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Structural Diversity and Bioactivities of Natural Benzophenones

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REVIEW

Structural Diversity and Bioactivities of Natural Benzophenones

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Natural benzophenones are a class of compounds consisting of more than 300 members, which exhibit great structural diversity and bioactive properties. Many benzophenones have been reported from higher plants or fungi, most with polyisoprenylated benzophenone skeketons, and are mainly found in the Clusiaceae (formerly Guttiferae) family, a number from edible or medicinal species. Owing to their variable substituents and complex ring systems, many new polyisoprenylated benzophenones (PPBS), including ones with unusual skeletons, were isolated and identified. These natural benzophenones exhibit a range of biological activities including antifungal, anti-HIV, antimicrobial, antioxidant, antiviral and cytotoxic. Due to the increased numbers and biological importance of these unique natural product polyphenols, we will review natural benzophenones and provide an in-depth discussion of their structural diversity and biological activity. By focusing on these key developments in benzophenones, we will contribute a focused review, selecting examples mostly from the last 15 years, but extending our scope to other historically important benzophenones discovered prior to that time.

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1 Introduction

The battery of natural products produced by a given plant is at times highly specific, such as the limonoids produced by the Meliaceae family,[1] oxygenated nortriterpenoids from the Schisandraceae family,[2] and the cucurbitacins from the Cucurbitaceae.[3] Likewise, the Clusiaceae (formerly Guttiferae) is characterized by the benzophenones.[4] Natural benzophenones are a class of compounds consisting of more than 300 members, which have great structural diversity but share a common phenol-carbonyl-phenol skeleton. The A-ring, derived from the shikimic acid pathway, is a benzene ring generally containing 0, 1, or 2 substituents. The B-ring, derived from the acetate-malonate pathway, undergoes prenylation and cyclization producing a wide variety of structurally unique compounds with bi-, tri-, and/or tetracyclic ring systems. Some publications have examined benzophenones in conjunction with other natural products produced by a specific plant genus.[4-7] Recently, owing to their variable substituents and complex ring systems,

many more new benzophenones, especially the polyprenylated benzophenones (PPBS), have been identified and reported from higher plants and certain fungi, and some of these reported new compounds have unusual rearranged skeletons with strong antibacterial or anti-cancer activity.[8,9] In addition, the strategy to synthesize benzophenones has attracted considerable attention. Thus, this review will select some natural benzophenones in higher plants and fungi and provide an in-depth discussion of their structural diversity and biological activity, as well as a discussion of their structure-activity relationship (SAR). It will be a useful resource in the fields of natural products chemistry, synthetic chemistry, pharmacology, food chemistry, and agricultural science.

2 Structural diversity of natural benzophenones

Chemical structures of natural benzophenones are diverse (Fig. 1). Natural benzophenones without side chains are rare, as most of them are linked with various numbers of -OH, -OMe, prenyl, or geranyl groups. Prenyl and geranyl groups can be rearranged to form new unusual complex ring systems. Fig. 1 shows examples of some benzophenone structures which reported in these 15 years. Many of them have been previously highlighted and discussed in top natural products review journals. For example, owing to their complex ring systems or unusual skeletons, doitunggarcinone A (**1**), guignasulfide (**2**), and plukenetione A (**3**) have been highlighted in Hot off the Press articles in *Nat. Prod. Rep.*[10-12] In addition, clusianone A (**4**) has been used twice in the table of contents (TOC) graphics of *Nat. Prod. Rep.* because of its strong anti-HIV and antimicrobial activity;[13] guttiferone A (**5**) also has been used in a *Nat. Prod. Rep.* TOC graphic owing to its strong antiviral activity.[14]

The structural diversity of benzophenones is due to different substitutions of the prenyl and geranyl group as well as the hydroxyl group of ring B, allowing many opportunities for rearrangement to form new skeletons. Some benzophenone dimers, such as guignasulfide (**2**) and microsphaerin D (**7**), also attract considerable attention.

2.1 Natural sources of benzophenones

At this time, more than 300 natural benzophenones have been isolated and identified, half of them are basic benzophenone skeletons (BBS) and the other half are PPBS. The vast majority of benzophenones have been isolated from higher plants, with 77% of them coming from the Clusiaceae family (Table 1). About 50 compounds were isolated from other families (such as Gentianaceae,[15] Moraceae,[16] Polygalaceae,[17-21] Rosaceae[22,23] and Thymelaeaceae[24]), 15 compounds were isolated from anamorphic fungus,[25] plant endophytic fungus,[26,27] or marine fungus[28-30] and 4 compounds were reported from Cuban propolis.[31,32] Owing to space limits, this review focuses only on selected complex benzophenones reported in the latest 15 years, most of these structures are type-A, B, C and D PPBS which were isolated from Clusiaceae family and other natural sources.

2.2 Classification

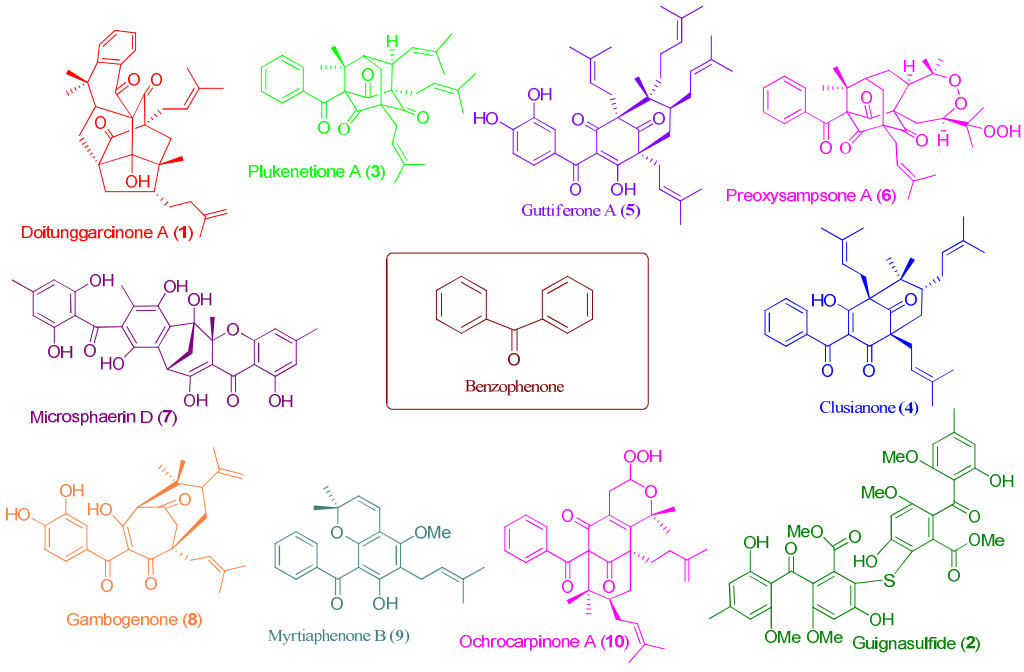

Fig. 1 Chemical structures of selected benzophenones.

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Many natural benzophenones reported in Clusiaceae family are non-polar phenolic compounds, which mostly share a bicycle [3,3,1]-nonane-2,4,9-trione core structure linked to a 13,14-dihydroxy substituted phenyl ring. Their hydrophobicity will increase as the number of prenyl functional groups grows. In previous studies, the classification and structure numbers of natural benzophenones have been confusing and inconsistent. Benzophenones can be classified straight-forwardly into two major types (Fig. 2). In the first structural group benzene rings A and B are complete, these benzophenones are comparatively simple and we call them basic benzophenone skeletons (BBS, Fig. 2). They have a 13-membered skeleton with various numbers of -OH, -OMe, prenyl, or geranyl groups attached which are usually uncyclized or have only undergone one cylization. The other structural group of benzophenones is that in which benzene ring A is complete while ring B is attached to additional prenyl or geranyl groups and hence ring B is elaborated by the production of bi-, tri-, or tetracyclic rings, or epoxide, oxo bridges, or peroxide groups in the structures (PPBS, Fig. 2). The benzophenones group called PPBS, are more complicated than the BBS as prenylation, geranylation, and cyclization may produce numerous structurally unique compounds containing bi-, tri-, and/or tetracyclic ring systems.

Most of the natural benzophenones previously reported in the Clusiaceae family belong to the PPBS structural group. Cuesta-Rubio and Zhang each reported that these PPBS can be classified into three types according to the relative position of the benzoyl group.[33,34] In this review, we have updated this classification and added one more type for the first time. Most PPBS have an eight-member ring that arises from the prenylation and cyclization of benzene ring B. The most common way to number these structures is that the carbon next to the isopropyl group is C-1 and the eight-membered ring was numbered from C-1 to C-8, then the last carbon in original benzene ring is C-9 and the ketone is C-10, the complete benzene (ring A) is arranged from C-11 to C-16. Based on this rule, polyprenylated benzophenones can be classified into four types. Type-A: with the complete benzoyl group linked at C-1; type-B, with the benzoyl group linked at C-3; type-C, with the benzoyl group at C-5; and type-D, without the eight-membered ring and a modified conjugated system in the B-ring formed and saturated due to the addition of carbonyl groups (Fig. 2). If a PPBS does not fit into types A, B or C it will also go in type D. Among these four, type-A is more complicated than the other kind of types, since there are more conformations of the six-membered B ring and it is easier to rearrange.

