Stilbenoids

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Contents

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K.G. Ramawat, J.M. Mérillon (eds.), *Natural Products*,
DOI 10.1007/978-3-642-22144-6_63,

Abstract

Stilbenoids are a class of plant phenolics containing C6–C2–C6 unit in their structures and classified into five groups, covering stilbenes, oligostilbenes, bibenzyls, bisbibenzyls, and phenanthrenes. They have been a hot research topic for their intricate structures and diverse biological activities. Resveratrol and combretastatin A-4 are the star compounds due to their potent cardioprotective, chemopreventive, and antitumor properties and have the potential to be developed as new drugs. The stilbenoids do not enjoy a wide distribution and are only found in special genus. Although the constituent unit is simple, the structures of stilbenoids highlight the chemical diversity by different substitutes and various oligomeric styles. In a biogenesis viewpoint, they are formed by a branch of the flavonoid biosynthetic pathway. This chapter provides a summary of the occurrence, phytochemisty, biosynthesis, and biological aspects of the stilbenoids.

Keywords

Bibenzyls • bioactivities • biosynthesis • bisbibenzyls • occurrence • oligostilbenes • phenanthrenes • phytochemistry • stilbenes • stilbenoids

1 Introduction

The term "stilbenoids" was proposed by Gorham in 1980 [1, 2], which refers to a class of plant phenolics with 1,2-diphenylethylene or 1,2-diphenylethane nucleus in their structures. Stilbenoids are regarded as plant phytoalexins and have been a hot research topic for their intricate structures and diverse biological activities. The phytochemical research concerning the stilbenoids developed quickly in recent years. More than 1,000 compounds belonging to this group have been discovered, compared with just over 100 listed in 1980 and about 300 in 1995 [2]. Recent advances in analytical and spectroscopic techniques, especially the NMR methods, speed up the discovery and elucidation of the intricate structures of stilbenoids. The intricate structures and stereochemistry of oligostilbenes and bisbibenzyls were established based on the modern techniques. Furthermore, these compounds demonstrated diverse biological activities, including antitumor, antimicrobial, antioxidant effects, antiplatelet aggregation, phytotoxicity, etc. These bioactive compounds and their derivatives are of great interest for drug research and development as a result of their potential in therapeutic or preventive applications, exemplified by resveratrol and combretastatin A-4. In this chapter, we will give an overview of structural features, occurrence, phytochemical aspects, biosynthesis, and biological activities of the stilbenoids.

2 Phytochemical Aspects

According to their structural characteristics, stilbenoids are mainly divided into five categories, stilbenes, oligostilbenes, bibenzyls, bisbibenzyls, and phenanthrenes.

In the section of phytochemical aspects, the structural characteristic, distribution, typical representatives, and their structures of each group are introduced.

2.1 Stilbenes

Stilbenes possess a skeleton with two aromatic rings joined by a methylene bridge. The simple stilbene nucleus is generally substituted by different groups of hydroxyl, methyl, methoxy, prenyl, geranyl, etc., and combined with sugars to form glycosides. The double bonds in naturally occurring stilbenes are usually *E*-configuration, but stilbenes with *Z*-configuration are also observed. The compounds of this group highlight the chemical structural diversity through the modification of above styles on the nucleus. About 125 new stilbenes have been discovered between the year of 1995 and 2008 [3]. They mainly occur in the families of Aceraceae, Anchinoidae, Asteraceae, Bombycidae, Burseraceae, Combretaceae, Cyperaceae, Dipterocarpaceae, Euphorbiaceae, Gnetaceae, Hepaticae, Iridaceae, Leguminosae, Lejeuneaceae, Liliaceae, Meliaceae, Moraceae, Ophioglossaceae, Orchidaceae, Polygonaceae, Rosaceae, Stemonaceae, Vitaceae, and Zingiberaceae.

Resveratrol **1** is the most famous representative of this group and occurs in *Polygonum cuspidatum* root and *Vitis* species. It is a phytotoxin produced by several plants in response to infection or other stresses and attracted attention for its cardioprotective effect in red wine. In addition, it is the most important unit for the construction of oligomeric stilbenes.

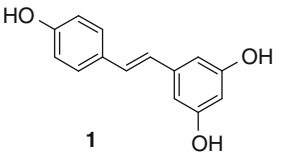
Combretastatins, a series of bioactive stilbenes (combretastatin A series), bibenzyls (B series), phenanthrenes (C series), and macrocyclic lactone (D series), were obtained from the African willow tree *Combretum caffrum* (Combretaceae). Among them, the A series of combretastatins belonging to stilbenes, including combretastatins A-1 to A-6 **2**–**7**, are found to be tubulin polymerization inhibitors.

Typical stilbenes substituted with hydroxyls, methyl, methoxy, menthane groups, and their origin were listed as follows. *Trans*-4-[2-(3,5-dimethoxyphenyl) ethenyl]-1,2-benzenediol **8** was isolated from *Sphaerophysa salsula* (Leguminosae) [4]. Thunalbene **9** was obtained from *Thunia alba* (Orchidaceae), and the structure was designated as 3,3′-dihydroxy-5-methoxystilbene [5]. The *Phragmipedium* species produced three new stilbenes including 2,3′-dihydroxy-5′-methoxystilbene **10**, 2,3-dihydroxy-3′,5′-dimethoxystilbene **11**, and 2,3′-dihydroxy-5,5′-dimethoxystilbene **12** [6]. Phoyunbenes A-D **13**–**16** were found in *Pholidota yunnanensis* (Orchidaceae) [7]. 5,4′-Dihydroxy-3-methoxystilbene **17**, 3,5-dihydroxy-4′-methoxystilbene **18**, and (*E*)-3,3′-dimethoxy-4,4′-dihydroxystilbene **19** were isolated from *Rumex bucephalophorus* and *Leuzea carthamoides* [8, 9], respectively. Two *Z*-type stilbenes named (*Z*)-3-methoxy-5-hydroxystilbene **20** and (*Z*)-3,5-dihydroxystilbene **21**, together with a menthane-substituted stilbene (*E*)-1-(1-terpinen-4-olyl)-3-methoxystilbene **22**, were obtained from aerial parts of *Alpinia katsumadai* (Zingiberaceae) [10, 11].

There are two stilbene representatives isolated from special origins. Bryophytes are characterized by the production of bisbibenzyls, and no stilbene has been

obtained before the isolation of 3,4-dihydroxy-3′-methoxystilbene **23** from *Marchesina bongardiana* (Lejeuneaceae) [12]. *Kirkpatrickia variolosa*, a kind of Antarctic red sponge of Anchinoidae family, yielded a triacetate derivative 3,4,5-triacetoxystilbene **24** which was the only marine natural stilbene [13].

Two stilbene glycosides, named (*E*)-3,4′-dimethoxyl-5-rutinosyl stilbene **25** and 3,5-dimethoxy-4′-*O*-(β-rhamnopyranosyl-(1→6)-β-glucopyranoside)stilbene **26**, were isolated from *Guibourtia tessmanii* (Leguminosae) [14, 15]. *Acer mono* (Aceraceae), a Korean folk medicine for hemostasis, produced two new stilbene glycosides 5-*O*-methyl-(*E*)-resveratrol 3-*O*-β-D-glucopyranoside **27** and 5-*O*-methyl-(*E*)-resveratrol 3-*O*-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside **28** [16].



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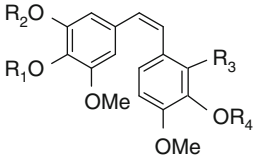
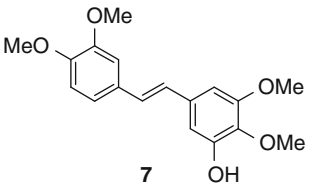


2 R_1=R_2=Me, R_3=OH, R_4=H
3 R_1,R_2= –CH_2–, R_3=R_4=H
4 R_1=Me, R_2=R_3=R_4=H
5 R_1=R_2=Me, R_3=R_4=H
6 R_1=R_4=Me, R_2=R_3=H



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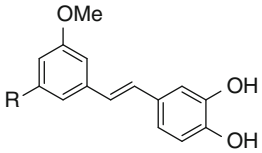
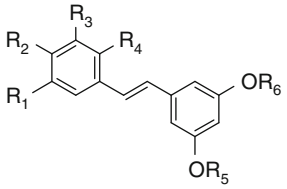
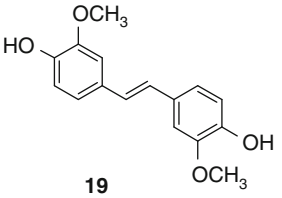


8 R=OMe
23 R=H



9 R_1=R_2=R_4=R_5=H, R_3=OH,R_6=Me
10 R_1=R_2=R_3=R_5=H, R_4=OH,R_6=Me
11 R_1=R_2=H, R_3=R_4=OH, R_5=Me,R_6=Me
12 R_1=OMe, R_2=R_3=H, R_4=OH, R_5=H,R_6=Me
13 R_1=R_2=R_4=OMe,R_3=OH,R_5=H,R_6=Me
14 R_1=R_5=H,R_2=OH,R_3=OMe,R_4=OMe,R_6=Me
15 R_1=R_2=R_5=H,R_3=OH,R_4=OMe,R_6=Me
16 R_1=R_2=R_5=H,R_3=OMe,R_4=OMe,R_6=Me
17 R_1=R_3=R_4=H,R_2=OH,R_5=H,R_6=Me
18 R_1=R_3=R_4=H,R_2=OMe,R_5=R_6=H



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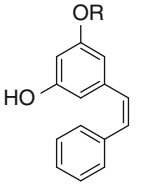
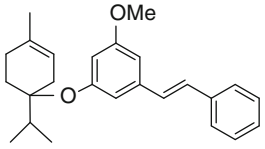


20 R=Me
21 R=H



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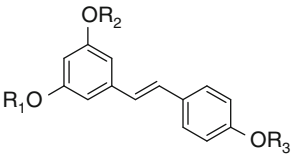
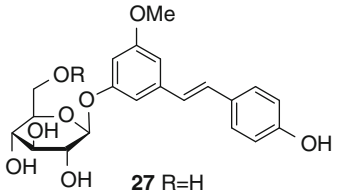
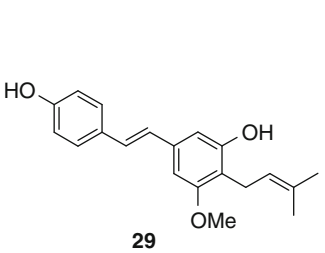


24 R_1=R_2=R_3=Ac
25 R_1=rutinosyl,R_2=R_3=Me
26 R_1=R_2=Me,R_3=rutinosyl



27 R=H
28 R=apiose

Prenyl substitution is a conventional derivatization style in stilbenes, exemplified by artoindonesianin N **29** from *Artocarpus gomezianus* [17]. The prenyl groups in stilbenes cyclize to form new derivatives. 4-Hydroxy-5′-methoxy-6″,6″-dimethylpyran[2″,3″:3′,4′]stilbene **30**, 3,5′-dimethoxy-4-hydroxy-6″,6″-dimethylpyran[2″,3″:3′,4′]stilbene **31**, and 3,4,5-trimethoxy-6″,6″-dimethylpyran [2″,3″:3′,4′]stilbene **32**, with dimethylchromene ring in their structures, have been obtained from *Lonchocarpus utilis* (Leguminosae) [18]. Furthermore, schweinfurthins A-C **33**–**35** from the leaves of *Macaranga schweinfurthii* (Euphorbiaceae) are typical samples of the prenylated stilbenes [19].



