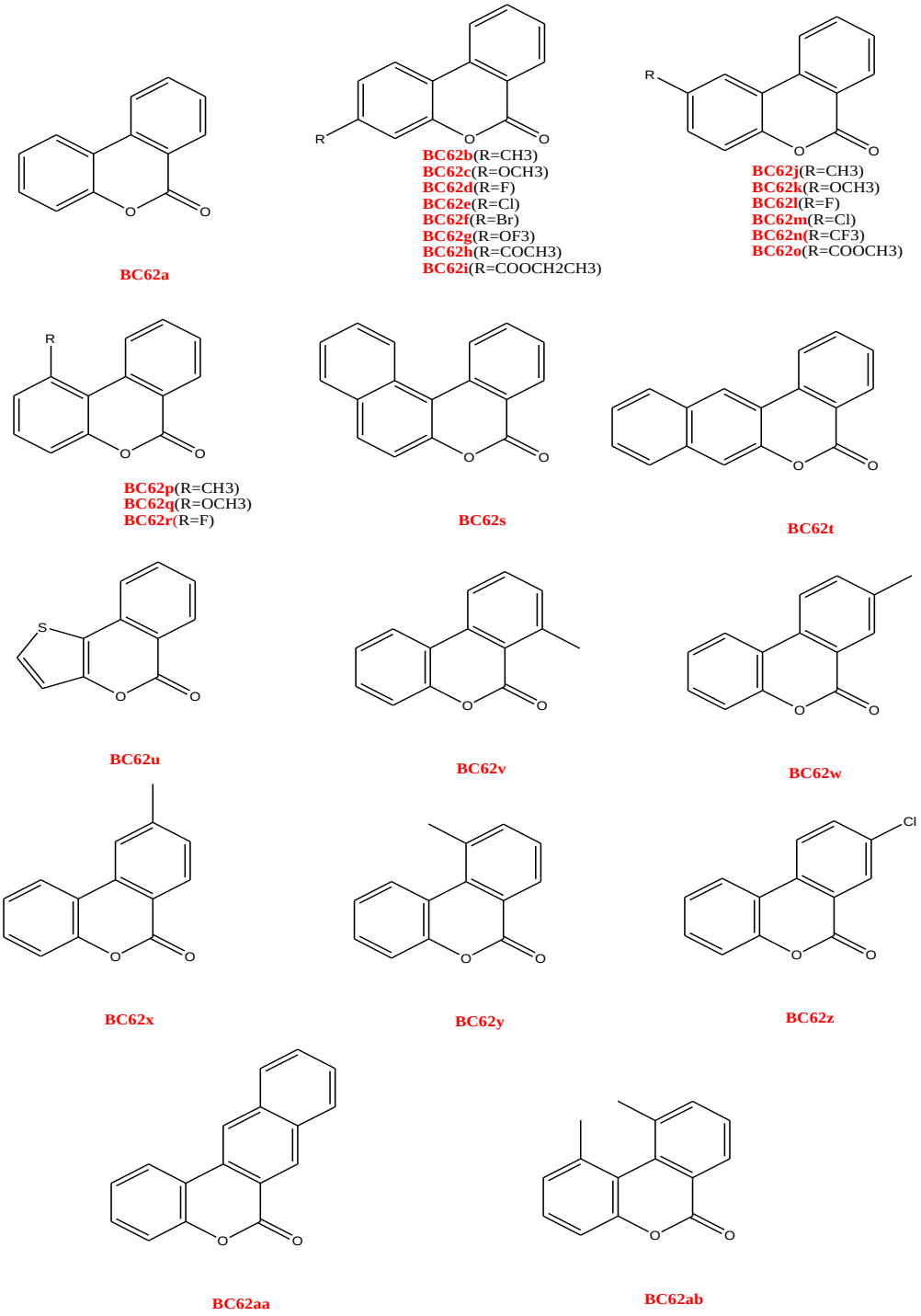


Figure 10: The chemical backbone of benzocoumarins BC62a-ab

Benzocoumarin's Total Synthesis Efforts

Many efforts have been performed for the total synthesis of benzocoumarins in the last decades due to their unique structures and remarkable pharmacological bioactivities.