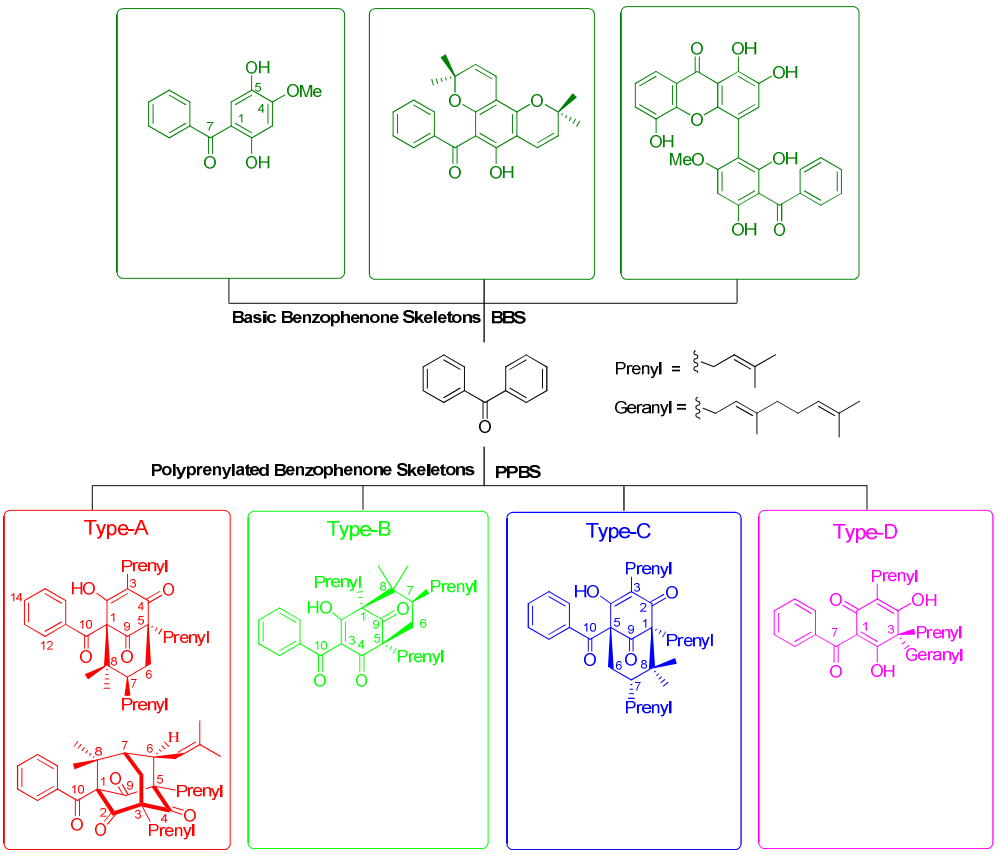


Fig. 2 Basic skeletons of natural benzophenones.

Table 1 Botanical species (Clusiaceae family) from which benzophenones have been isolated and reported.

No.	Species	Tissue	Ref.
1	*Allanblackia stuhlmannii*	Root wood	35
2	*Clusia grandiflora*	Floral resins	36-38
3	*C. havetioides* var. *stenocarpa*	Leaves, twigs	39
4	*C. hilariana*	Floral resins	40
5	*C. insignis*	Floral resins	40
6	*C. lanceolata*	Floral resins	40
7	*C. nemorosa*	Fruits	37,41,42
8	*C. obdeltifolia*	Trunk	43,44
9	*C. plukenetii*	Fruits	45,46
10	*C. portlandiana*	Leaves, twigs	47
11	*C. rosea*	Flowers	33
12	*C. sandiensis*	Fruits	48
13	*C. scrobiculata*	Floral resins	40
14	*C. spiritusanctensis*	Floral resins	40
15	*C. weddelliana*	Floral resins	40
16	*Garcinia aristata*	Fruits	49
17	*G. assugu*	Barks	50
18	*G. cambogia*	Latex	51-54
19	*G. cochinchinensis*	Barks	55
20	*G. eugeniaefolia*	Barks, stems	56
21	*G. griffithii*	Barks	57
22	*G. hombroniana*	Wood	58
23	*G. humilis*	Barks, stems	59
24	*G. kola*	Fruits	60
25	*G. livingstonei*	Fruits	61
26	*G. macrophylla*	Twigs	62
27	*G. multiflora*	Fruits	63
28	*G. nujiangensis*	Leaves	64
29	*G. oblongifolia*	Barks, stems	65,66
30	*G. ovalifolia*	Leaves	61
31	*G. paucinervis*	Leaves	67
32	*G. pedunculata*	Pericarps	53
33	*G. propinqua*	Twigs	8
34	*G. semseii*	Barks, stems	68
35	*G. solomonensis*	Barks, stems	69
36	*G. subelliptica*	Pericarps, fruits	70
37	*G. virgata*	Barks	71
38	*G. xanthochymus*	Fruits	72-75
39	*Hypericum cohaerens*	Aerial parts	76
40	*H. henryi*	Aerial parts	77
41	*H. humifusum* ssp. *austral*	Aerial parts	78
42	*H. sampsonii*	Aerial parts	79-87
43	*H. scabrum*	Aerial parts	88
44	*Moronobea coccinea*	Stem wood	89
45	*Ochrocarpos punctatus*	Barks	90
46	*Rheedia calcicola*	Fruits	91
47	*R. edulis*	Fruits	92
48	*R. gardneriana*	Fruits	93
49	*Symphonia globulifera*	Roots	61,94

2.2.1 Type-A PPBS

Type-A PPBS is one of the most complicated structures for natural benzophenones. They were often isolated from *Clusia* and *Hypericum* genera. Compounds **3**, **6** and **10-33** are typical type-A PPBSs isolated and reported from *Clusia* genus, one of the characteristics of these compounds is the unusual adamantyl skeleton of ring B (Fig. 3), such as compounds **3**, **11-33**.

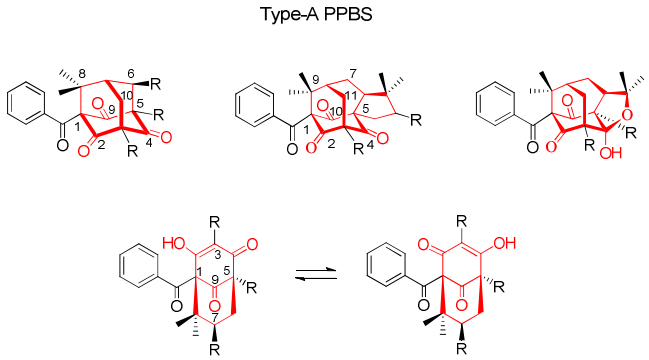
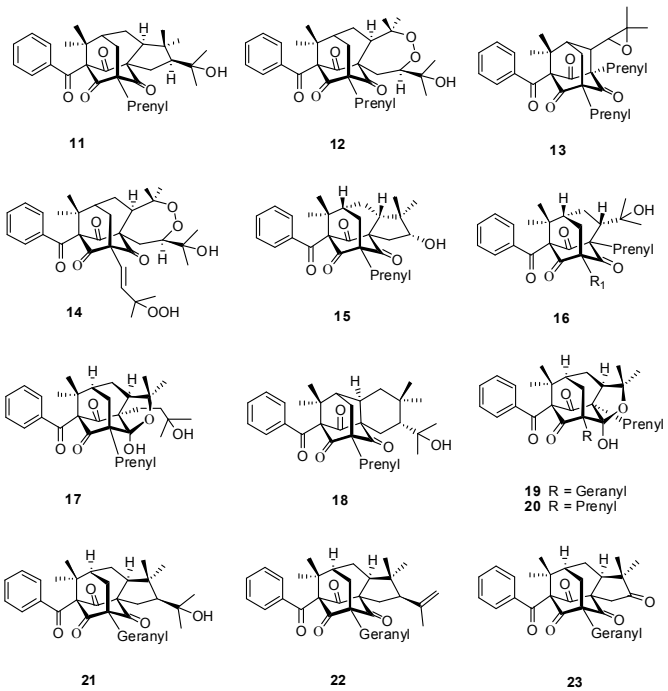


Fig. 3 Basic skeletons of type-A PPBS

Plukenetione A (**3**) was the first unusual adamantyl ketone benzophenone found from *Clusia plukenetii* in 1996,[45] plukenetiones B (**11**) and C (**12**) were also reported from Barbadian *C. plukenetii* fruits by the same group.[46] Plukenetione B (**11**) contains an unusual tetracyclo [5,3,3,1,^{9,12}0^{1,5}] tetradecane-10,11,14-trione moiety and plukenetione C (**12**) contains another 4,5-dioxatetracyclo [7,3,3,1,^{11,14}0^{1,7}] hexadecane-12,13,16-trione moiety.[46]

In 2001, Christian reported that 28,29-epoxy-plukenetione A (**13**) and 33-hydroperoxy-isoplukenetione C (**14**) were found in fruits of *Clusia havetiodes* var. *stenocarpa* collected from Jamaica.[39] Compounds **13** and **14** were two more adamantyl ketone benzophenones similar to plukenetione A (**3**) and plukenetione C (**12**).[39] In 2004, Cruz reported three complex



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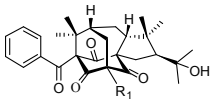
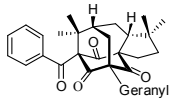
tricycle [4,3,1,1^{3,8}]undecane skeleton, compounds **15**-**17**, from the hexane extract of *Clusia obdeltifolia*.[43] Their structures also contain an adamantyl skeleton. Compound **18** was also isolated and reported from this species by the same group.[44]

As for the genus *Hypericum*, Hu and Sim's group studied the type-A PPBS from this genus for the first time. They isolated and identified 13 type-A PPBS structures, sampsoniones A-M (**19**-**31**), from *Hypericum sampsonii*.[79-82] Among them, sampsoniones A (**19**) and B (**20**) contained two novel 5-oxatetracyclo-skeletons arising from cyclizations of two prenyl substituents,[79] and sampsoniones C-H (**21**-**26**) contained an unusual carbotetracyclo-skeleton formed by complex cyclizations of three prenyl substituents.[80] In addition, sampsoniones I (**27**) and J (**28**) are complex adamantyl derivatives, and **27** is the first PPB derivative with the unique caged tetracyclo [7.3.1.1^{3,11}.0^{3,8}] tetradecane-2,12,14-trione skeleton.[81] In 2003, Lin et al. also reported their similar structures, hypersampsones D-E (**32**-**33**), in the same plant.[83] Recently, Mu's group also reported some new type-A PPBS from *H. sampsonii*, such as hypersampsones G (**34**), H, I (**35**), J (**36**), K, L and sampsoniones N, O, P, Q (**37**). The structures of compounds **34**-**37** were confirmed by X-ray crystallographic analysis.[85-87] Peroxysampsones A (**6**) and B were also reported from *H. sampsonii* by this group.[84]