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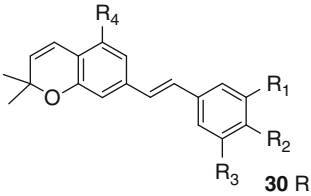
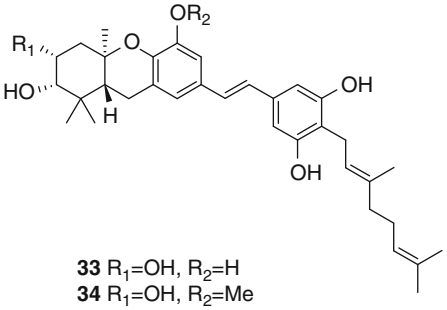
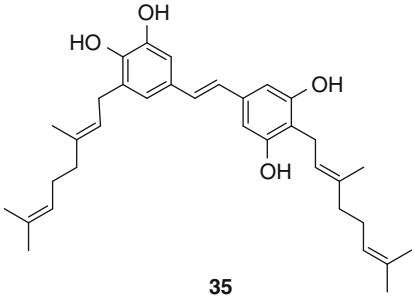


30 R_1=R_3=H,R_2=R_4=OMe
31 R_1=R_4=OMe,R_3=H,R_2=OH
32 R_1=R_2=R_3=OMe,R_4=H

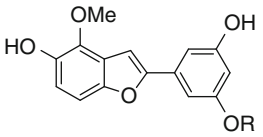


33 R_1=OH, R_2=H
34 R_1=OH, R_2=Me

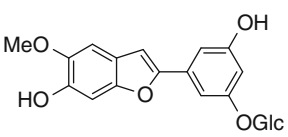


35

Arylbenzofuran derivatives are a group of special stilbenes formed by C_7–O–C_7 linkage, for instance, gnetofurans B **36** and C **37** from *Gnetum klossii* [20]. In addition, schoenoside **38**, a phenylbenzofuran glucoside discovered from *Schoenocaulon officinale* (Liliaceae), as well as stemofurans A-C **39**–**41** from *Stemona collinsae* belongs to this group [21, 22].



36 R=Me
37 R=H



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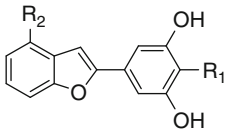


39 R_1=R_2=H
40 R_1=H,R_2=OH
41 R_1=Me,R_2=H

2.2 Oligostilbenes

The structures of oligostilbenes are produced by coupling between homogeneous or heterogeneous monomeric stilbenes, leading to the construction of dimer, trimer, and even the octamer. They do not enjoy a wide distribution in plant kingdom and have been found in the family of Agavaceae, Apiaceae, Arecaceae, Celastraceae, Cyperaceae, Dipterocarpaceae, Gnetaceae, Haemodoraceae, Iridaceae, Leguminosae, Moraceae, Musaceae, Orchidaceae, Pinaceae, Polygonaceae, Ranunculaceae, Vitaceae, and Welwitschiaceae. Thereinto, Vitaceae, Leguminosae, Gnetaceae, and Dipterocarpaceae are particular rich resource of this group.

Oligostilbenes are constructed by C–C or C–O–C linkage of various stilbene units with diverse coupling patterns and producing structures with diverse skeletons, complex configurations, and different degrees of oligomerization. The most common monomeric stilbene units which comprised the oligostilbenes are resveratrol, isorhapontigenin, piceatannol, oxyresveratrol, etc. (Fig. 62.1). Therefore, oligostilbenes are classified into six groups which are resveratrol oligomers, isorhapontigenin oligomers, piceatannol oligomers, oxyresveratrol oligomers, resveratrol and oxyresveratrol oligomers, and finally miscellaneous oligomers [3].

2.2.1 Resveratrol Oligomers

The group of resveratrol oligomers comprises the largest number of oligostilbenes and is characterized by the polymerization of two to eight resveratrols. About 180 constituents of this group covering dimer to octamers have been reported, which is produced by diverse polymeric styles.

Vitisinol A **42** isolated from *Vitis thunbergii* is a dimer linked by four C–C or C–O–C bonds [23]. Two dimeric stilbene glycosides **43** and **44** were reported from *Polygonum cuspidatum* (Polygonaceae) [24]. Thereinto, **44** is a symmetrical molecule and possesses a novel four-membered ring which is very rare in natural products. Isoampelopsin F **45** linked by three C–C bonds and heimiol A **46** with seven-member ring were isolated from *Parthenocissus tricuspidata* and *Neobalanocarpus heimii* [25]. A novel resveratrol dimer with a five-membered lactone ring, namely, shorealactone **47**, was obtained from *Shorea hemsleyana* [26]. Schneide reported the isolation of anigopreissin A **48** from the *Anigozanthos*

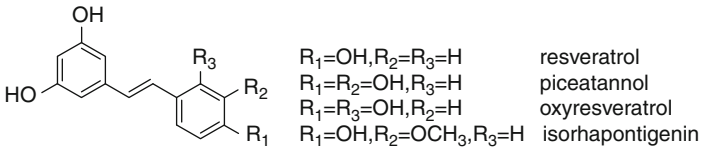
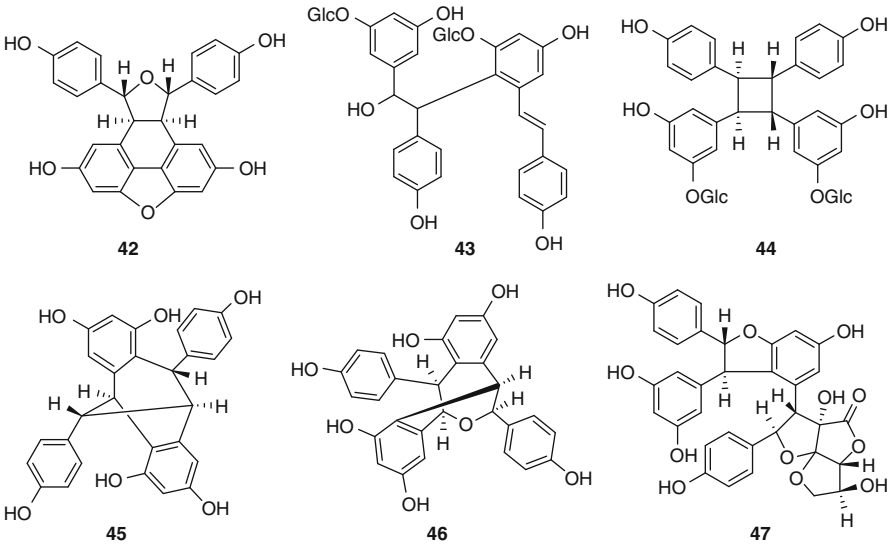


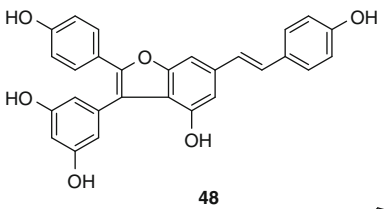
Fig. 62.1 Units comprising oligomeric stilbenes

preissii (Haemodoraceae) and *Musa cavendish* (Musaceae), which is the first dimer containing unsaturated benzofuan moiety [27]. Moreover, an aldehyde-substituted derivative, (−)-viniferal **49**, was isolated from *Vitis vinifera* [28].

Two trimers containing rare tribenzobicyclo[3.3.2]decatriene system were isolated from *Vatica rassak* and *V. pauciflora*, named vaticanol G **50** and vaticaside D **51** [29, 30]. Caragaphenol A **52**, with a nine-membered ring in the molecules, was found in *Caragana stenophylla* [31]. Three isomers which have bicyclo[5.3.0]decane ring system were obtained including amurensin G **53** from *Vitis amurensis* [32] and suffruticosols A **54** and B **55** from *Paeonia suffruticosa* (Ranunculaceae) [33].

Two new resveratrol pentamers, named amurensins E **56** and F **57**, have been isolated from *Vitis amurensis* [34]. The isolation and structural elucidation of a hexamer vaticanol D **58** and a heptamer vaticanol J **59** from *Vatica rassak* have been reported [29]. An octamer vateriaphenol A **60** from *Vateria indica* was reported by Ito and coworkers, and it is the largest molecules of stilbenoids [35].





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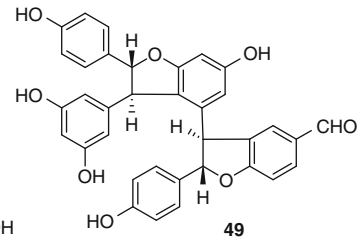

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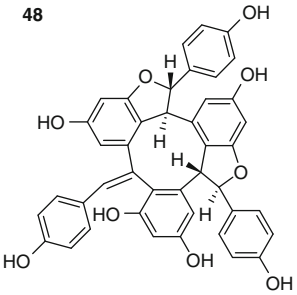

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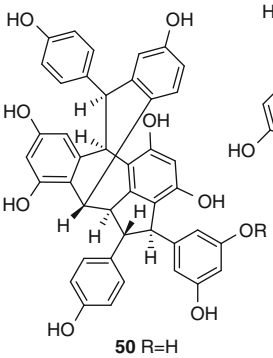
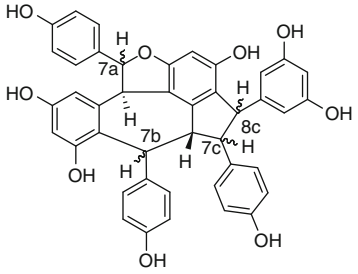
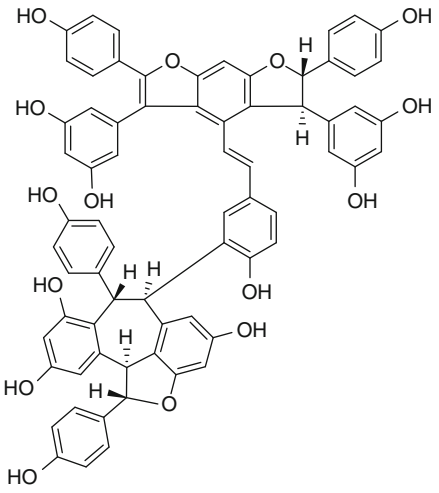