Alternariol Total Synthesis

The total synthesis of **BC5** and its closely related compounds is an important issue in total benzocoumarins synthesis since they are famous mycotoxins. Sóti completed the first production of **BC5** along with its methyl ether **BC6** in 1977 [62]. Subba Rao's research group published a straight forward technique for the 6-aryl-2,4-dimethoxybenzoic acid synthesis, which is the **BC5** precursor [63], that made the production of **BC5** derivatives easier. A highly efficacious technique for the total synthesis of **BC5** was proposed by Koch in 2005, which involved 7 stages beginning with 3,5-dimethoxy-bromobenzene and orcinol. The main reaction is

a Suzuki-type coupling of the orcinol-derived boronic acid along with a brominated resorcylic aldehyde catalysed by palladium. The final demethylation yielded 73% **BC5**, besides a little amount of **BC6** in a yield about 20% [64].

Abe and colleagues reported another simple synthesis approach to **BC5** in 2007, employing palladium reagent which catalysed the phenyl-benzoate derivatives intramolecular biaryl coupling reactions [65].

Away from **BC5**, Podlech's team produced **BC12** in 10 stages utilizing protocatechuic aldehyde and phloroglucinol acid as original materials, in a yield of 23%. A Suzuki Miyaura reaction with subsequent lactone ring formation was the critical step. The ^{1}H NMR of the synthesized **BC12** showed that the NMR spectrum did not match that obtained from natural sources [66,67]. Mikula and colleagues published the procedure of synthesizing two Alternaria mycotoxins synthesis including alternariol sulphated methyl ether named **BC10** and glucosylated alternariol methyl ether named **BC27** [68].

Graphislactone Total Synthesis

From the *Cephalosporium acremonium*, which is a type of fungus in Trachelospermum jasminoides [35], or from the lichen mycobiont of *Graphisscripta var. pulverulenta* [20,22], **BC19-BC25** were recovered. Nishioka and colleagues, via an intramolecular-biaryl coupling process of diphenylcarboxylate derivative mediated by Palladium, were chemically synthesized **BC19-BC21** [69]. Also, **BC24** and **BC25** were synthesized in a similar manner attributing to their structural similarities [70].

Podlech and colleagues created a novel synthesis technique for the configurationally similar benzocoumarin derivatives **BC19, BC21-BC25** based on Suzuki coupling. This team work utilized the biaryl linkage formation to build the benzocoumarin backbone and dakin reaction to provide it with additional hydroxy moieties [69–71].

Neo-Tanshinlactone Total Synthesis

Lee and colleagues reported the discovery of a novel natural benzocoumarin, symbolized as **BC48**, using a bioassay-guided technique for isolation. Tandem alkylation/intramolecular aldol plus tandem esterification/intramolecular Friedel–Crafts acetylation reactions were used to complete the total synthesis of **BC48**. Six steps were required for this synthesis, which provided an overall 18% yield [72].

Mal and colleagues developed a convergent method to produce **BC48** using benzannulation-lactonization as a crucial step. This procedure also allowed for the production of unexpected 6-alkoxy carbonyl-substituted **BC48** as well as their analogues directly [73].

Juncus Benzocoumarin Total Synthesis

From the *Juncus acutus* plant's rhizomes, Della-Greca and colleagues extracted several bioactive benzocoumarins which symbolized as **BC 31-BC37** [31]. Then, starting with β-tetralone and through two different pathways including a one-pot aromatization and rearrangement chain reactions, Hon's research team reported the total synthesis of the **BC33** for the first time [74].

Bioactivities of Benzocoumarins and Their Analogues

Because of their strong cytotoxic as well as anti-dyslipidemic properties, benzocoumarin-based structures have attracted a lot of interest. In laboratory trials, several natural benzocoumarins were investigated for their bioactivities from various species and their synthesized analogues [75–85].