Type-A adamantyl PPBS is a type of rearranged benzophenone, with most of their variety focusing on the adamantyl group. The adamantyl can be changed into isoadamantyl if there are 11 carbons in the skeleton. In this case, another side-ring can be formed from isoadamantyl side chains, for example, a five-membered side-ring in compounds **11**, **15**, **17**, **19**-**26** and **32**-**36**, and a six-membered side-ring in



24 R = Geranyl
25 R = Prenyl



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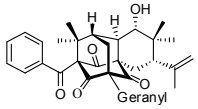

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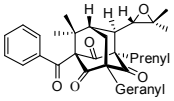

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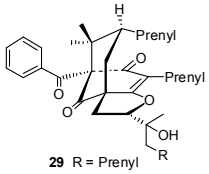
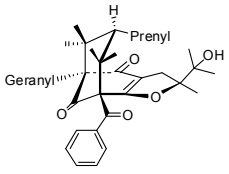


29 R = Prenyl
30 R = H



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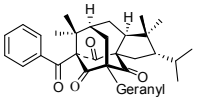

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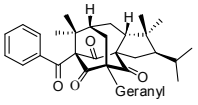

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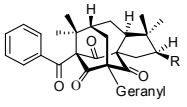
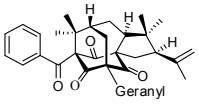


34 R = Isopropyl
35 R = H



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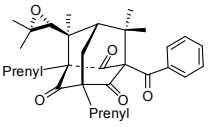

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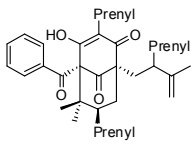

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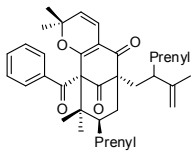

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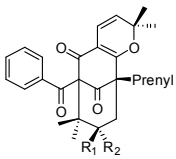
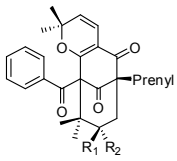
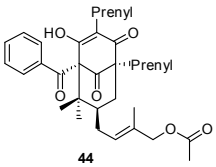


40 R_1 = H; R_2 = Prenyl
42 R_1 = Prenyl; R_2 = H



41 R_1 = H; R_2 = Prenyl
43 R_1 = Prenyl; R_2 = H



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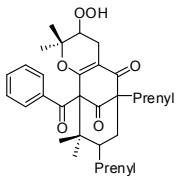

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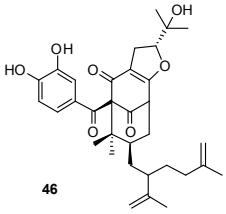

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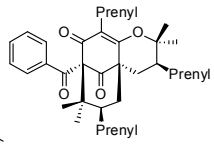

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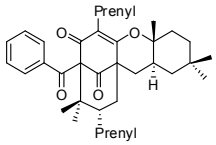

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compounds **18** and **27**. In brief, due to their variable substituents and complex adamantyl ring systems type-A adamantyl PPBS attract considerable attention from phytochemical researchers.

As for type-A PPBS without adamantyl skeleton, their characteristics are similar to type-B, C and D PPBS, as the side chain form a new five- or six-membered ring after dehydration of the hydroxyl group. For example, chamones I (**38**) and II (**39**) are two type-A PPBS isolated from *Clusia grandiflora* trunk latex.[38] Compound **39** has an additional six-membered ring in the C-2/C-3 location of ring B. Similarly, scrobiculationes A (**40**) and B (**41**), [40] plukenetione F (**43**) and plukenetione G (**42**),[46] as well as 15,16-dihydro-16-hydroperoxy-plukenetione F (**45**)[39] also have additional six membered rings, compounds **40** and **42** are located on C-3/C-4, **41**, **43** and **45** are located on C-2/C-3. Insignone (**44**) does not have such a ring but is linked with an acetyl in the prenyl group.[40] Also, garcinielliptone FB (**46**) has an additional five-membered ring on C-3/C-4 and garcimultiflorones A (**47**) links a hexatomic ring to C-4/C-5 of the ketone.[63] Compound **48** is noteworthy as it has a novel 9-oxa-tetracyclic [11,3,1,0^{1,10},0^{3,8}]heptadec-10-ene-12,17-dione moiety arising from complex cyclizations of isopentenyl and lavandulyl substituents.[44]

2.2.2 Type-B PPBS

Type-B PPBSs are the most common type of natural benzophenone structure. The characteristic of these structures is an additional eight-membered-ring is formed after prenylation and cyclization, with the benzoyl group linked at C-3 of the ring B (Fig. 4). Most of the PPBSs isolated from *Garcinia* genus[95] were type-B PPBS with the *Hypericum* genus also contributing many type-B PPBS.

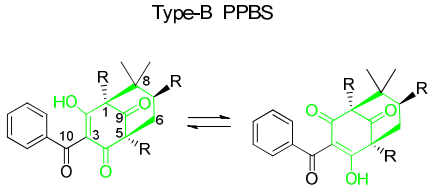
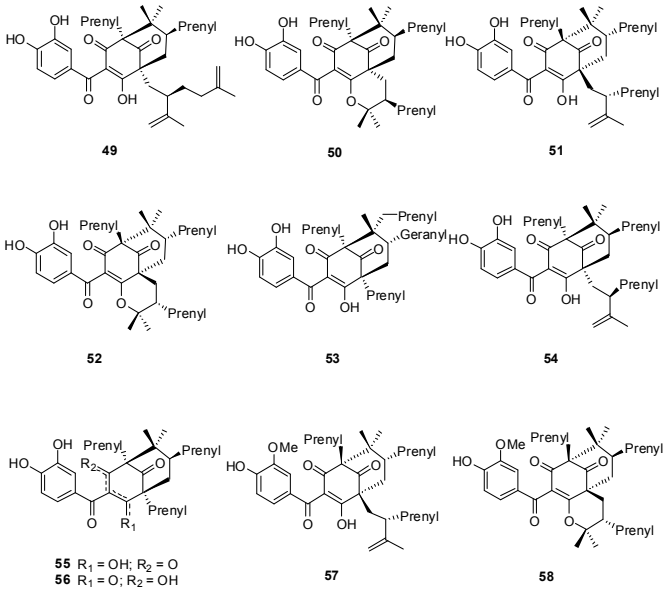
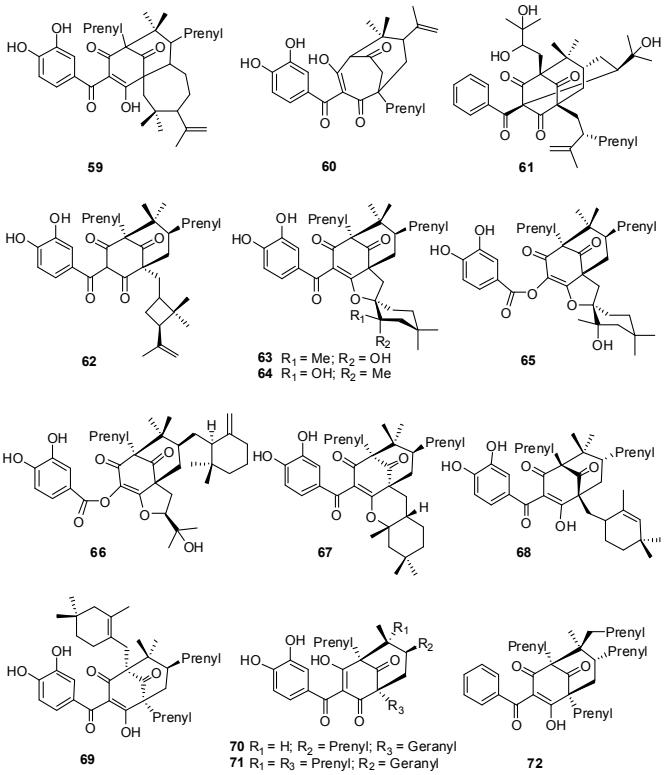


Fig. 4 Basic skeletons of type-B PPBS

Different from type-A, almost all of the natural type-B PPBS have two hydroxyl groups linked at C-13 and C-11 of their phenyl ring, and most of their variety is focused on the side chains, such as prenyl, geranyl, hydroxyl or methoxyl groups. For example, xanthochymol (**49**), isoxanthochymol (**50**) garcinol (syn. camboginol, **51**) and cambogin (syn. isogarcinol, **52**) reported from *G. xanthochymus*.[51-53,72-74] Guttiferones A (**5**) and G (**53**), found in *G. macrophylla* [62] and guttiferone E (**54**) from *G. ovalifolia*.[61] In addition, aristophenones A (**55**) and B (**56**) were a tautomeric pair of PPBS isolated in *G. aristata*.[49] Another two 13-*O*-methyl derivatives of **51** and **52**, garcinol 13-*O*-methyl ether (**57**) and isogarcinol 13-*O*-methyl ether (**58**) were identified from *G. assigu*.[50]

Another typical characteristic of type-B and type-C, as well as the type-A PPBS that do not have the adamantyl ring, is that most of their structures have a keto-enol equilibrium (Fig. 3-5). This phenomenon can affect their ^{1}H & ^{13}C NMR spectra. In order to get NMR spectrum of a single tautomer, researchers have to add acid to the NMR solvent, such as trifluoroacetic acid (TFA), to make this keto-enol equilibrium into one stable configuration. However, if the hydroxyl group in the prenyl or geranyl has formed an ester bond after the loss of water with another hydroxyl in the benzene, such as compounds **10**, **40**-**48** and **52** the keto-enol equilibrium would disappear, and in that case no acid needs to be added to the NMR solvent.