50 R=H
51 R=Glc



53 H-7a=H-8c=H-7b=β,H-7c=α
54 H-7a=H-8c=α,H-7b=H-7c=β
55 H-7a=H-7b=H-8c=α,H-7c=β



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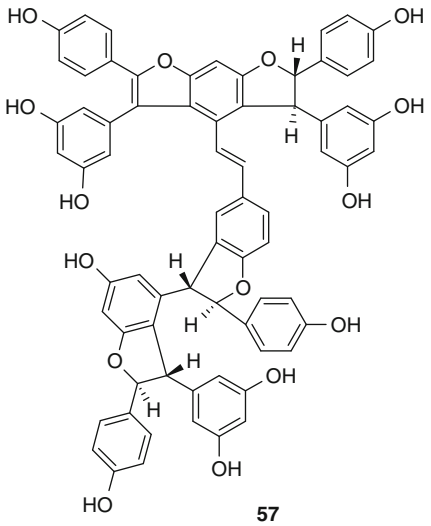

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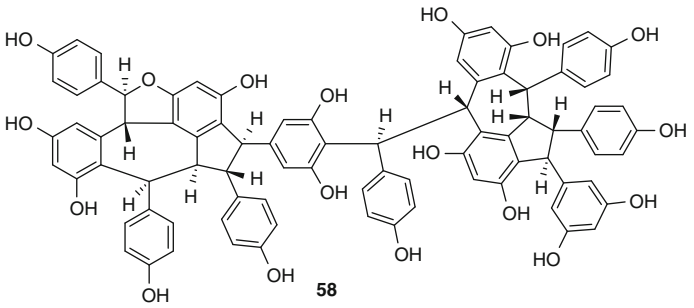

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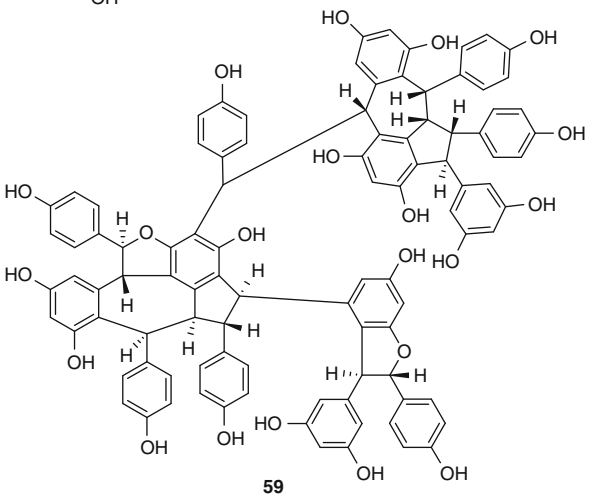

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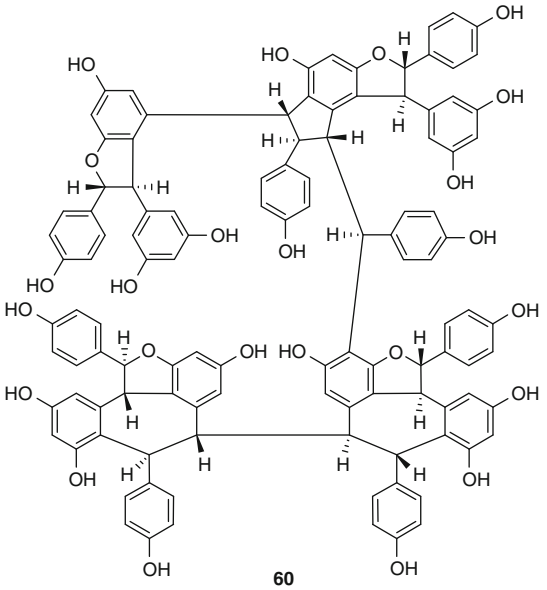
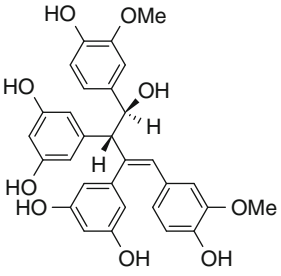


60

2.2.2 Isorhapontigenin Oligomers

Oligostilbenes of this group mainly occur in the genus of *Gnetum*. The representatives comprise gnetuhainins P **61** and I **62** from *G. hainanense* [36, 37], dimeric stilbene epimers gnetifolins M **63** and N **64** from *G. montanum* [38], gnemonol M **65** from *G. gnemon* [39], gneafricanin F **66** found in *G. africanum* [40], as well as bisisorhaphontigenin B **67** obtained from *G. africanum* [41]. With the exception of *Gnetum* species, *Salacia lehmbachii* produced three isorhapontigenin dimers, named lehmbachols A-C **68–70** [42]. The only two isorhapontigenin trimers, gnetuhainins N **71** and O **72**, which are stereoisomers have been found in *Gnetum hainanense* [43]. A tetramer named gnetuhainin R **73** was obtained from the same species (*G. hainanense*) [44].



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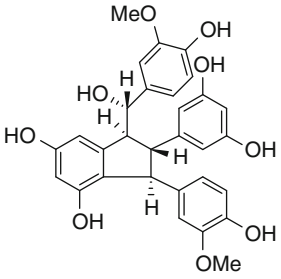

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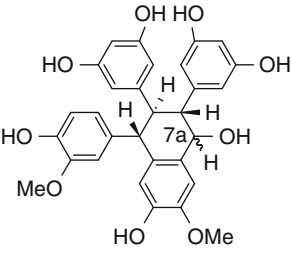
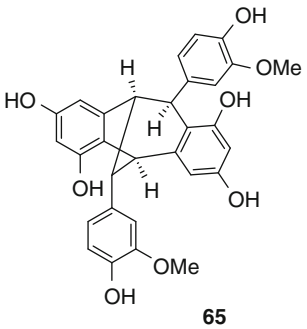


63 H-7a=β
64 H-7a=α



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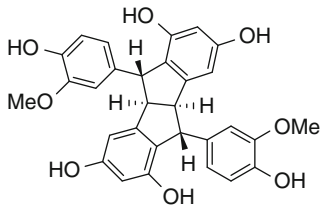

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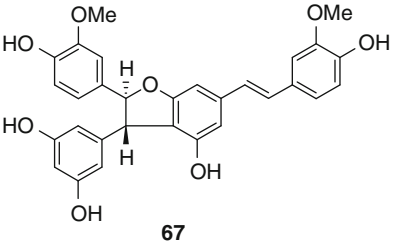

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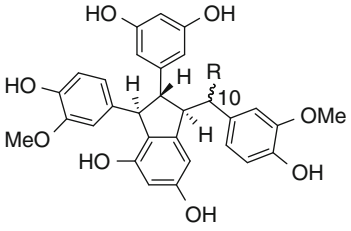
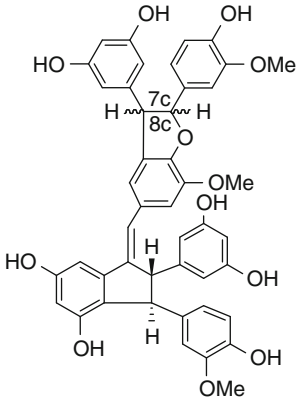
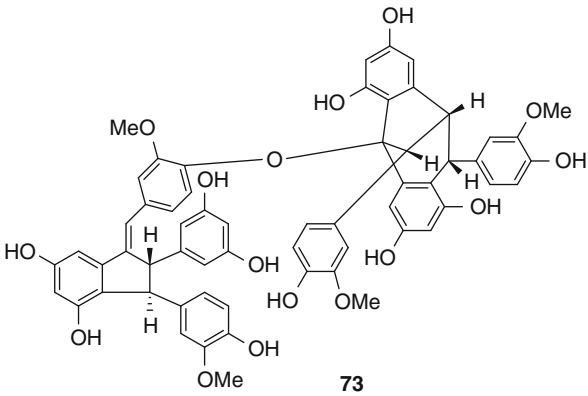


68 R=OMe
69 R=OMe diastereoisomer of **322**
70 R=OCH_2Me



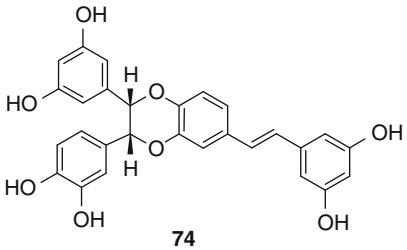
71 H-7c=α,H-8c=β
72 H-7c=β,H-8c=α



73

2.2.3 Piceatannol Oligomers

Only piceatannol dimers have been discovered from the plant species. Longusol C **74** and gneafricanin C **75** were isolated from *Cyperus longus* and *Gnetum africanum* [40, 45]. Tibeticanol **76** was obtained from *Caragana tibetica* [46]. Two piceatannol dimer glycosides named piceasides A–B **77**–**78** were isolated from Norway spruce *Picea abies* as a mixture in a ration of 1:1 [47].



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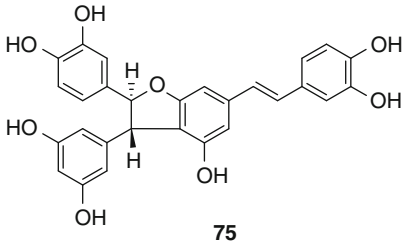

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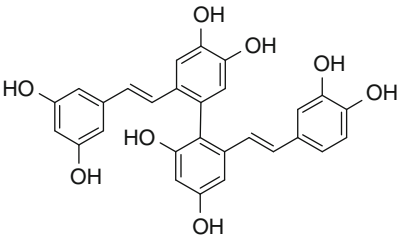
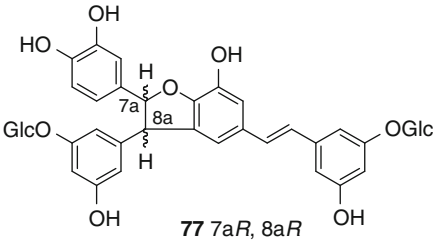


76

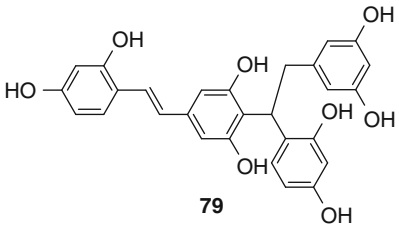


77 7a*R*, 8a*R*
78 7a*S*, 8a*S*

2.2.4 Oxyresveratrol Oligomers

Andalasin A **79** and artogomezianol **80** were isolated from *Artocarpus gomezianus* (Moraceae) [48]. Structures **79** and **80** are possible intermediates in the biogenesis

of oxyresveratrol dimers. Parvifolol C **81** and gnetumontanin A **82** were discovered in two *Gnetum* species *G. parvifolium* and *G. montanum* [49, 50].