This part of the review gives a bio-medical analysis of the natural and synthesized benzocoumarins, and also the development of structurally associated derivatives with better medicinal potentials.

Antitumor Activity

BC6, **BC19**, **BC24**, and **BC25** have been reported to be able to inhibit the SW1116 cells proliferation at half-maximal inhibitory concentrations (IC_{50}) of 14, 8.5, 21, and 12 μg/mL, in sequence, as found by Tan and colleagues [35].

With IC_{50} of 6.87-8.85 μg/mL values, **BC41** derived from the *Salvia miltiorrhiza* roots has demonstrated considerable antitumor activity towards cervical epithelioid carcinoma HeLa, hepatocellular carcinoma HepG2, and ovarian adenocarcinoma OVCAR-3 cell lines. In the same

side, bioassay-directed fractionation was used to isolate **BC46** and **BC47** from the root of *Vismia guianensis* in 2000. The first product with dimethyl pyran ring exhibited extreme cytotoxicity towards KB cell line, while the second with pyran 1,4-diazaphenanthrenes ring and hydroxyl isopropyl moiety was inactive. This finding recommended that dimethyl pyran in the skeleton of **BC46** seems to be necessary for cytotoxic action [42].

BC48, isolated by Lee and his colleagues from *Salvia miltiorrhiza*'s root in 2004, has revealed remarkable inhibitory activity towards two estrogenic receptors breast carcinoma cell lines. When analogized with tamoxifen citrate, this natural benzocoumarin exhibited 10 times greater potency and 20 times greater selectivity toward the test cell lines [43].

Compound **BC63**, which has an ethyl group at position 4, demonstrated high selectivity and excellent bioactivity, with a ED_{50} values of 0.45, 0.18, 13.5 & 10.0 µg/mL against MCF-7, ZR-75-1, MDA-MB-231, and HS-587–1, respectively. Additionally, with an ED_{50} of 0.10 µg/mL, **BC63** displayed strong action against SKBR-3 cancerous cells line [86].

Other analogues were examined as antibreast-cancer candidates including **BC64-BC68**. Compound **BC64** had a selectivity ratio of about 12 times for SK-BR-3 and MCF-7 cell lines, but compound **BC65** had a selectivity ratio of 23 times for ZR–75-1 cell line and 23 folds greater activity toward MCF-7. **BC66** had 2-3 times greater effectiveness towards SK-BR-3 and ZR-75-1 cell lines than compound **BC48**. Compared to **BC48**, **BC67** and **BC68** demonstrated wider anticancer activity. The anticancer efficacy of these two synthetic compounds, as indicated in preliminary SAR data, is dependent on the presence of nitrogen-related substitution [87-89].

In a follow-up data analysis, it was revealed that **BC72** can couple with microtubules to induce tubulin depolymerisation. This process may result in ERK-mediated mitotic arrest and successive apoptosis through JNK excitation in human colorectal tumor tissue [90]. Additional experiments suggested that adding the alicyclic ring to **BC72** might drastically alter its antitumor bioactivity, especially in carcinoma cell lines other than breast cancer [91]. For instance, **BC75** demonstrated extremely high efficacy towards SKBR-3 and ZR-75-1 breast carcinoma cells, with ED_{50} values of 0.7 and 1.7 µM, in sequence. This synthetic benzocoumarin had also a wider cytotoxic activity than **BC48** and **BC63**. A unique class of chemotherapeutics was discovered when the aromatic ring of **BC48** was saturated, and the most potent compounds were **BC76-BC79** [92,93].

For further structural engineering, a sequence of the insertion of alicyclic rings and secondary amines has been used to explore the potential pharmacologically active variants [94]. As a result, the structurally similar **BC48** and **BC67** indicated dramatically weaker inhibitory effect against tumor cell development, and this was inferior to those demonstrated by **BC80** and **BC81**. Lee and his colleagues investigated aqueous-soluble amine substituted analogues and discovered two novel active compounds, **BC82** and **BC83** in the cytotoxic activity experiment [95].