There are some other unique type-B PPBS structures reported recently. Guttiferone H (**59**) and gambogenone (**60**) were isolated and identified from *G. xanthochymus* by our group.[75] Compound **59** contains a seven-membered ring attached to the bicyclo[3.3.1]nonane system at positions 7 and 8. Compound **60** has a novel benzophenone bicycle [3.3.2]decane system which the ring B in the skeleton has changed into a seven-membered ring.[75]

Similar with **59**, garcimultiflorone C (**61**) also has an additional seven-membered ring attached to the skeleton.[63] In addition, eugeniaphenone (**62**) is the first PPBS example which has a cyclobutane-containing side chain.[56] Paucinones A-C (**63**-**65**) contain an unexpected cyclohexane-spiro-tetrahydrofuran moiety, and paucinone D (**66**) contains a 1-methylene-3,3-dimethylcyclohexane group.[67] Compounds **65** and **66** have an ester group, instead of ketone group in the benzophenone skeleton.[67] Coccinones A (**67**), F (**68**) and H (**69**) have hexatomic rings in their side chains.[89]

The reports regarding guttiferone I are complicated. From 2005-2006, three compounds (**70**-**72**) have been named guttiferone I.[57,59,71] According to their time of manuscript acceptance, compound **70**, which was isolated in *G. griffithii* was reported first;[57] compound **71** from *G. humilis* was reported next and we have designated as guttiferone I'.[59] Similarly, compound **72** found in *G. virgata* in 2006 have been designated as guttiferone I".[71]

Other Clusiaceae genera, such as *Symphonia*, *Allanblackia Ochrocarpos,* and *Moronobea* were also reported to yield type-B PPBS.[61,94]

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2.2.3 Type-C PPBS

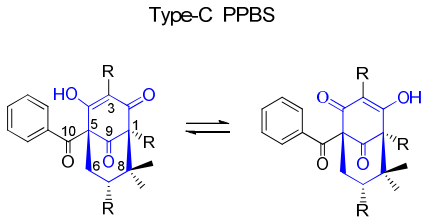
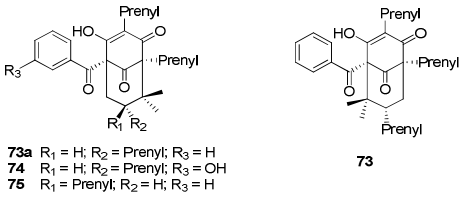


Fig. 5 Basic skeletons of type-C PPBS

Based on our classification rule (Fig. 2), the benzoyl group of type-C PPBS links at C-5 of ring B. However, unlike other types, natural type-C PPBS are rare; as most of them can only be found in synthetic structures.

Nemorosone (**73a**), hydroxy-nemorosone (**74**), and 7-epi-nemorosone (**75**) are type-C PPBS, first reported in some of the floral resins of *Clusia* species.[36,37] However, the structure of nemorosone (**73a**) was corrected to **73** on the basis of methylation and NMR experiments, and both of its keto-enol equilibrium isomers were completely characterized.[33] However, the authors did not mention that two derivative structures of nemorosone, compounds **74** and **75,** need to be corrected. Some of the reports published recently use their type-A structures.[96]



In order to understand why type-C PPBS is rare, we have analyzed the biosynthesis of natural benzophenones. Fig. 6 shows the proposed biosynthetic pathway of several types of benzophenones and related xanthones. L-phenylalanine is the precursor of both phlorbenzophenone (2,4,6-trihydroxy-benzophenone) and naringenin chalcone, and benzophenone synthase (BPS), one of the type III polyketide synthases (PKSs), is a key enzyme in the synthesis of benzophenone metabolism (Fig. 6). It catalyzes the formation of identical linear tetraketide intermediates from one molecule of benzoyl-CoA and three molecules of malonyl-CoA and uses intramolecular cyclization reactions (Diechmann condensation) to provide phlorbenzophenone. After synthesis, these simple BBS undergo either polyprenylation, giving bridged polycyclic compounds (polyprenylated benzophenones), or regioselective cyclization, yielding xanthones.[97]

Types A-D of PPBS are further synthesized from 2,4,6-trihydroxybenxophenone. This compound is converted into the phloroglucinol moiety with the help of an enzyme-catalyzed addition of prenyl (or geranyl) pyrophosphate.[98] Then, the type-D PPBS, which just have two or three prenyls or geranyls in ring B, are obtained (Fig. 6, purple structures). Cuesta-Rubio et al. reported that both type-A and -B PPBS are synthesized from a common precursor.[33] Attack of one of the geminal prenyl groups of this precursor on prenyl pyrophosphate gives the tertiary carbocation (**76**). In this intermediate, attacking C-1 of **76** on the pendant carbocation (or the corresponding pyrophosphate) would provide a type-A PPBS (Fig. 3, red structures), whereas attacking C-5 of **77** would provide a type-B PPBS (Fig. 6, green structures), which was supported by other studies.[65] The 7-prenyl group of type-A PPBS may further repeat this route and attack its C-5 and obtain another adamantyl type-A PPBS configuration (Fig. 6). Compound **77** is a diasteroisomer, as a result, most type-A PPBS have exo-prenyl group and most type-B PPBS have endo 7-prenyl groups.[99]

In contrast, during biosynthesis of type-C PPBS, the precursor requires another phloroglucinol moiety which should have one prenyl or geranyl group at C-1. The pendant carbocation can then attack the C-3 location to obtain type-C PPBS (Fig. 6, blue structures). Severe conditions are necessary to obtain this C-1 quaternary center precursor thus the occurrence of type-C PPBS is rarer than types-A, -B and -D in nature.

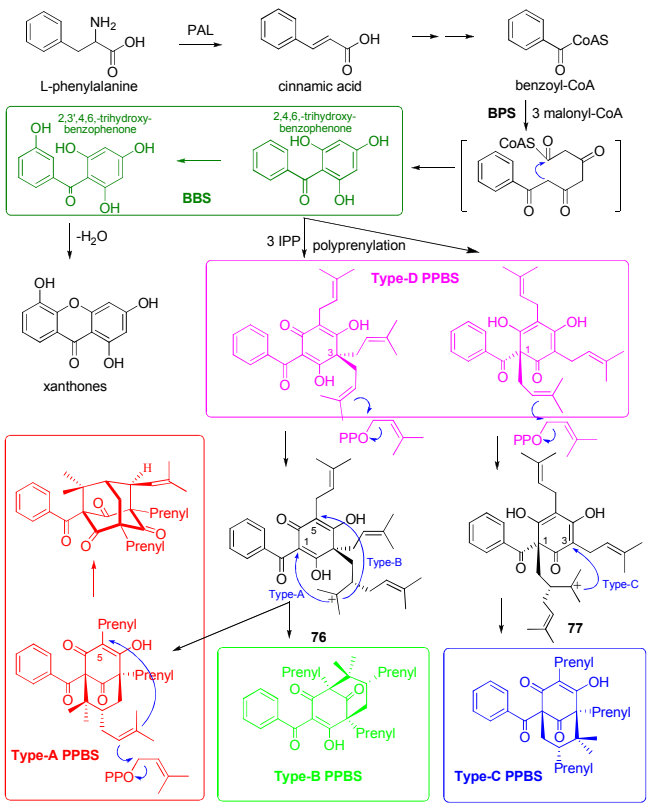


Fig. 6 Biosynthetic pathway of benzophenones.[65,97-99]

2.2.4 Type-D PPBS

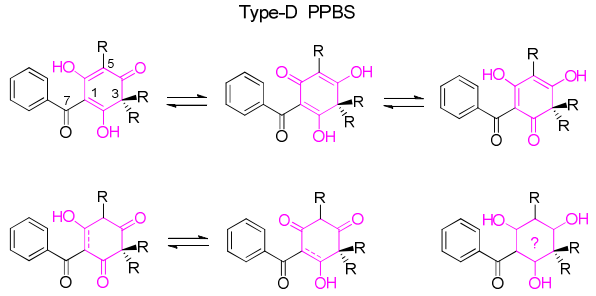
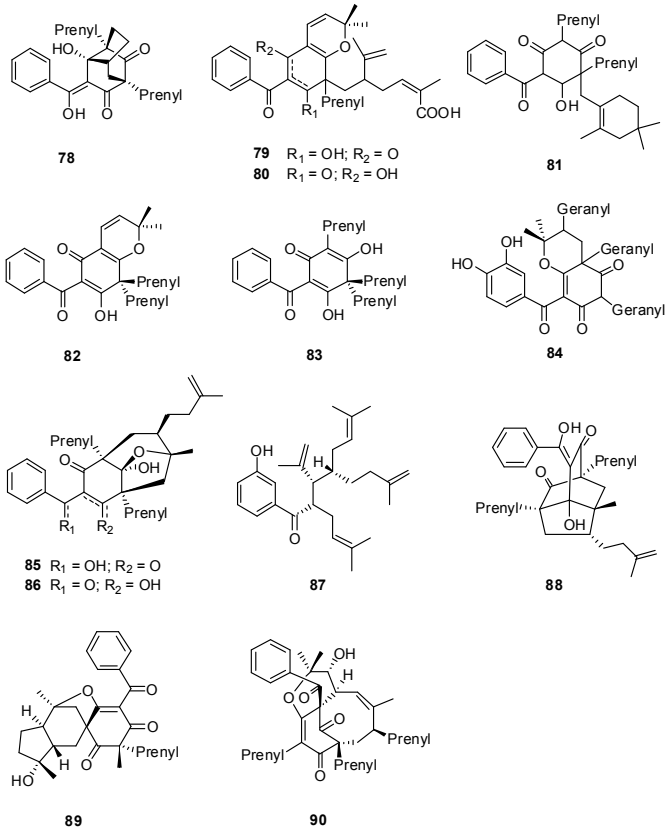


Fig. 7 Basic skeletons of type-D PPBS

Type-D PPBS is another common benzophenone, which we classify as not having an eight-membered ring or with one of their benzene rings saturated by one or two hydroxyl groups (Fig. 2). Also, other unique or rearranged PPBS structures that do not fit into types A, B, or C will be considered type-D (Fig. 7), such as compounds **1**, **78** and **85-90**.