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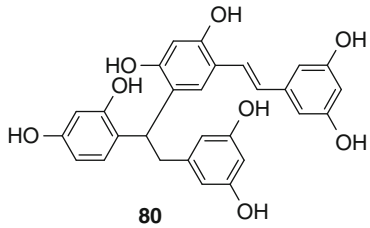

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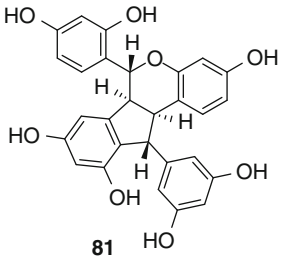

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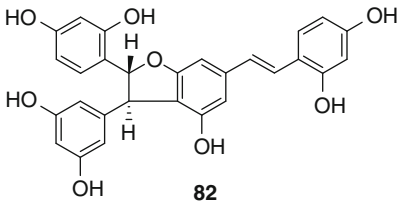
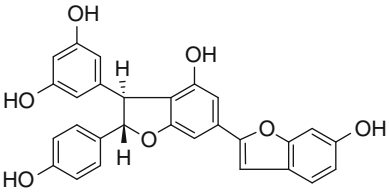


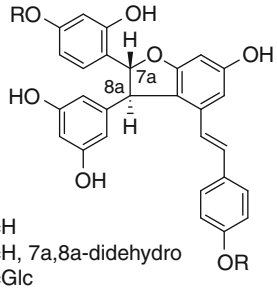
82

2.2.5 Resveratrol and Oxyresveratrol Oligomers

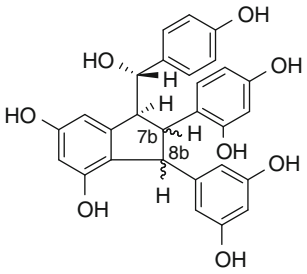
The resveratrol and oxyresveratrol oligomers are only obtained from the genus *Gnetum* (Gnetaceae) and polymerize by oxidative coupling between resveratrol and oxyresveratrol. About 24 compounds of this group have been elucidated. A dimer containing a benzofuran and a dihydrobenzofuran moiety, named gnemonol G **83**, was isolated from *G. gnemon* [51]. Four stilbene dimers, gnetuhainins A **84**, B **85**, D **86** and E **87**, were obtained from *G. hainanense* [52]. Gnemonoside J **88**, a diglucoside of **84**, was isolated from *G. africanum* [53]. Three stereoisomers including parvifolols A **89** and B **90** and gnetuhainin S **91** have been founded from *G. parvifolium* and *G. hainanense* [44, 49, 54]. Gnemonol A **92** and its stereoisomers and gnemonol I **93** composed of two resveratrol units and one oxyresveratrol unit were discovered in *G. gnemon* [51, 55]. Gnemonol J **94** from *G. gnemon* possesses the same skeleton of **92** and **93**; however, it is coupled by one resveratrol unit and two oxyresveratrol units [51]. Gnemonol C **95** from *G. gnemonoides* is a stilbene tetramer constructed by three resveratrol and one oxyresveratrol units [55].



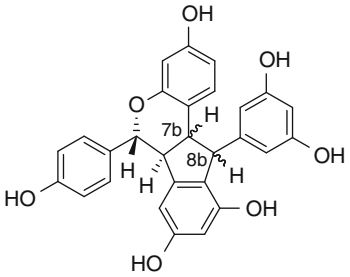
83



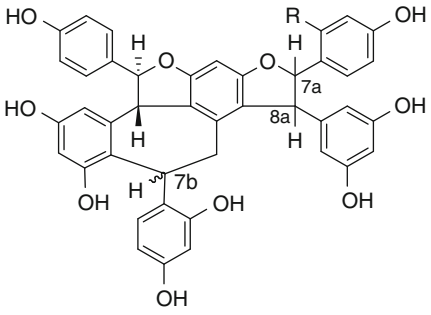
84 R=H
85 R=H, 7a,8a-didehydro
88 R=Glc



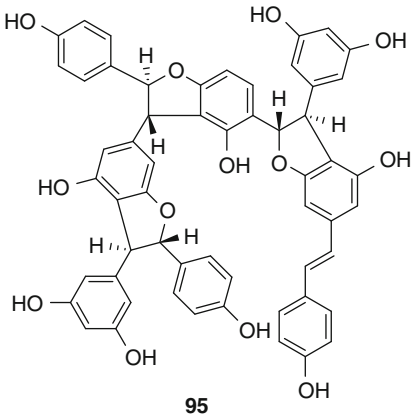
86 H-7b=β,H-8b=α
87 H-7b=α,H-8b=β



89 H-8b=α,H-7b=β
90 H-8b=β,H-7b=β
91 H-8b=β,H-7b=α



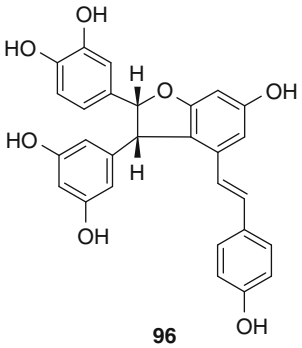
92 R=H,H-7b=α,H-7a/8a=*trans*
93 R=H,H-7b=β,H-7a/8a=*trans*
94 R=OH,H-7b=α,H-7a/8a=*trans*



95

2.2.6 Miscellaneous Oligomers

Oligostilbenes polymerize from different stilbene units with the exception of resveratrol and oxyresveratrol oligomers, and containing miscellaneous structural skeleton will be classified into this group. Longusol B **96** from *Cyperus longus* [45] is a stilbene dimer composed of resveratrol and piceatannol units. Gnetuhainin Q **97**, an isorhapontigenin and resveratrol dimer, was found in *Gnetum hainanense* [36]. The first isorhapontigenin and oxyresveratrol dimer named gnetuhainin J **98** was isolated from *G. hainanense* [37]. An isorhapontigenin and piceatannol dimer, gneafricanin B **99** was discovered in *Gnetum africanum* [41]. Two isorhapontigenin and 2-hydroxyisorhapontigenin dimers were obtained from *G hainanense* and named gnetuhainin G **100**. An isorhapontigenin and gnetol dimer gnetuhainin K **101** was isolated from *G. hainanense* [36].



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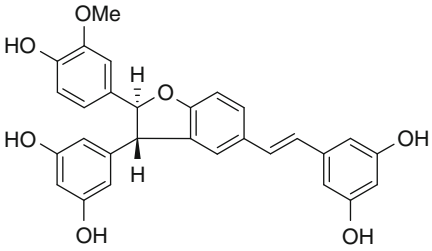

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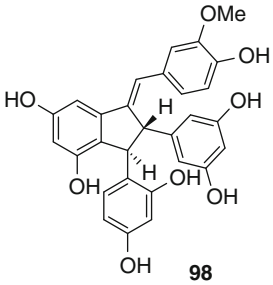

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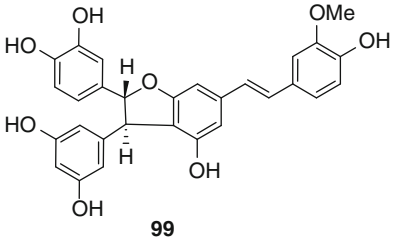

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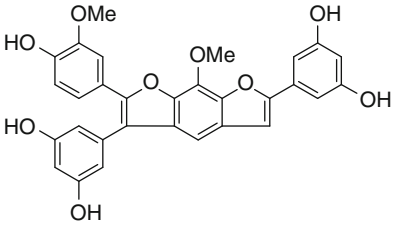

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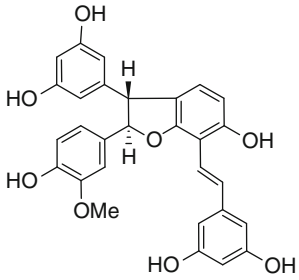


101

2.3 Bibenzyls

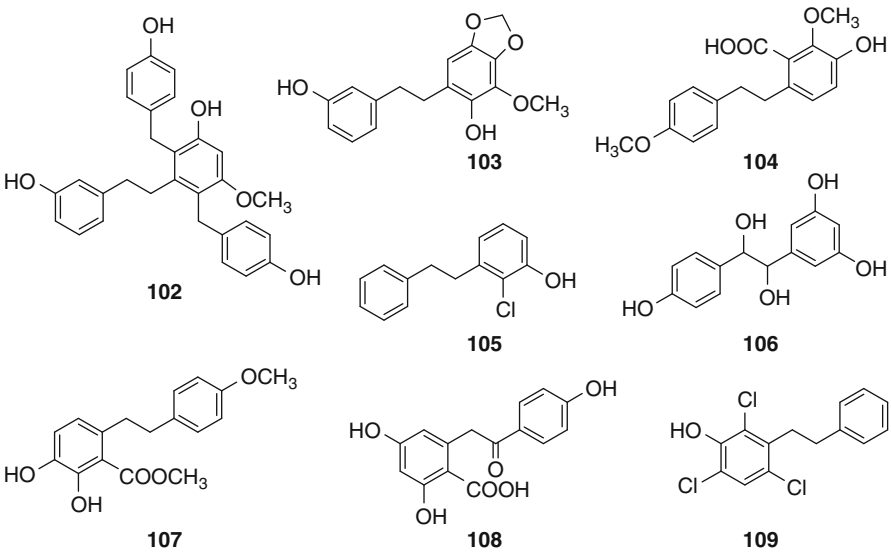
The bibenzyls are characterized by the presence of one 1,2-diphenylethane structure in their molecules. Similar with the stilbene structures, there are hydroxyls, methyl, methoxy, prenyl, geranyl, etc., located in the structures of bibenzyls. Bibenzyls have been mainly isolated from bryophytes. In addition, a few compounds of this group were reported from the genera of *Stemona*, *Dendrobium*, and *Polygonum*.

According to the suggestion given by Gorm et al. [56], bibenzyl compounds are classified into four groups. However, a few groups of bibenzyls are new addition to

the growing list of naturally occurring bibenzyls, such as tyrolobibenzyls. In addition, bibenzyls containing isoprene units, regardless of branched or heterocyclic ring-forming isoprene units, are regarded as the same group. Therefore, the bibenzyls are reclassified into five groups according to their substitute patterns on both the benzene nucleus and ethylidene bridge.

2.3.1 Group A: Simple Bibenzyls

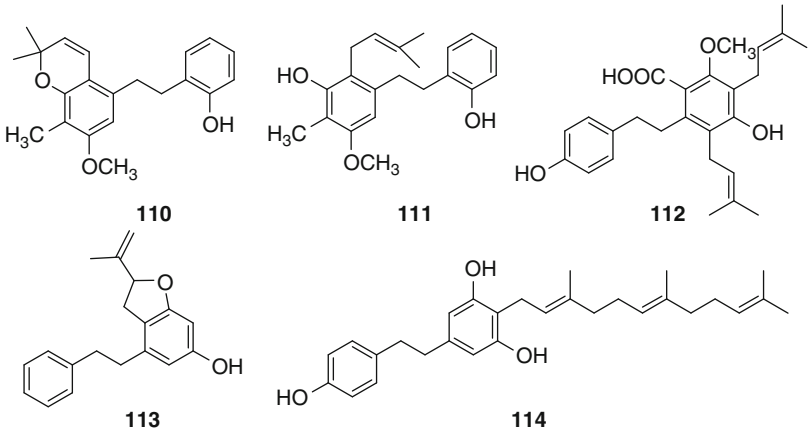
Bibenzyls having halogenated, hydroxylated, methyled, methoxylated, carboxylate, benzoyl, and/or methylenedioxy substitutes constitute the group of simple bibenzyls. The representatives are 2′,6′-bis(*p*-hydroxybenzyl)-3,3′-dihydroxy-5-methoxybibenzyl **102** from *Bletilla formosana* [57], bulbophyllum **103** from *Bulbophyllum protractum* [58], 2-carboxy-4-hydroxy-3,4′-dimethoxybibenzyl **104** from *Plagiochila* species [59], 2-chloro-3-hydroxybibenzyl **105** from *Riccardia marginata* [60], 1-(3′,5′-dihydroxyphenyl)-2-(4′-hydroxyphenyl)-ethane-1,2-diol **106** from *Polygonum cuspidatum* [61], methyl 4-hydroxy-4′-*O*-methyllunularate **107** from *Plagiochila spinulosa* [62], tragopogonic acid **108** from *Tragopogon porrifolius* [63], and 2,4,6-trichloro-3-hydroxybibenzyl **109** from *Riccardia marginata* [60].