When compared to the previous compound **BC67**, compound **BC82** had a 50 times higher aqueous solubility. Compounds **BC82** and **BC83** effectively led to decreasing the mammary cells account in genetically modified mice. In malignancy susceptible mammary glands, a single week of therapy with **BC82** led to an approximately 80% decrease in BrdU-positive cells [96].

Sashidhara and colleagues have published a research paper dealing with the neo-tanshinlactone associated medical chemicals which included the library development of completely new benzocoumarin's related compounds depending on the chemical backbone of the natural **BC48**. Testing the antineoplastic bioactivity of the synthesized compounds towards breast carcinoma MCF-70 and MDA-MB-231 revealed that the benzocoumarins **BC84-BC86** can suppress MCF-7 tumorigenesis with IC_{50} values of 3.8, 7.9, and 6.5 µM, respectively [96].

Very recently in 2021, Salmaan and colleagues synthesized new benzocoumarin- chalcone

hybrids substituted with ester or arylamide moiety. The spectral and mass data corroborated the structures of the newly synthesized benzocoumarin compounds. The activity of the synthesized compounds against prostate carcinoma was tested, and the findings revealed that two of them were the most effective compounds among this group. As a result, these candidates appear to be the most attractive antiproliferative agents towards CYP450 dependent prostate carcinoma cells [97].

Anti-dyslipidemic Activity

Sashidhara and colleagues conducted a comprehensive research to synthesize and evaluate the benzocoumarin derivatives' antidyslipidemic efficacy in 2008. In the early stages, they prepared a series of new benzocoumarin-based compounds and found that products **BC87-BC89** can reduce cholesterol, phospholipid, and triglyceride plasma levels by about 23%, in an experiment on rats' model with significant hyperlipidemias.

In a non-enzymatic system, **BC87** and **BC88** exhibited scavenging ability towards superoxide and hydroxyl radicals' formation. Furthermore, **BC87-BC89** inhibited microsomal lipid peroxidation by 27 %, 24 %, and 31 %, for each. The benzocoumarin derivatives **BC87** and **BC88** were shown to have strong lipid-lowering and antioxidant characteristics [98].

Synthetic benzocoumarins **BC90-BC92** were found to have excellent hypolipidemic activity with major cholesterol- and triglyceride-lowering activities. These synthetic candidates appeared to be great choices for creating a new lead with anti-atherosclerotic benefits and hypolipidemic bioactivity, in follow-up studies [99–101].

During the last years, Sashidhara and colleagues created a variety of new benzocoumarins functionalized with an amide group to afford effective anti-thrombotic candidates. **BC93** demonstrated the most promising antithrombotic activity among the compounds examined, which was equivalent to currently used acetylsalicylic acid or warfarin. However, **BC93** differs from these conventional medications in that it did not cause an increase in bleed time, indicating its great potential as a new anti-thrombotic agent [102]. In an experiment on an animal model, **BC94-BC96** showed potential anti-thrombotic property owing to their capacity to drop the platelets coagulation and aggregation. Furthermore, these two compounds may enhance the thrombin time considerably. From these findings, Sashidhara and colleagues proposed that these amidebenzocoumarin derivatives can be considered as anti-thrombotic candidates owing to their antiplatelet and anticoagulant properties [103]. Figure 11 displays the skeletal formulas of the synthetic benzocoumarins with a potential to act as anti-thrombotic applicants.