Nemorosonol (**78**), a derivative of tricycle-[4,3,1,0]-decane, was the first PPBS isolated from *Clusia* genus by Delle Monache *et al*.[41] As there is no isopropyl group in the eight-membered ring, it is difficult to arrange into type A, B or C, we classify it as type-D PPBS. Its structure was further confirmed by X-ray crystallography.[42] Nemorosinic acids A (**79**) and B (**80**) was two type-D keto-enolic equilibrium PPBS which have a carboxyl group in their side chains. Hilarianone (**81**) is another typical type-D PPBS which have a hexatomic ring in the side chains; however, its stereo configuration still unclear.



Machuone (**82**), grandone (**83**) and bronianone (**84**) are common type-D PPBS; compound **84** only has geranyl, not prenyl, groups and their stereochemistry is not defined. Xerrophenones A (**85**) and B (**86**), a tautomeric pair of PPBS incorporating a novel oxatricyclic skeleton, were found in *C. portlandiana*.[47] These two compounds also have no isopropyl group in the eight-membered ring. Also, garcinielliptones FA (**87**) has a broken B-benzene ring.[100] Doitunggarcinones A (**1**) and B (**88**) were identified by Tantapakul et al.[8] These two compounds have unusual novel rearranged skeletons.[8] Sampsonol C (**89**), together with its derivatives, were reported as acylphloroglucinols possessing a spiro skeleton with one monoterpene moiety.[101] Hypercohin A (**90**) was reported by Xu's group as a rare type-D PPBS featuring a unique bicycle[5.3.1]hendecane core.[76]

2.3 Structural determination of natural benzophenones

Natural basic benzophenone skeletons are straight forward to identify by combining routine 1D and 2D NMR spectra with high resolution MS for exact mass calculation. However, polyprenylated benzoylphloroglucinol compounds are substituted derivatives with enantiomeric enolized bicycle [3.3.1]-onane-2,4,9-trione cores and have diverse isoprenoid units, such as prenyl, geranyl, or their isomers. The ^{1}H and ^{13}C NMR spectra often show the multiplicity of peaks for structures having a keto-enol equilibrium. In this case, adding 0.1% TFA into the NMR solvent can make the multiplicity disappear and a single set of signals can be observed.[70] In order to make the bicycle [3.3.1]-onane-2,4,9-trione core more stable, some studies were expedited by derivatization with CH_2N_2 to obtain their stable methyl ethers.[33,38] In 2001, the previously announced structure for methyl-nemorosone was corrected on the basis of application of chemical methylation combining with 2D NMR and NOE difference spectroscopy experiments by Cuesta-Rubio et al.[33]

If the ^{1}H and ^{13}C NMR spectra exhibit only one set of signals, that means the absence of a tautomeric equilibrium. In those cases, the hydroxyl group in the keto-enol equilibrium maybe chelated, cyclized, or oxidized. The ^{13}C NMR signals observed in δ_C 193-208 can indicate the presence of one or more nonconjugated or conjugated carbonyls in ring-A.[44] The linkage of the other side chains (e.g. prenyl or geranyl groups) can be resolved after extensive analysis of 2D NMR, such as HMQC and HMBC spectra. MS/MS fragmentation analysis is also used to identify certain benzophenones.[53,94,102,103]

In order to confirm the structures of benzophenones, especially their stereochemistry, X-ray crystallography has frequently been employed.[20,25,27,29,36,56,89,104,105] Recently, some groups have identified the absolute configurations of benzophenones on the basis of electronic circular dichroism (ECD) data using computational methods, such as TDDET-predicted curves, and comparisons with literature data for model compounds[106] or their experimentally measured circular

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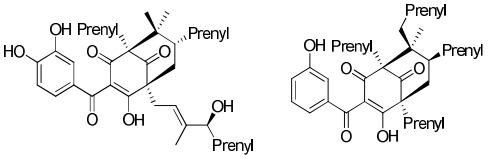
dichroism (CD) curves. [92,107] For example, our group determined the absolute configurations of the new benzophenones, 32-hydroxy-ent-guttiferone M (**91**) and 6-epi-guttiferone J (**92**), by comparison of their experimental optical rotation and ECD measurements with those values predicted by DET calculations.[92] The molecular modeling studies can also help to figure out the low-energy conformers.[108] In addition, detailed analysis of their biogenetic pathways can confirm their proposed structures.[8,20,25,65,67,80,109] For example, Hu et al. analyzed the biogenetic pathways of sampsoniones A-M (**19-31**) and supported these unique and complex family of caged polyprenylated benzoylphloroglucinol derivatives which isolated from *Hypericum*. [79-82]



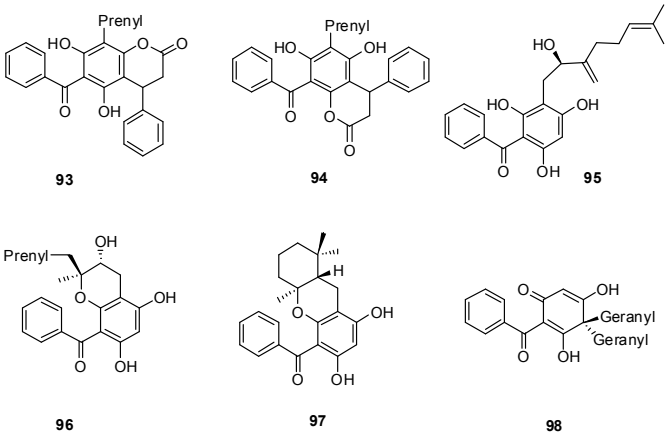
3 Biological activities of natural benzophenones

3.1 Cytotoxic and effects on cancer cells

The effects on cancer cells are the most commonly reported biological activity of benzophenones. Many benzophenones have cytotoxic or anti-tumor effects on human cancer cell lines. The IC_{50} values of most of these compounds are less than 10 μM or μg/mL, such as xanthochymol (**49**), with 0.475 and 0.62 μM against MCF-7 and Colo-320-DM cell lines and isoxanthochymol (**50**), with 2.85 and 4.85 μM against the same cell lines.[110] Guttiferones A (**5**) and G (**53**), have activity at 6.8 and 8.0 μg/mL against A2780 human ovarian cell line.[62] Vismiaguianones D (**93**) and E (**94**) were found to be significantly cytotoxic with IC_{50} at 2.4 and 3.3 μg/mL against KB cell lines.[105] Compounds **95-97** demonstrated cytotoxic activities against MCF-7, SF-268 and H-460 cell lines (IC_{50}s: 1.7-7.8 μg/mL).[108] Also, moronone (**98**), a common type-D PPBS isolated from *Moronobea coccinea*, has strong antiproliferative activity against human breast tumor MDA-MB-231 and T47D cells.[9]

Although many publications report the cyctotoxic or antiproliferative activity of benzophenones, a literature search only shows a few articles concerning their mechanism of action. In our earlier study, we have examined parallel molecular pathways that are targeted by xanthochymol (**49**), guttiferones E (**54**) and H (**59**) in three human colon cancer cell lines (HCT116, HT29, and SW480).[111] The result showed that these benzophenones inhibit the growth of cancer cells by activating the endoplasmic reticulum stress response and inhibiting the mTOR cell survival pathway (Fig. 8).[111]

In 2012, 7-epi-nemorosone (**75**) was reported to exhibit cytotoxicity in both androgen-dependent and independent



prostate carcinoma LNCaP cell lines with IC_{50} values between 4 and 7.5 μM.[96] The cell cycle analysis obtained from FACS showed a significant increase in the sub-G0/G1, G1 count, and depletion in the S phase populations. The Western blot detected a concomitant down-regulation of cyclins D1/D3 and CDK 4/6 in LNCaP cells. Its apoptotic effect was confirmed by Annexin-V-FITC labeling and caspase-3 cleavage assays.[96] Major signal transduction elements, such as p38 MAPK and Akt/PKB as well as androgen receptor AR and PSA production were found to be down-regulated after exposure to this compound. The EPK1/2 protein levels and phosphorylation status were also reported. Finally, the authors demonstrate that 7-epi-nemorosone exerts cytotoxicity activity by targeting the MEK1/2 signal transducer.[96]

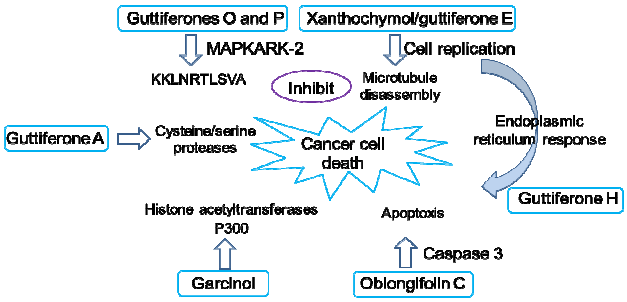


Fig. 8 Several specific actions of PPBS toward cancer cells.[96,111,112]

Moronone (**98**) is another benzophenone with reported mechanistic studies on its antitumor actvitiy.[9] Compound **98** exhibited enhanced antiproliferative activity in the presence of rotenone-imposed metabolic stress on tumor cells. However, this compound did not inhibit glycolysis, but rather functions as a protonophore that dissipates the mitochondrial proton gradient. Tumor cells may be hypersensitive to protonophores due to increased ATP utilization by ATP synthase in the presence of rotenone.[9] In addition, guttiferone A (**5**) was reported to produce genotoxic effects in leukocytes, liver, bone marrow, brain and testicle cells and clastogenic/aneugenic effects in bone marrow erythrocytes of mice.[113]