2.3.2 Group B: Isoprene Unit–Substituted Bibenzyls

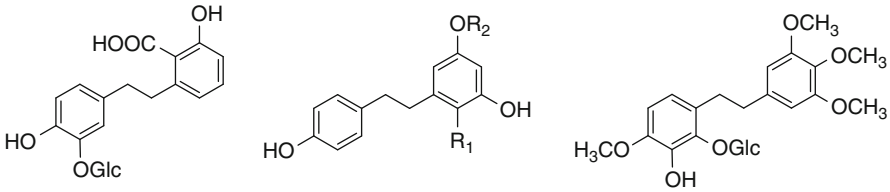
Bibenzyls of this group are characterized by the presence of prenyl, geranyl, and/or farnesyl substitutes. Isoprene units in the structures may be branched and/or form five- to seven-member rings. The typical compounds of this group are bauhinols A **110** and B **111** from *Bauhinia saccocalyx* [64],

2-carboxy-3-methoxy-4,6-di-(3-methyl-2-butenyl)-5,4′-dihydroxy-bibenzyl **112** from *Lethocolea glossophylla* [65], 2-isopropenyl-6-hydro-4-(2-phenylethyl) dihydrobenzoluran **113** from *Radula perrottetii* [66], and 3,5,4′-trihydroxy-4-(3,7,11-trimethyl-2,6,10-dodecatrienyl)bibenzyl **114** from *Radula* species [67].



2.3.3 Group C: Glycosylated Bibenzyls

Bibenzyls conjugated with glycosyl substitutes on the aromatic rings or benzylic methylenes (excluding tyrolobibenzyls) belong to this group. The representatives of this group include 2′-carboxy-4,3′-dihydroxybibenzyl-3-*O*-β-D-glucopyranoside **115** from *Ricciocarpus natans* [68], 2-carboxyl-3,4′-dihydroxy-5-β-D-xylopyranosyloxybibenzyl **116** and 5,4′-dihydroxy-3-α-L-rhamnopyranosyl-(1→3)-β-D-xylopyranosyloxybibenzyl **117** from *Tragopogon porrifolius* [63], and combretastatin B-1,2′-β-D-glucoside **118** from *Combretum erythrophyllum* [69].

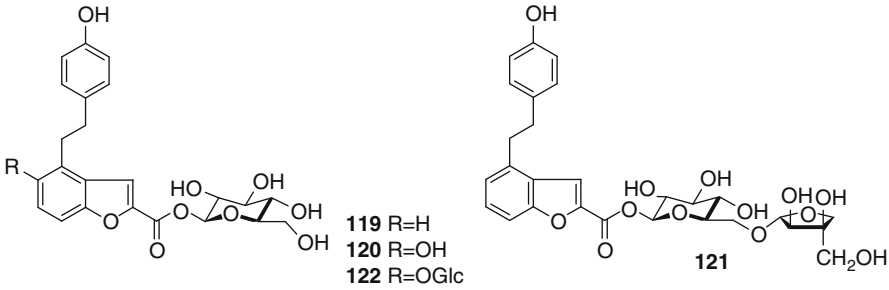


116 R_1=COOH, R_2=β-D-xylopyranosyl
117 R_1=H, R_2=α-L-rhamnopyranosyl-(1→3)-β-D-xylopyranosyl

2.3.4 Group D: Tyrolobibenzyls

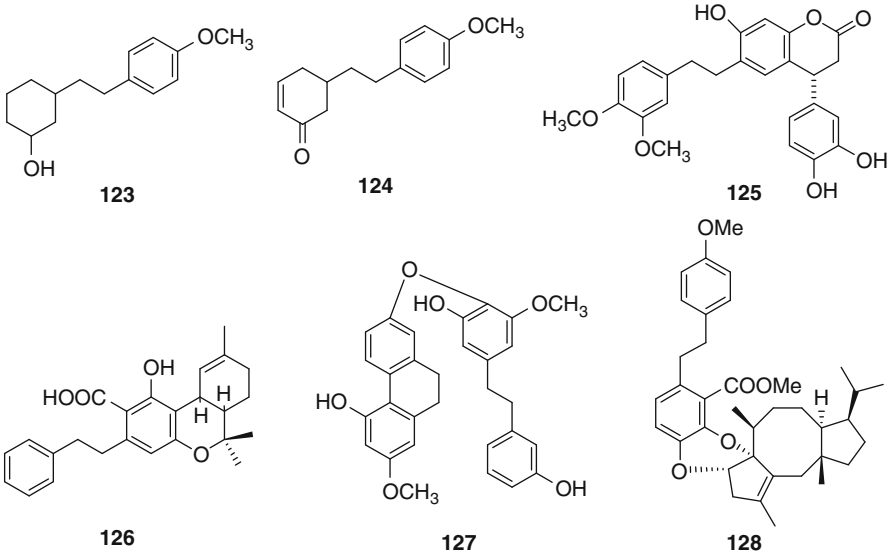
Tyrolobibenzyls are a new class of naturally occurring bibenzyl derivatives possessing a unique phenylethyl-benzofuran skeleton. Tyrolobibenzyls A **119**,

B **120**, D **121**, and F **122** from *Scorzonera humilis* L. (Asteraceae) are the typical constituents of this group [70–72].



2.3.5 Group E: Other Bibenzyls

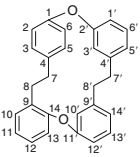
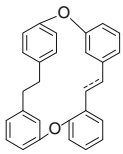
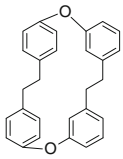
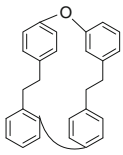
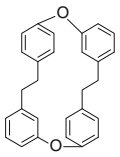
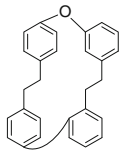
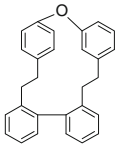
The hydrogenated bibenzyls **123**–**124** from *Plagiochila longispina* [73], dihydrocoumarin-type bibenzyl **125** from *Vittaria anguste-elongata* [74], cannabinoid-type bibenzyl **126** from *Radula marginata* [75], and dihydrophenanthrene hybrids such as shancilin **127** from *Pleione bulbocodioides*, and terpenoid hybrid spinuloplagin A from *Plagiochila spinulosa* **128** are classified into this group.



2.4 Bisbibenzyls

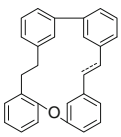
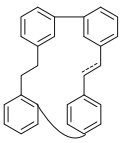
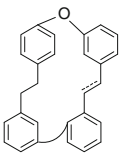
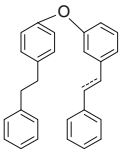
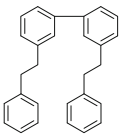
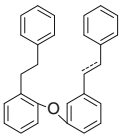
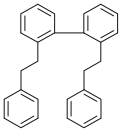
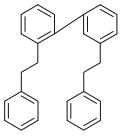
Bisbibenzyls are dimeric bibenzyls and chemically constructed by two lunularin moieties with diarylether and/or biphenyl linkages, and producing cyclic and acyclic four aromatic rings system. They are usually distributed in liverworts and

Table 62.1 Cyclic and acyclic bis(bibenzyl) types and their distribution

Subclass	Type	Structure	Linkage pattern	Family member	Distribution
Cyclic	Marchantin		C_1-O-$C_{2'}$ and C_{14}-O-$C_{11'}$ linkage	Marchantins A-P, Marchantinquinone	Aneuraceae Grimaldiaceae Jungermanniaceae Marchantiaceae Monocleaceae
	Isomarchantin		C_1-O-$C_{2'}$ and C_{13}-O-$C_{10'}$ linkage	Isomarchantins B and C Ptychantols A-C	Jungermanniaceae Lejeuneaceae Marchantiaceae
	Neomarchantin		C_1-O-$C_{2'}$ and C_{12}-O-$C_{11'}$ linkage	Neomarchantins A and B; Pakyonol	Grimaldiaceae Marchantiaceae Monocleaceae Schistochilaceae
	Riccardin I		C_1-O-$C_{2'}$ and C_{14}-$C_{12'}$ linkage	Riccardins A, C-H	Grimaldiaceae Marchantiaceae Monocleaceae Aneuraceae Jungermanniaceae
	Riccardin II		C_1-O-$C_{2'}$ and C_{13}-O-$C_{12'}$ linkage	Riccardin B	Aneuraceae Marchantiaceae
	Isoriccardin		C_1-O-$C_{2'}$ and C_{12}-$C_{10'}$ linkage	Isoriccardin C Isoriccardinquinones A and B	Marchantiaceae
	Plagiochin		C_1-O-$C_{2'}$ and C_{14}-$C_{10'}$ linkage	Plagiochins A-E	Plagiochilaceae

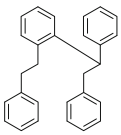
(*continued*)

Table 62.1 (continued)

Subclass	Type	Structure	Linkage pattern	Family member	Distribution
	Isoplagiochin I		C_6-$C_{2'}$ and C_{14}-O-$C_{11'}$ linkage	Isoplagiochins A-B, E-G.	Plagiochilaceae
	Isoplagiochin II		C_6-$C_{2'}$ and C_{14}-$C_{12'}$ linkage	Isoplagiochins C and D; Bazzanins A-J, L-S	Blasiacea Herbertaceae Plagiochilaceae
	Planusin		C_6-O-$C_{2'}$ and C_{13}-$C_{10'}$ linkage	Planusin A	Plagiochilaceae
Acyclic	Perrottetin		C_1-O-$C_{2'}$ linkage	Perrottetins E-H	Jungermanniaceae Pelliaceae Radulaceace
	Isoperrottetin		C_6-$C_{2'}$ linkage	Isoperrottetin A	Moraceae Radulaceace
	Paleatin		C_{14}-O-$C_{11'}$ linkage	Paleatins A-B	Marchantiaceae
	Plagilin		C_5-$C_{3'}$ linkage	Plagilin, Vitamin E	Plagiochilaceae
	Isoplagilin		C_5-$C_{2'}$ linkage	Isoplagilin	Plagiochilaceae

(*continued*)

Table 62.1 (continued)

Subclass	Type	Structure	Linkage pattern	Family member	Distribution
	Plagiolin		C_5-$C_{7'}$ linkage	Plagiolin	Plagiochilaceae

rarely found in other plant species. The first bisbibenzyl not obtained from liverworts is perrottetin H **149**, which was isolated from a pteridophyte *Hymenophyllum barbatum* [2]. It is also believed that the distribution of bisbibenzyls in both pteridophytes and liverwort is an important marker of determining the evolutionary ladder of terrestrial spore-forming plants.