Estrogenic and Anti-estrogenic Activities

Benzocoumarins were discovered to have steroid-like properties in 1956 [104]. The potential of these agents as agonists or antagonists towards estrogen receptor phenotype was studied by Jha and colleagues. The synthetic compounds **BC97** and **BC98**, which are depicted in Figure , displayed estrogenic activity at 10 mg/kg, resulting in a 21% and 25% increase in uterine weight above the control. When these benzocoumarins transformed to their dibenzopyrans **BC99-BC101** by adding 6,6-dimethyl group, as illustrated in Figure , the authors concluded that **BC101** had an antagonistic effect since the weight of uterus has dropped by 20%. The effect of the agents symbolized as **BC99** and **BC100** can be considered to be more estrogenic than anti-estrogenic [105].

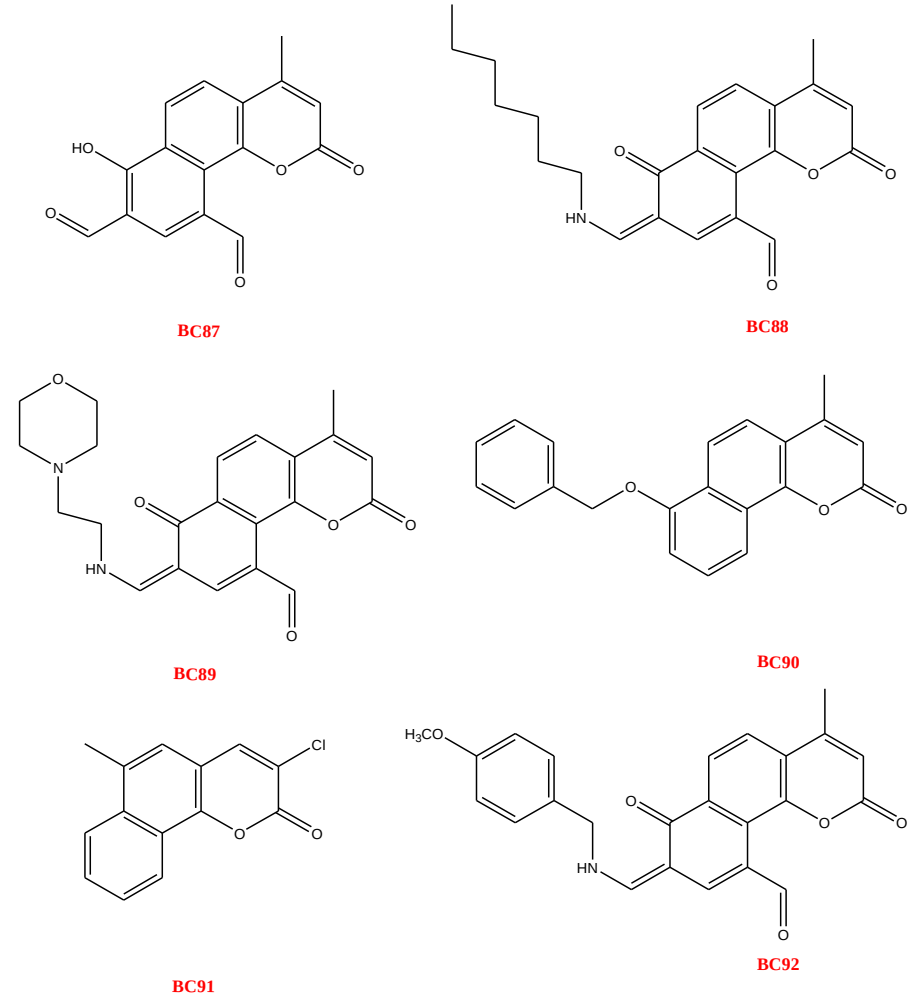


Figure 11: The Chemical backbone of the synthetic benzocoumarins that may be considered as potential anti-dyslipidemic agents