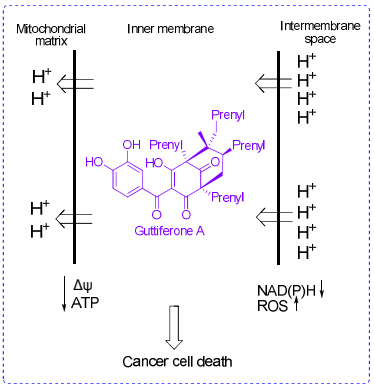


Fig. 9 Mechanism proposed to guttiferone A (**5**) on mitochondria.[112]

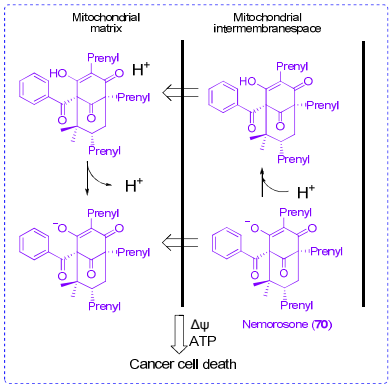


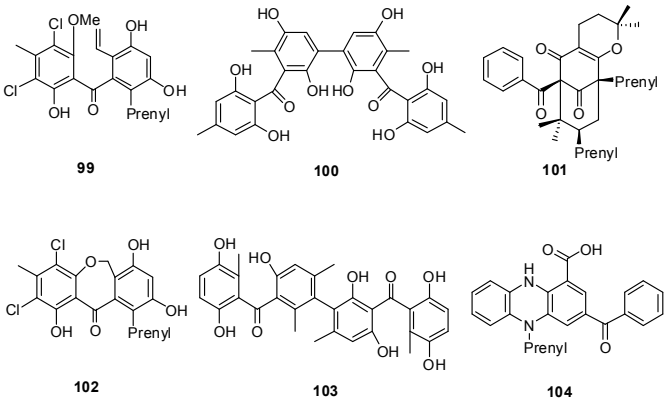
Fig. 10 Mechanism proposed to nemorosone (**74**) on mitochondria isolated from rat liver.[114]

Guttiferone (**5**) has potential as an anti-cancer agent. In HepG2 cells this compound decreased cell viability, dissipated mitochondrial membrane potential, depleted ATP and increased reactive oxygen species (ROS) levels (Fig. 9).[112] Nemorosone (**74**) was also reported to have similar mitochondrial membrane potential-dissipating and ATP-depleting activity on cancer cells, which could make it a new potent protonophoric mitochondrial uncoupler. Its mechanism is shown in Fig. 10.[114] As for other guttiferone E (**54**), it was reported to inhibit microtubule disassembly with implications in cell replication.[115] Recently, garcinol (**51**) together with its related compounds were reported to have inhibitory effects on cytokine signalling pathways.[54]

3.2 Antibacterial, antimicrobial and antifungal activity

Most benzophenones have been reported from higher plants, but those found in fungi, plant endophytes, microorganisms, and propolis, have shown significant antibacterial, antimicrobial, and antifungal activity against a range of organisms, e.g. Gram positive/negative bacteria and yeasts,[31] such as conidial germination,[104] human bacterial pathogen,[116] honeybee pathogens.[38]

Xanthochymol (**49**) displayed a low inhibitory concentration at 3.1-12.5 μg/mL against methicillin-resistant



Staphylococcus aureus (MRSA).[70] This concentration is nearly equal to that of vancomycin, a known antibiotic which is currently used to treat MRSA infections.[70] Pestalone (**99**), isolated from a cultured marine fungus, has two chlorine atoms in its molecule.[30] This compound was also found to show potent antibiotic activity against methicillin-resistant *Staphylococcus aureus* (MIC: 37 ng/mL) and vancomycin-resistant *Enterococcus faecium* (MIC: 78 ng/mL). The strong potency of this compound toward drug-resistant pathogens suggests that pestalone (**99**) should be evaluated in more advanced, whole animal models of infectious disease.[30]

Similarly, chamones I (**38**) and II (**39**) showed potent antibacterial activity against honeybee pathogens.[38] Guignasulfide (**2**) has inhibitory effects on human bacterial pathogens.[116] Two rearranged benzophenones, doitunggarcinones A (**1**) and B (**88**),[8] and two novel benzophenone dimers, microphaerins A (**100**) and D (**7**),[25] as well as propolone A (**101**)[31] also have antibacterial effects on Gram-positive/negative bacteria or yeasts. In addition, peroxysampsone (**5**) and 7-epi-clusianone were found to show inhibitory effects against NorA overexpressing MDR *S. aureus* strain SA-1199B.[84,85]

As for the other antifungal activities, pestalachloride B (**102**) displayed significant antifungal effects against *Gibberella zeae*.[27] Phomalevone B (**103**) exhibited antifungal effects on some fungal strains.[106] Also, another benzophenone alkaloid, chromophenazine D (**104**), showed moderate activity against *B. subtilis*, *E. coli*, and *M. mieher*.[117]

It is noteworthy that most of the antibacterial or antifungal benzophenones identified thus far are dimers, such as guignasulfide (**2**),[116] phomalevone B (**103**),[106] microphaerins A (**100**) and D (**7**),[25] or derivatives with a chlorine atom, such as pestalachloride B (**102**)[27] and pestalone (**99**).[30]

3.3 Antioxidant activity

Our group has studied the antioxidant activity of benzophenones since 2005.[75,92] In 2005, we found two new benzophenones, guttiferone H (**54**) and gambogenone (**60**), that had antioxidant activity at 64 and 38.7 μM in DPPH assay.[75] Also, the known compounds, xanthochymol (**49**), isoxanthochymol (**50**), guttiferone E (**54**), cycloxanthochymol

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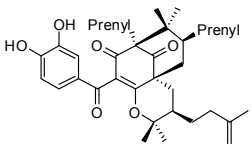

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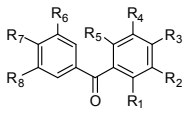
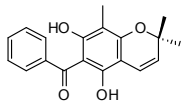


106 $R_1 = OCH_3$; $R_2 = R_8 = H$; $R_3 = R_5 = R_6 = R_7 = OH$
107 $R_1 = R_5 = R_6 = R_8 = OH$; $R_2 = R_3 = R_4 = R_7 = H$
108 $R_1 = R_5 = R_7 = H$; $R_2 = R_3 = R_4 = R_6 = R_8 = OH$
109 $R_1 = R_5 = R_7 = H$; $R_2 = R_4 = R_6 = R_8 = OH$; $R_3 = OMe$



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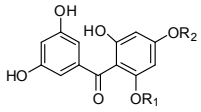


111 R_1 = OXyl; R_2 = H
112 R_1 = 4-OAc-Xyl; R_2 = H

(**105**), and aristophenones A (**55**) and B (**56**) displayed activity in the range of IC_{50} = 73-125 μM in the same assay.[75] In 2010, we reported that one new benzophenone, 32-hydroxy-ent-guttiferone M (**91**) showed DPPH and ABTS radical scavenging activity at 38 and 46 μM. In addition, the known compound, guttiferone A (**5**), had IC_{50} at 31 and 13 μM, respectively.[92]

Similarly, garcinol (**51**) was found to show nearly 3 times greater DPPH antioxidant activity than DL-α-tocopherol.[118] In addition, garcinol (**51**) and isogarcinol (**52**) were reported to show 10 and 13 μM in the DPPH assay by Itoigawa et al.[50] In this study, the relative free-radical-scavenging activity of garcinol (**51**) was 2 times stronger than that of positive control vitamin E (IC_{50}, 23 μM). 4, 6, 3', 4'-Tetrahydroxy-2-methoxybenzophenone (**106**) was also found to exhibit antioxidant activity (IC_{50} = 7.8 μM) in the same assay by Fukuyama and his co-authors.[119]

The antioxidant activities of benzophenones were also reported using other assays, such as on human low-density lipoprotein oxidation,[120,121] total antioxidant capacity through the TRAP measurement,[122] and toward the production of reactive oxygen species (ROS) by human polymorphoneutrophils (PMNs).[102] Jantan et al. reported that 2,6,3',5'-tetrahydroxybenzophenone (**107**), 3,4,5,3',5'-pentahydroxy benzophenone (**108**), and 3,5,3',5'-tetrahydroxy-4-methoxy benzophenone (**109**) showed activity at 3.63-6.63 μM on human low-density lipoprotein (LDL) oxidation assay, which was measured quantitatively by the TBARS method based on malondialdehyde (MDA) production.[121] Also, cariphenone A (**110**) was found to be active at 1.6 and 3.2 mM in total antioxidant capacity through a total radical-trapping parameter assay. This compound exhibited inhibition of chemiluminescence similar to that of quercetin at the same concentration and this data was 10-20 times lower than that of Trolox.[122]

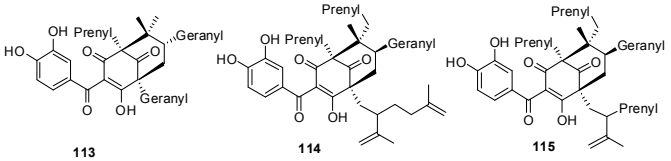
In 2009, lucigenin- and luminal-based chemiluminescence assays were employed to monitor the inhibitory activity of 3',4,5',6-tetrahydroxy-2-*O*-β-D-xylosylbenzophenone (**111**) and its derivative (**112**) towards the production of reactive oxygen species (ROS) by human polymorphoneutrophils (PMNs), and compounds **111** and **112** were extracellular inhibitors of ROS production with IC_{50} at 18.5 to 37.4 μg/mL.[102]

As for the antioxidant mechanism, Ho and his group first reported the mechanism of garcinol (**51**) in 2001 and first provided the proof that the principal sites of antioxidant reactions are on the 1,3-diketone and the phenolic ring part of 166.[123]

3.4 Anti-viral activity

The plant family Clusiaceae has been proven to be a valuable source of leads of human immunodeficiency virus (HIV)-inhibitory natural products since 1992.[35,61,124] In 1992, guttiferones A-E (**5**, **113**-**115**, and **54**) were found to inhibit the cytopathic effects of HIV infection in human lymphoblastoid CEM-SS cells *in vitro*, with EC_{50} values of l-10 μg/mL, however, cytotoxicity occurred at concentrations greater than 50 μg/mL.[61] In 1999, guttiferone F (**116**) was reported to exhibited partial (not achieving 100%) cytoprotection against HIV-1 *in vitro* (EC_{50} = 23 μg/mL), as well as direct cytotoxicity (IC_{50} of 82 μg/mL) to the host cells.[35] Similarly, vismiaphenone D (**59**), isolated from the leaves of *Vismia cayennensis*, was found to exhibit HIV-inhibitory activity (EC_{50} ca. 11 μg/mL).[124] In 2003, a new digeranylbenzophenone, garciosaphenone A (**117**), was also reported to be active in an HIV-1 reverse transcriptase (RT) assay (IC_{50}: 23.9 μg/mL), but toxic in the syncytium test. This data showed garciosaphenone A to be 7-13 times less sensitive than nevirapine.[125] Overall, most of the guttiferone benzophenones show anti-HIV activity; however, their cytotoxicity remains the largest barrier to further development into anti-HIV agents.