Bisbibenzyls are classified into ten types of cyclic bisbibenzyls and six types of acyclic bisbibenzyls on the basis of basic bisbibenzyls skeletons (see Table 62.1). Over 100 cyclic and acyclic bisbibenzyls have been obtained from plant kingdom to date.

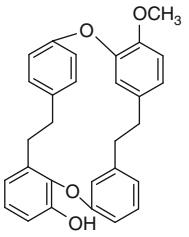
2.4.1 Macrocyclic Bisbibenzyls

According to the constitution of the macrocyclic ring, these bisbibenzyls can be divided into three main groups, those with two diarylether bonds (marchantins, isomarchantins, neomarchantins, and riccardins II), those with two biphenyl bonds (isoplagiochin II), or those with one diarylether bond and one biphenyl bond (riccardin I, isoriccardin C, plagiochins, isoplagiochin I, and planusin A) (see Table 62.1). The range of macrocyclic structures is extended ultimately and derived from additional functions (e.g., carbonyl, hydroxyl, and methoxyl) on both the benzene nucleus and ethylidene bridge and the ways in which aromatic rings are linked.

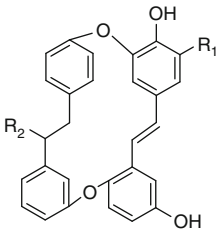
Asakawa and his coworkers reported the isolation of a marchantin-type macrocyclic bisbibenzyl marchantin P **129** from the liverwort *Marchantia chenopoda* collected in Venezuela [76]. Three isomarchantin-type macrocyclic bisbibenzyls were isolated from the liverwort *Ptychantus striatus*, belonging to the Lejeuneaceae, and designated them as ptychantols A-C **130–132** [77]. Neomarchantins A and B **133–134** were obtained from *Schistochila glaucescens* [78].

Two riccardin I-type compounds, riccardins F **135** and H **136**, were isolated from *Blasia pusilla* [79] and *Marchantia polymorpha* [80], respectively. Riccardin B **137** from *Preissia quadrata* belongs to the riccardin II-type bisbibenzyls. Isoriccardin C **138**, a compound of isoriccardin group, was obtained from *Plagiochila sciophila* [81].

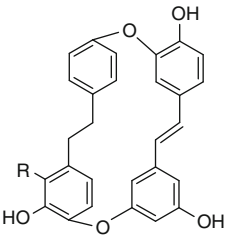
Plagiochins A-B **139** and **140** were plagiochin-type constituents from *Plagiochila fruticosa* [81]. Isoplagiochins E-F **141–142**, belonging to the isoplagiochin I-type bisbibenzyls, have been isolated from several *Plagiochila* species. Isoplagiochins C **143** and D **144** with two biphenyl linkages, which are different from isolagiochin I-type bisbibenzyls, represent isolagiochin II-type of macrocyclic bisbibenzyls. Planusin A **145** with a *cis*-stilbene moiety was discovered from cultured cells of the liverwort *Heteroscyphus planus* and classified into planusin-type bisbibenzyls [82].



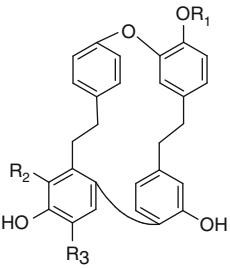
129



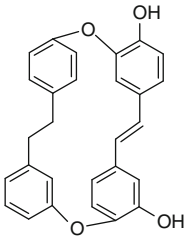
130 R_1=R_2=H
131 R_1=OH, R_2=H
132 R_1=H, R_2=OH



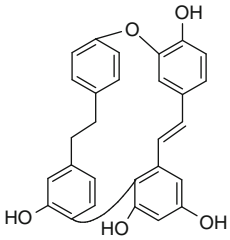
133 R=H
134 R=OH



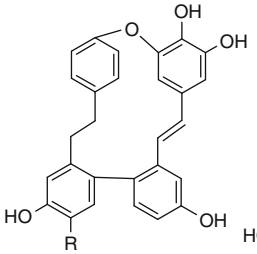
135 R_1=CH_3, R_2=R_3=H
136 R_1=H, R_2=R_3=OH



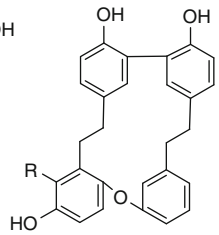
137



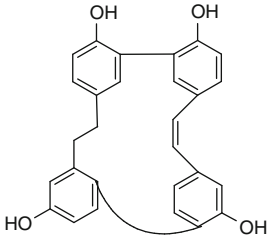
138



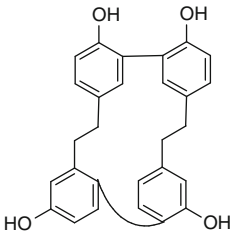
139 R=OH
140 R=H



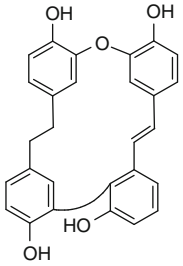
141 R=H
142 R=OH



143



144



145

2.4.2 Acyclic Bisbibenzyls

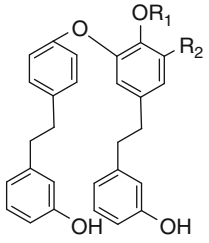
Compared with cyclic bisbibenzyls, acyclic bisbibenzyls receive less attention due to their small number and poor structural diversity. Some novel acyclic bisbibenzyls, however, have been obtained in the past few years. These bisbibenzyls can be divided into two main groups, those with one diarylether bond (perrottetins and paleatins) or those with one biphenyl bond (isoperrottetin A, plagilins, isoplagilin, plagiolin, artogomezianol, and andalasin). The linkages occurred between two aromatic rings or between one benzene nucleus and ethylidene bridge (see Table 62.1).

Perrottetins and isoperrottetins represent the most frequently encountered skeletal types of acyclic bisbibenzyls. They are of much interest for the investigation of biogenesis of macrocyclic bisbibenzyls, for example, the derivatives of riccardin, plagiochin,

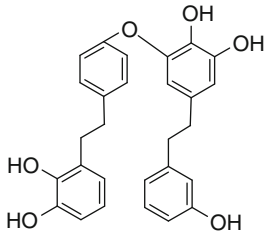
ptychantol, and isoplagiochin types. Examples of the perrottetin-type compounds are perrottetins E-H **146**–**149**. They have been found in different liverwort species and a fern *Hymenophyllum barbatum* [83]. Isoperrottetin A **150** and its chlorinated derivative **151** belong to isoperrottetin-type compounds [66, 84], which contain one biphenyl bond between aromatic rings instead of one diarylether bond for perrottetins.

Plagilin **152**, isoplagilin **153**, and plagiolin **154** were obtained from a neotropical *Plagiochila* species [85]. Another plagilin-type bisbibenzyl, vittarin-E **155**, has been isolated from the whole plant of *Vittaria anguste-elongata* [74]. This is one more evidence for the occurrence of acyclic bisbibenzyls in the pteridophytes.

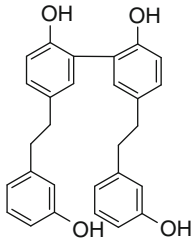
Paleatins A **156** and B **157** were isolated from the methanol extract of *Marchantia paleacea* var. *diptera* [86]. These phenolic compounds are of interest because they are the linear analogues of the macrocyclic bisbibenzyl ethers and possible biogenetic precursors of the plagiochins and riccardins.



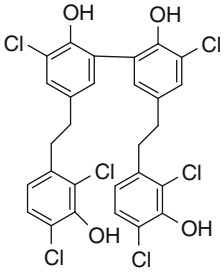
146 R_1=R_2=H
147 R_1=H, R_2=OH
148 R_1=CH_3, R_2=OH



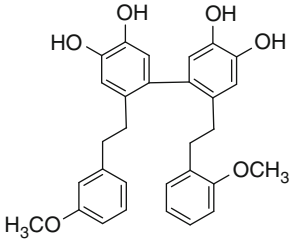
149



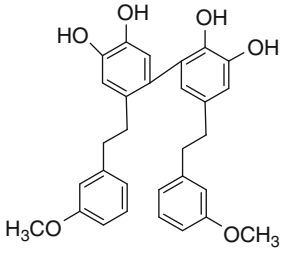
150



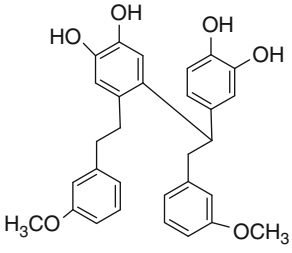
151



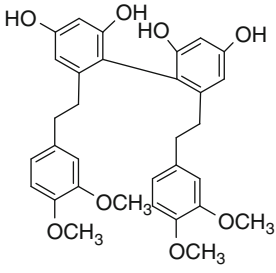
152



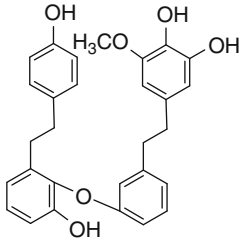
153



154



155



156 R=OCH3
157 R=H

2.5 Phenanthrenes

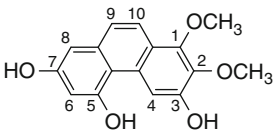
The phenanthrenes are a rather uncommon group of aromatic constituents formed by oxidative coupling of the aromatic rings of stilbene precursors and existed in the form of monomers, dimers, and even trimers [87]. A large number of phenanthrenes have been isolated from higher plants (mainly in the Orchidaceae family) and covering 49 species. The genera *Dendrobium*, *Bulbophyllum*, *Eria*, *Maxillaria*, *Bletilla*, *Coelogyna*, *Cymbidium*, *Ephemerantha*, and *Epidendrum* were particularly rich resources of phenanthrenes. In addition, a few phenanthrenes have been discovered in the family of Dioscoreaceae, Combretaceae and Betulaceae, and the Hepaticae class. The greatest number of phenanthrenes has been obtained from the *Juncus* species.

2.5.1 Monomeric Phenanthrenes

Most of the phenanthrenes are present in the form of monomers, containing about 210 compounds. Hydroxyl and methyloxyl are the most common substitutes located in the phenanthrene skeletons and occupy about 50% of all monomers. For instance, coeloginanthrin **158** from *Coelogyne cristata* [88], 4-methoxyphenanthrene-2,3,7-triol **159** and 4-methoxyphenanthrene-2,3,6,7-tetrol **160** from *Bulbophyllum vaginatum* [89], as well as 2-methoxy-3,4,7-trihydroxy-phenanthrene **161** from *B. inconsipicum* [90] are hydroxyl- and/or methyloxyl-substituted ones.