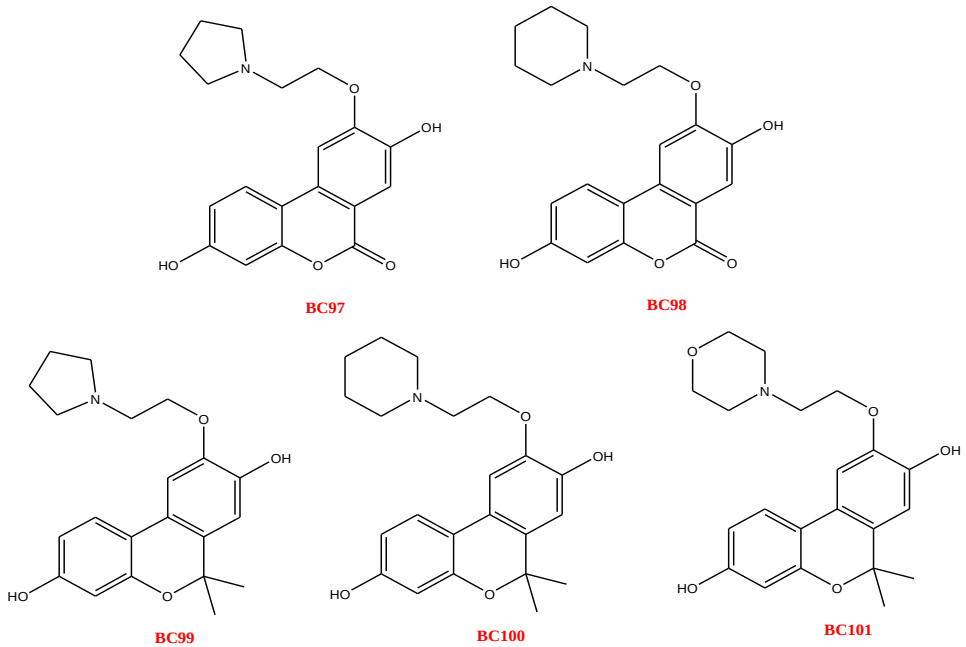


Figure 12: The chemical structures of the synthetic benzocoumarins with estrogen receptor agonist or antagonist activity

The planer structure of the ring system and the small core structure compared with estradiol might explain the weaker antagonistic properties of these compounds, **BC97-BC101**. Based on this

finding, Sun and colleagues have synthesized a number of class-A benzocoumarin's derivatives as well as their pyranonated products in order to assess their capability to modulate estrogen receptor selectively. An estrogen receptor ligand binding experiment was used to determine the affinity and selectivity of these analogues over the alpha subtype of the estrogen receptor. As a result, several of these analogues have been discovered to be effective and selective agonists towards the beta estrogen receptor. Small lipophilic groups like methyl group were shown to be necessary at multiple sites for good interaction, as shown in SAR assay [106].

Conclusions

Research investigating benzocoumarin backbone synthesis and its medicinal potential has attracted a large mass of intention during the past decades by many researchers involving medicinal chemists. Due to the presence of a phenyl ring, benzocoumarins have a longer π conjugation backbone than typical coumarins. This structural feature has attracted investigators' desire to study the natural sources of benzocoumarins, their synthetic methods, and possible medical effects. As a result, both natural and synthetic benzocoumarins have been examined for a variety of biomedical activities, including anticancer, anti-estrogenic, and anti-dyslipidemic properties. Furthermore, the intriguing biological activities of benzocoumarins stimulate the development of a variety of synthetic techniques to meet the demand for synthesizing superior analogues with improved activities.

The successful progress of benzocoumarins with respect to separation, synthesis, biological activity investigation, and SAR analyses has been observed throughout the last several decades. Regardless of the reality that surveys on benzocoumarins have become more coherent and detailed, reviews on their pharmacological properties were in the early stages until now, as so many of them are focused on the synthesis of benzocoumarins, and there are few research findings on comprehensive activity mechanisms for this family of coumarins. Upcoming research should focus on investigating more about the biochemical pathways through which these benzocoumarins can react with their various molecular targets inside the body. As a result, the authors concluded that the benzocoumarin chemical nucleus is a promising scaffold for developing new drugs in the near future.

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Authors' contributions

All authors contributed toward data analysis, drafting and revising the paper and agreed to responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

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