In 2010, (2,4,dihydroxy-3,3'-dimethoxy-benzophenone (**118**) was found to show selective inhibitory activity against herpes simplex virus type 1 (HSV-1) proliferation with an IC_{50} of 4 μg/mL and a protection index (PI) of 16 (i.e., 16-fold more activity towards HSV-1 with respect to toxicity towards Hela cells). However, it showed no anti-cytopathic activity on poliovirus Sabin 1 (1S) infection *in vitro*.[17]



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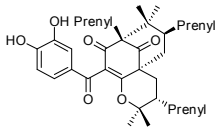

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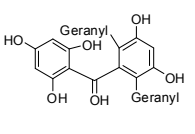

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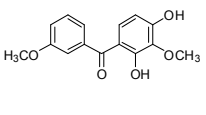

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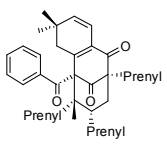

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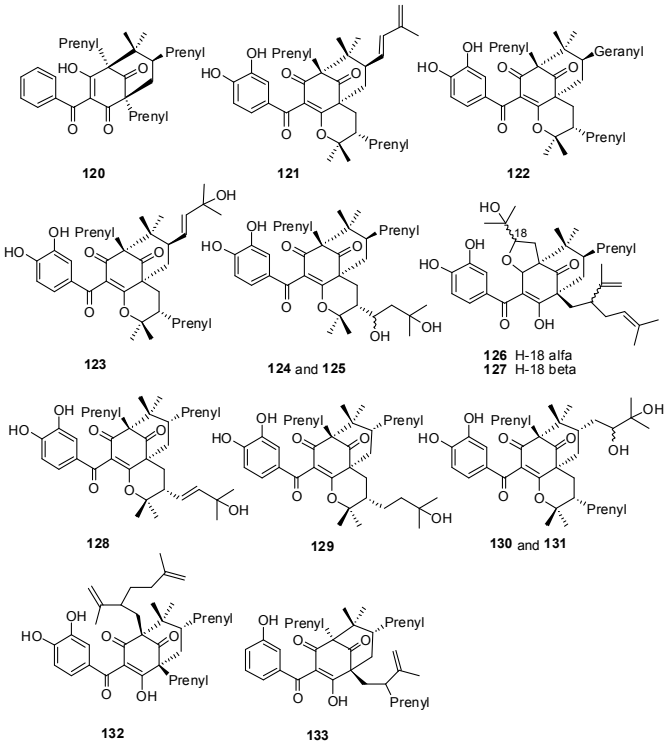
Hypersampsones D-F (**32**, **33**, and **119**), which isolated from an *Hypericum* species used in the folk herbal medicines of Taiwan, were found to show mild inhibition of hepatitis B virus (HBV) antigen (HBeAg secretion at 10 μg/mL on MS-G2 hepatoma cell line, but no inhibition of viral particle replication.[83]

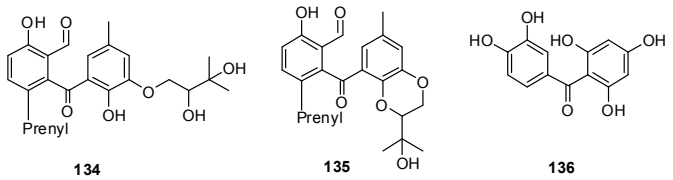
As for anti- EBV-EA activity, clusianone (**4**), garcinol (**51**), isogarcinol (**52**), garcinol 13-*O*-methyl ether (**57**) and isogarcinol 13-*O*-methyl ether (**58**) were found to inhibit the Epstein-Barr virus early antigen (EBV-EA) activation induced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) in Raji cells.[50] These compounds have a detectable inhibition on EBV-EA activation at a concentration of greater than 1×10^2 mol ratio/TPA (11.0-15.1%) and a strong effect (80.3-85.6%) at a higher concentration 1×10^3 mol ratio/TPA) without causing a decrease in viability of the Raji cells. Among these compounds, garcinol (**51**) was found to show the strongest activity.[50]

3.5 Antiparasitic activity

In 2004, guttiferone A (**5**) was reported to show trypanocidal activity against epimastigotes and trypomastigotes of *Trypanosoma cruzi* by Abe's group, with MC_{100}=100 and 83 μM, respectively. This data was more potent than the positive control gossypol (MC_{100} : 540 and 96 μM).[126] Similarly, 7-epi-clusianone (**120**) also reported to be active *in vitro* against trypomastigotes of *T. cruzi*, with an LC_{50} at 518 μM. However, it was inactive *in vivo* in experimentally infected mice.[127]

As for leishmanicidal activity, guttiferone A (**5**) and 7-epi-clusianone (**120**) were reported to show significant activity on





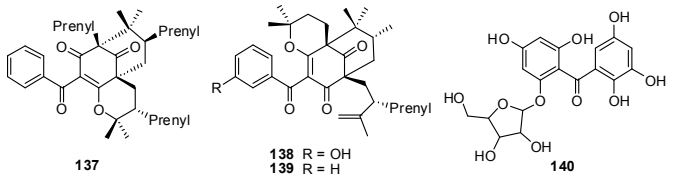
Leishmania amazonensis with IC_{50} values from 1.69 to 19.13 μg/mL, with little toxicity for mammalian cells.[128] Symphonones A-G (**121**-**127**) and its derivatives were found to exhibit significant antiplasmodial activities on a chloroquine-resistant strain of *Plasmodium falciparum* (FcB1) strain with IC_{50} values ranging from 2.1 to 10.1 μM.[94] Coccinones A-H (**67**, **128**-**131**, **68**, **132** and **69)** and 14-deoxygarcinol (**133**) also found to exhibit the same antiplasmodial activities on EcB1 strain (IC_{50} values ranging from 3.3 μM to 37.2 μM).[89]

In 2005, Singh et al. reported that tenellones A (**134**) and B (**135**) could inhibit parasite cGMP-dependent protein kinase (PKG), which has been validated as a biochemical target for the treatment of coccidiosis, malaria, and toxoplasmosis.[26] Both tenellones A (**134**) and B (**135**) have ability to inhibit *Eimeria tenella* cGMP-dependent protein kinase (EtPKG) with IC_{50} values of 12.6 and 8.7 μM using a radiometric assay. Tenellone A (**134**) also inhibits the related apicomplexan parasite *T. gondii* (TgWC) with IC_{50} at 1.8 μM using β-galactosidase whole cell reporter assay.[26] In addition, maclurin (**136**) was found to show toxicity in the brine shrimp lethality test (ED_{50}: 7.7 μM).[119]

3.6 Anti-inflammatory and antianaphylactic activity

13,14-Didehydoxyisogarcinol (**137**), 13-hydroxy-garcimultiflorone B (**138**), and garcimultiflorones A (**47**) and B (**139**) were reported to exhibit inhibition with an IC_{50} range of 0.11-5.58 μM on superoxide anion generation and elastase release by human neutrophils in response to fMet-Leu-Phe/cytochalasin B (fMLP/CB), which indicated these compounds have the anti-inflammatory activities.[63] Also, sampsonol C (**89**) was found to show potent inhibitory effects against LPS-induced NO production in RAW 264.7 macrophages.[101]

Also, polymorphonuclear neutrophils (PMNs) are important cells involved in the bacterial host defense system through the respiratory burst and play a critical role in immune-inflammatory processes. Yu's group in 2009 found that aquilarinoside (**140**), a rare benzophenone mono-glycoside, showed inhibition activity with IC_{50} at 89.92 μM against PMNs respiratory burst stimulated by PMA, indicating this compound also has anti-inflammatory activity.[129] In 2007, Martins and his



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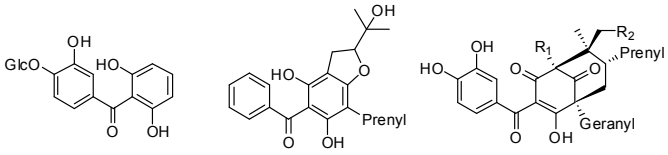
co-workers first reported that 7-epi-clusianone (**120**) inhibited antigen-induced contractions of guinea pig ileum with IC_{50} values at 2.3 ± 1.1 μM. This data reveal that 7-epi-clusianone (**120**) is clearly active against the anaphylactic response and could be considered as a molecular template in drug discovery for allergic syndromes.[130]