With the exception of hydroxy and methyloxy groups, methyl-, hydroxymethyl-, carboxy-, formyl-, prenyl-, and vinyl-substituted compounds are observed, with stemanthrenes A-D **162–165**, **166**, **167**, dehydroeffusal **168**, and gancaonin U **169** as the representatives [91–94]. Furthermore, glycosides were isolated from the plants of *Juncus effusus*, *Epimedium koreanum*, *Dendrobium chrysanthum*, and *Bulbophyllum striata*, for example, effuside I **170**, epimedoicarisoside A **171**, and denchryside A **172** [95–97].

Phenanthraquinones are special phenanthrenes with quinone group in the structures. Ephemeranthoquionone **173** from *Dendrobium plicatile*, cymbinodin A **174** from *C. aloifolium*, and moniliformin **175** from *D. moniliforme* were typical constituents of this group [98–100].



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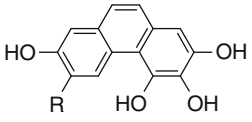
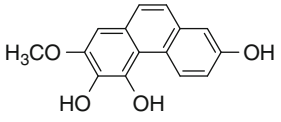


159 R=H
160 R=OH



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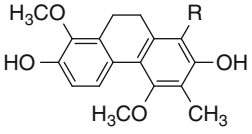
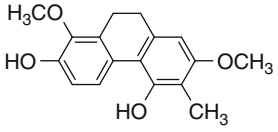


162 R=H
164 R=CH_3



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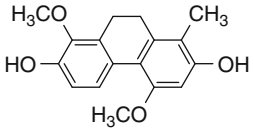

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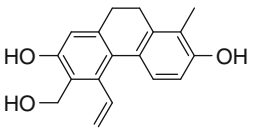

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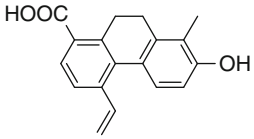

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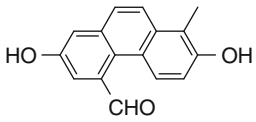

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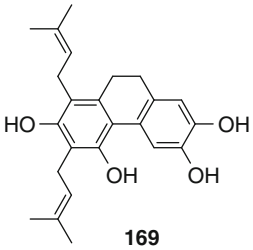

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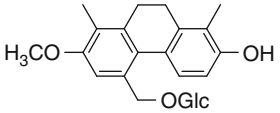

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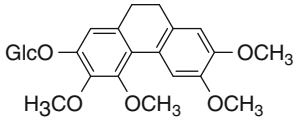

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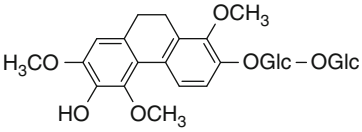

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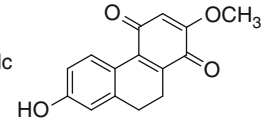

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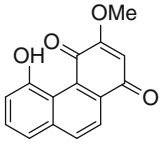

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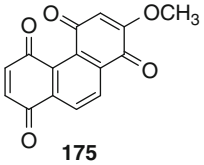
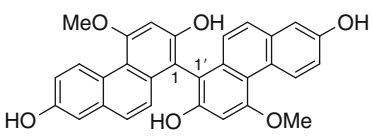


175

2.5.2 Dimeric Phenanthrenes

The dimeric phenanthrenes are commonly constructed by 1-1′ linkage of monomers, and the dimers with 1-3′, 1-8′, and 3-3′ link patterns also existed. Nearly 40 dimeric phenanthrenes have been found in the plants [87]. The representatives are cirrhopetalanthrin **176** from *Cremastra maculosum* [101], blestrianol A **177** from *Bletilla striata* [102], blestriarene B **178** from *Bletilla formosana* [57], and spiranthesol **179** from *Spiranthes sinensis* [103].



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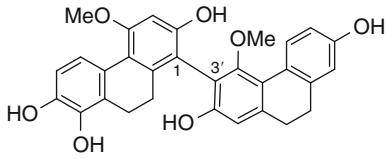

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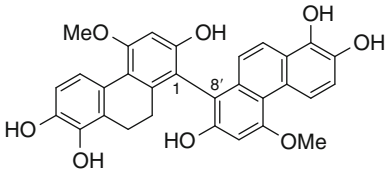

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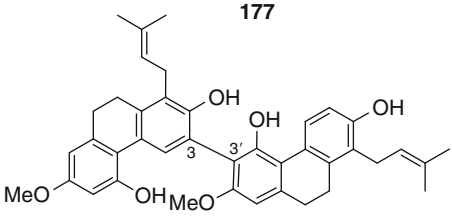

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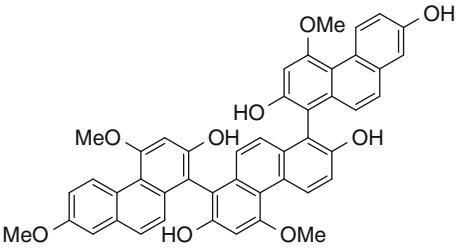
2.5.3 Triphenanthrene

Hitherto, only one triphenanthrene **180** has been reported from the tubers of an orchidaceous plant *Cremastra appendiculata* [104].



180

3 Biosynthesis

3.1 Biosynthesis of Stilbenes

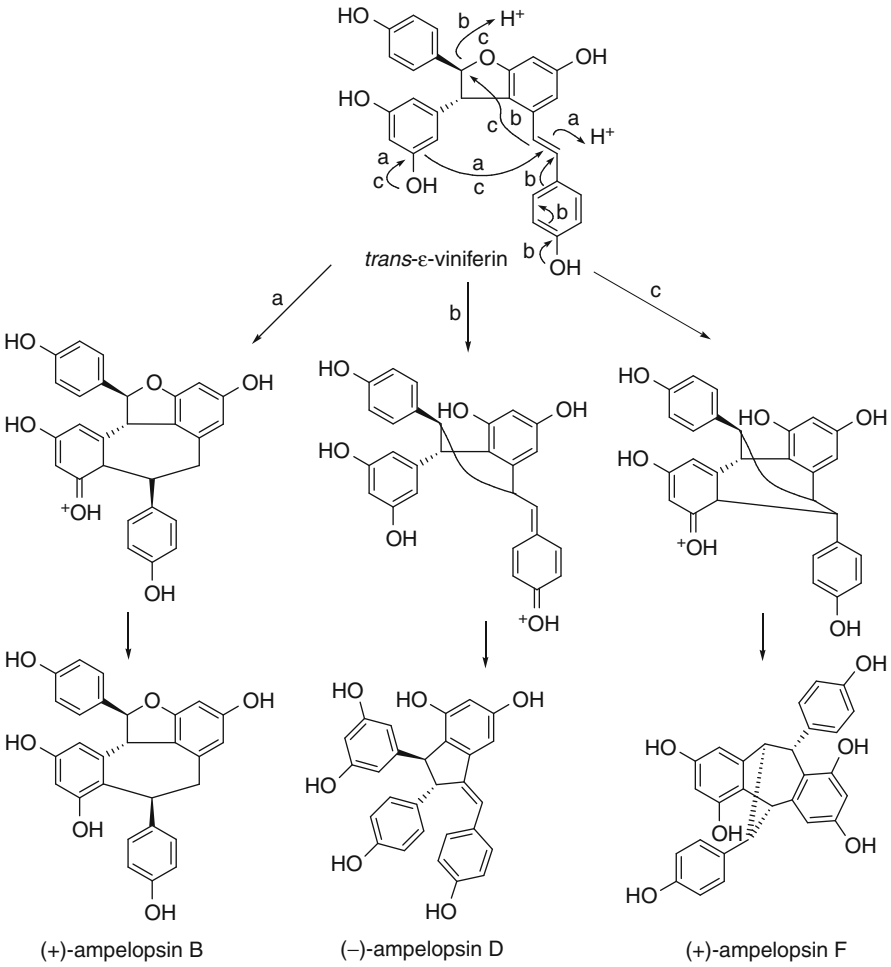
The biosynthesis of simple stilbenes has been found out, and it shared a similar biosynthetic pathway with the flavonoids. Taking resveratrol for example, it starts from a cinnamoyl-CoA unit and extended the chain with three malonyl-CoA molecules (Scheme 62.1) [105]. Then, the resveratrol structure is produced by aldol reaction with the presence of stilbene synthase. Nevertheless, the flavonoids are formed depending on chalcone synthase and Claisen reaction.

3.2 Biosynthesis of Oligostilbenes

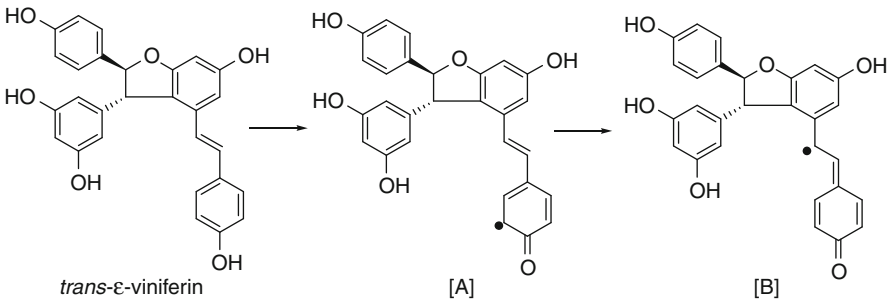
Sotheeswaran has mentioned that the oligostilbenes with dihydrobenzofuran moiety are biosynthesized through an important intermediate *trans*-ε-viniferin [106]. Combined with the reported work of oligostilbenes, the biosynthesis of oligostilbenes is summarized. For instance, the dimers named (+)-ampelopsin B, (−)-ampelopsin D, and (+)-ampelopsin F are produced by isomerization and/or rearrangement of *trans*-ε-viniferin (Scheme 62.2). The differences in their structures are caused by the different protonation position at the initial stage of reaction. Furthermore, *trans*-ε-viniferin is able to transform to the isomers (Scheme 62.3) and then forming the tetramers, (+)-vitisin A, (−)-vitisin B, (+)-hopeaphenol, and (+)-viniferol A, etc., by oxidative coupling (Scheme 62.4) [2, 107].