3.7 Transcriptional regulation



Retinoid X receptors (RXR) are ligand-controlled transcriptional factors which are members of the nuclear receptor superfamily, and they play an important role in many diverse physiologic processes, such as embryogenesis, calcium homeostasis, and lipid and glucose metabolism. Prunifloroside C (**141**) was found to affect the transcriptional activity of RXRα (IC_{50}: 10 μM) (Fig. 11).[131] Also, liver X receptors (LXR) have been implicated in cholesterol homeostasis. Agonists of LXR are expected to increase efflux, lower LDL, and raise HDL levels. Guttiferone I' (**71**), isolated from *G. humilis*, was found to inhibit the binding activity to the LXR α-receptor with an IC_{50} at 3.4 μM in LXRα-SPA binding assay (Fig. 11). It was less effective against β-receptor binding and exhibited at least 5-fold selectivity.[59] Vismiaguianone B (**142**) was reported to exhibit DNA strand-scission activity (43 ± 12 % nicked at 2.5 μg/mL).[132] Guttiferones O (**143**) and P (**144**) also inhibited the phosphorylation of the synthetic biotinylated peptide substrate KKLNRTLSVA by the serine/threonine protein kinase MAPKAPK-2 with IC_{50} values at 22 μM.[69] This kinase is important in the regulation of cellular activities such as gene expression, mitosis, differentiation, and cell survival/apoptosis, and these two benzophenones could be beneficial in treating inflammatory diseases and cancer.[69]

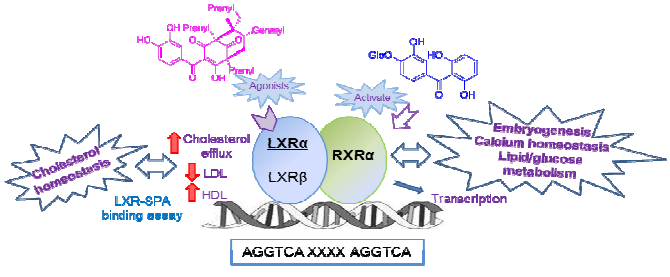


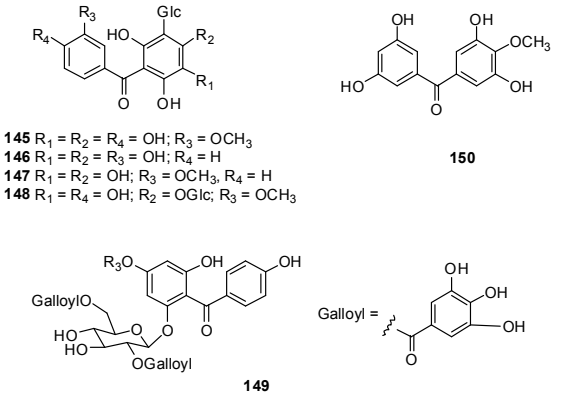
Fig. 11 Mechanism of transcriptional regulation mediated by LXR and RXR receptors. [59,131,133]

3.8 Hepatoprotective, anti-diabetic, and vascular effects

Four benzophenone C-glucosides, glomeratides A-D (**145-147**), which isolated from Polygalaceae, were reported to show hepatoprotective activities against D-galactosamine-induced toxicity in WB-F344 rat hepatic epithelial stem-like cells.[18] In the inhibitory assay against α-glucosidase type IV from *Bacillus stearothermophilus*, iriflophenone 2-*O*-(2,6,di-*O*-galloyl)-β-D-glucopyranoside (**149**) showed significant inhibition (91.4% and 15.0% at 100 and 10 μg/mL, resp.), indicating this compound can reduce the release of glucose from dietary carbohydrates and improve glycemic control.[134] The vascular effects of 7-epiclusianone (**120**) on the rat aorta was also investigated by Cortes et al. They concluded that this compound induced an endothelium-dependent vasodilator effect in rat aortic ring at low concentrations, but induced a vasocontractile effect at higher concentrations.[135] 3,5,3',5'-Tetrahydroxy-4-methoxy benzophenone (**150**) also exhibited strong inhibitory activity against platelet aggregation induced by arachidonic acid, adenosine diphosphate, and collagen (IC_{50}: 53.6 μM).[121]

4 Structure-activity relationship studies

The benzoyl group in the phloroglucinol skeleton plays a crucial role in their cytotoxic effects on cancer cell lines.[34] In 2003, Itoigawa et al. reported that the BBS with one or more directly bonded prenyl side chain to the aromatic nucleus have stronger inhibitory effects on TPA-induced EBV-EA activation than the one with a cyclized polyprenyl-benzophenone



nucleus.[50] Recently, Zhang et al. reported that some BBS with saturated hydrocarbon lateral chains, phenethyl derivatives or with OMe in their structures showed good inhibition on stomach and prostate cancer cell lines.[136] Also, galloyl residues and phenolic functions were found to provide better inhibitory activities against α-glucosidase type IV from *Bacillus stearothermophilus*, indicating these groups are important for their anti-diabetes activity (Fig. 12).[134]

As for antioxidant activity, Jantan et al. reported that the hydroxylation pattern on the phenyl rings was an important

structural feature for their antioxidant activity, with greater numbers of hydroxyl groups resulting in more antioxidant activity.[121] In addition, the dihydroxyl groups in ring B were able to give stability to the radical form which is important for their antioxidant activity.[121] The methoxy group at C-4 of ring A appeared to contribute significantly to the antiplatelet activity.[121]

In 2000, Sévenet's group studied the structure-activity relationship of PPBS. They found that etherification of the enol by methylation or cyclization, or oxidation or methylation of C-13 and C-14 hydroxyls caused the activities on tubulin of PPBS to be lost. However, some activity is preserved if only one of the hydroxyl groups at C-13 or C-14 is methylated, ethylated, or glycosylated.[115] In addition, not only the catechol and enol portions of the molecule, but also the lipophilic domain having the unsaturated prenyl chains are crucial for their activity on tubulin and microtubules.[115] Pereira reported that the leishmanicidal activity had a positive correlation with the number of prenyl groups, in other words, proportionally to lipophylicity (Fig. 12).[128] Recently, the existence of prenyl groups were also reported to contribute to the cytotoxic activity of PPBS.[66]

As for antibacterial activity, Iinuma et al. reported that a chelated hydroxyl group is involved in the inhibitory activity of type-B PPBS.[70] However, Lokvam et al. suggested that the presence of an enol functionality is necessary for antibacterial activity in type-A PPBS.[38]

The presence of phenolic and enolic functions and the numbers and saturation of prenyl groups play a crucial role in the activities of BBS and PPBS. In addition, some important benzophenone skeletons have special activity, such as guttiferones have strong anti-HIV activity,[35,61] symphonones and coccinones have antiplasmodial activity[89,94] and some BBS

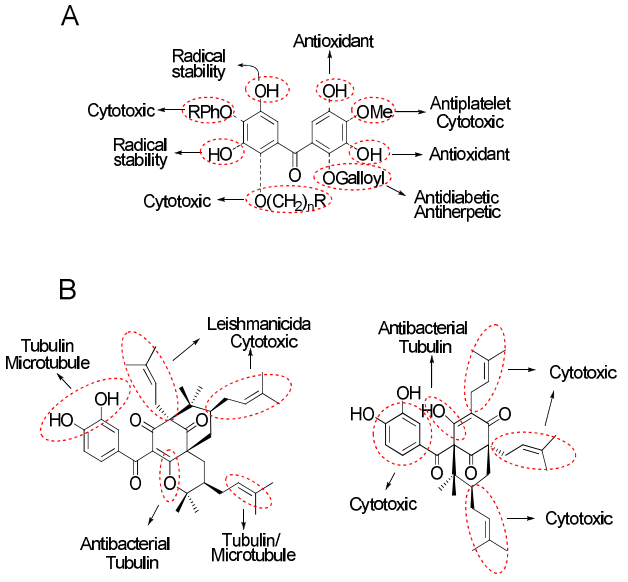


Fig. 12 Structure-activity relationships of benzophenones. **A**: BBS; **B**: PPBS. [66,70,115,121,128,134,136]

dimers have potent antibacterial or antifungal effects (Fig. 13).[25,106] These SAR discoveries can assist medicinal chemists to optimize benzophenone drugs.

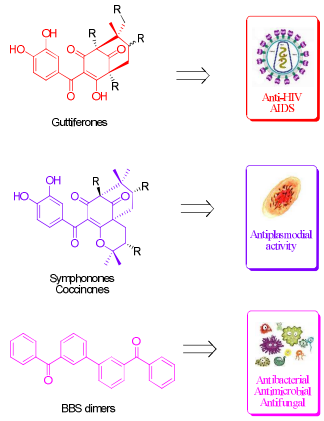


Fig. 13 Some key benzophenone skeletons with specific activity

5 Conclusions

This review summarizes the selected natural benzophenones which were reported from Clusiaceae and other plant families or fungi in the latest 15 years, but extends the scope to other historically important compounds discovered prior to that time. The information includes their structural diversity, biological activities and SAR discussion. These compounds have diverse pharmacological and they can be synthetically modified to produce new active molecules for future anticancer drugs and treatments for other diseases.[4] This review is a comprehensive reference in the fields of natural products chemistry, synthetic chemistry, pharmacology, food chemistry, and agricultural science.

Although there are many publications concerning new benzophenones and their various biological activities, most of the activities have been demonstrated *in vitro*, and lack significant animal or clinical data. Benzophenones are found in a number of edible and/or medicinal plant species, so more information about their effects in humans is warranted. Although some of the antitumor and apoptosis-inducing mechanisms of benzophenones *in vitro* have been reported, the molecular targets and mechanisms of action of other bioactivities are unknown and more studies need to be carried out. At this time, only a few bioactive benzophenones have been totally synthesized, and there is a need to develop more benzophenone synthesis strategies to obtain enough material for *in vivo* testing. In addition, SAR studies of benzophenones are scarce.[115] Further efforts to understand the function of each moiety and its relationship to the specific bioactivities of these complex and fascinating compounds are needed.

6 Acknowledgements

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