OH
CoAS
O
4-hydroxycinnamoyl-CoA
chain extension
x3
CO2
HO
O
O
SCoA
O
O
OH
SCoA
O
O
O
O
Claisen
flavonoids
aldol reaction
stibene synthase
CO2
OH
HO
OH
resveratrol

Scheme 62.1



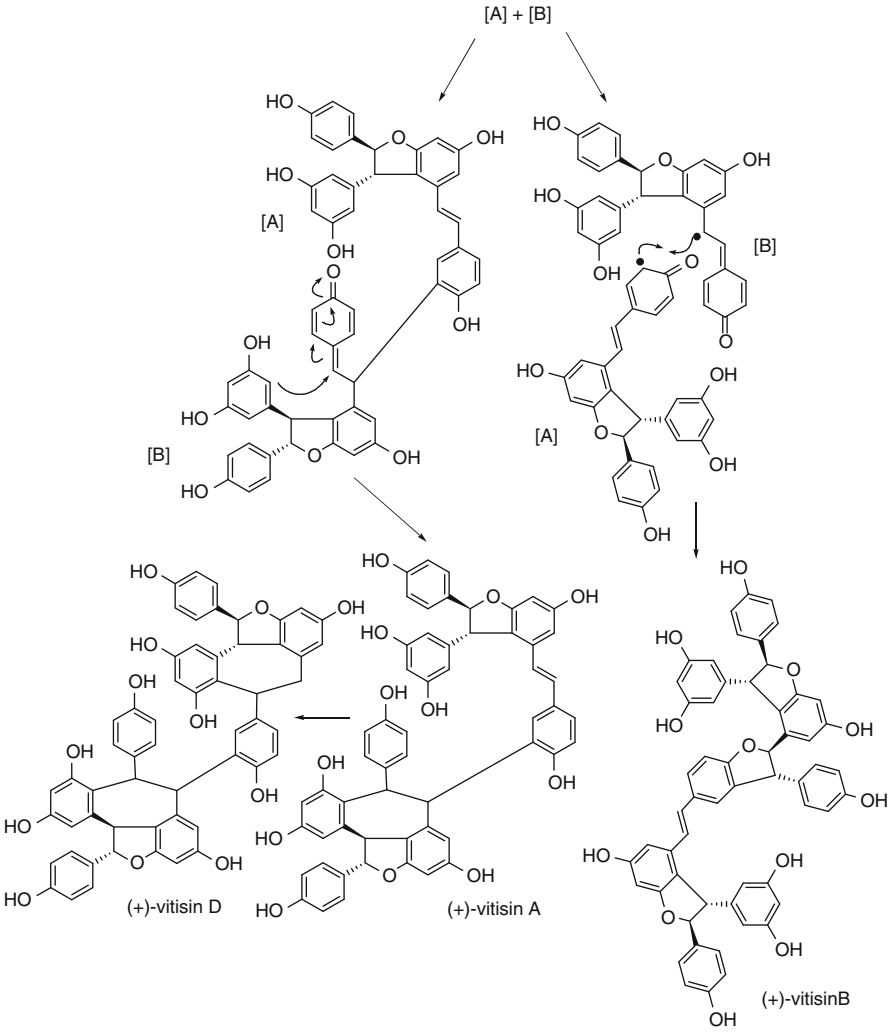
Scheme 62.2



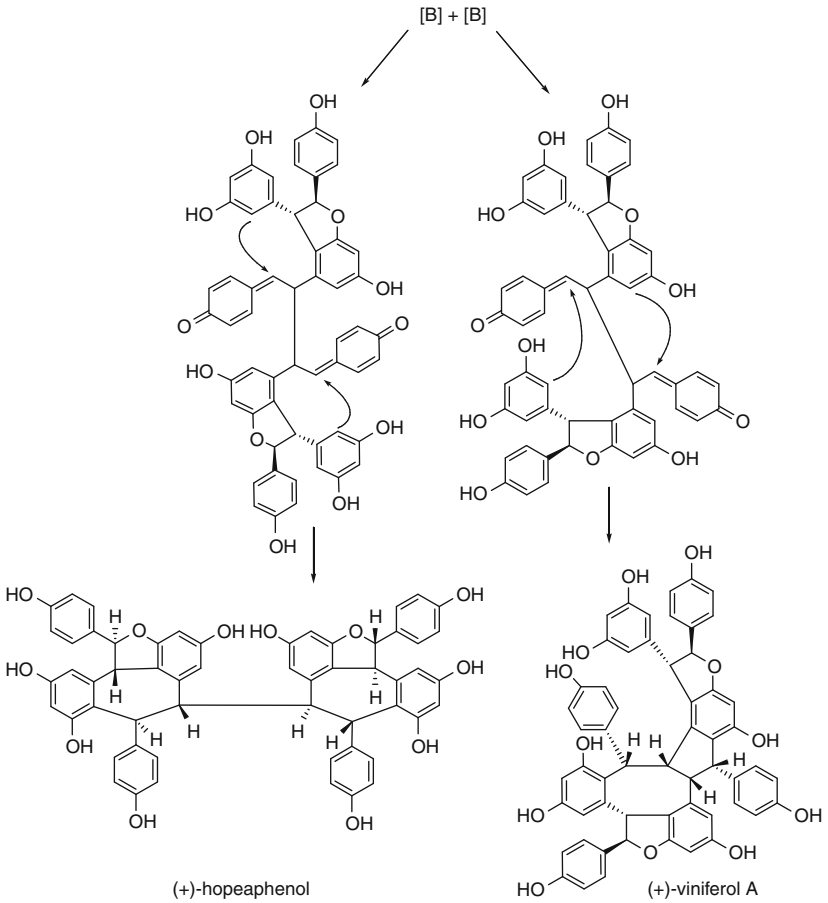
Scheme 62.3

3.3 Biosynthesis of Bibenzyls and Bisbibenzyls

The biosynthesis of marchantins A and C has been certified by a C-labeled precursor feeding experiment. It shows that rings A and C of the marchantin molecules are derived from the benzene ring of L-phenylalanine. The bibenzyl



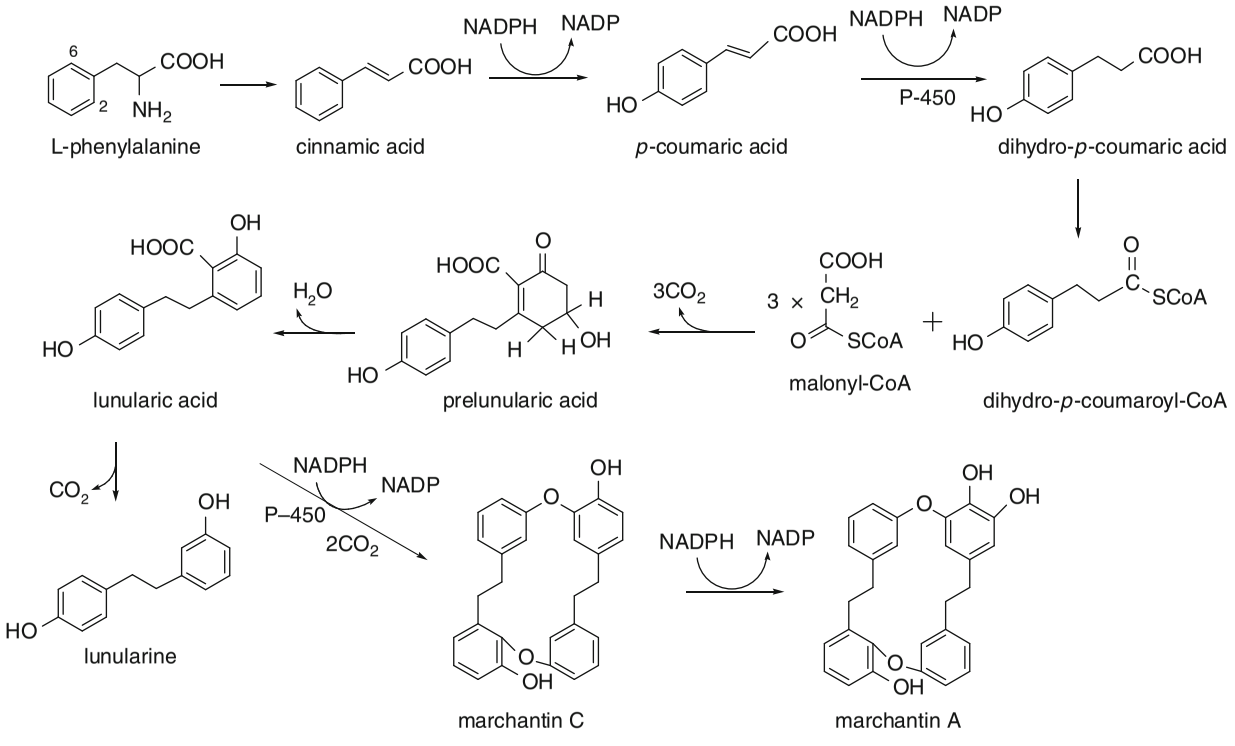
Scheme 62.4 (continued)



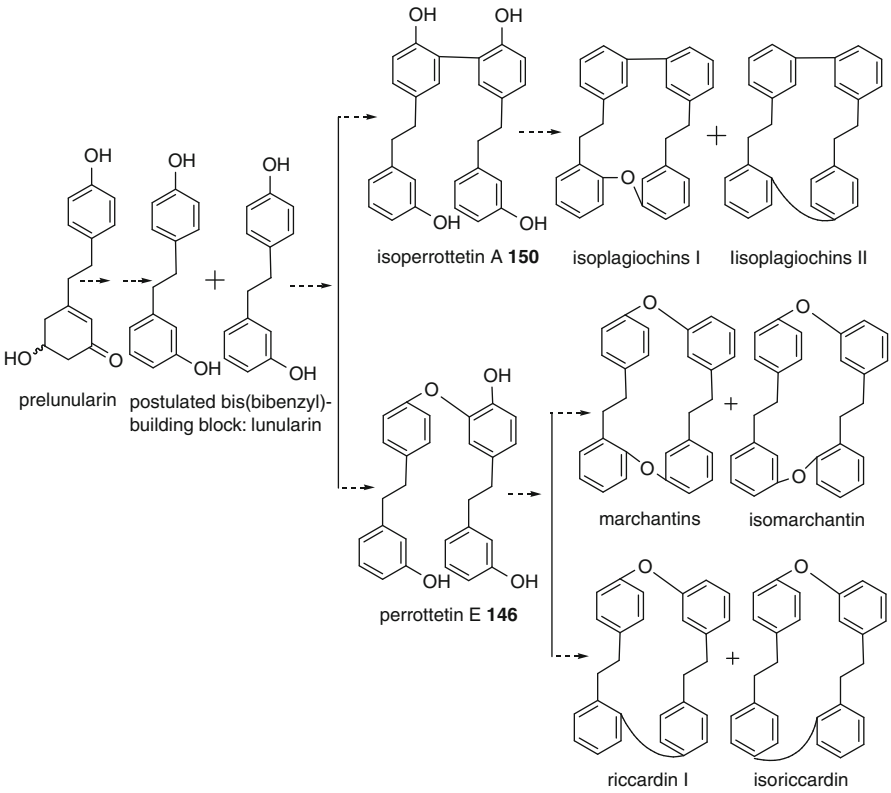
Scheme 62.4

lunularic acid is biosynthesized through dihydro-*p*-coumaric acid coupling with three malonyl-CoA units and then coupled in typical ways to form bisbibenzyls marchantins A and C (Scheme 62.5) [108].

Evidences have confirmed that bisbibenzyls can be produced by the coupling of two phenolic systems by means of free-radical reactions. These reactions can be mediated by oxidase enzymes. C–C bonds involving positions *ortho* or *para* to the original phenols, or ether linkages, may be formed in coupling of two of these bibenzyl structures [105]. A previous hypothesis for the biogenesis of


L-phenylalanine
cinnamic acid
NADPH
NADP
p-coumaric acid
P-450
dihydro-p-coumaric acid
lunularic acid
H2O
prelunularic acid
3CO2
3 ×
malonyl-CoA
dihydro-p-coumaroyl-CoA
CO2
lunularine
P–450
2CO2
marchantin C
marchantin A

Scheme 62.5

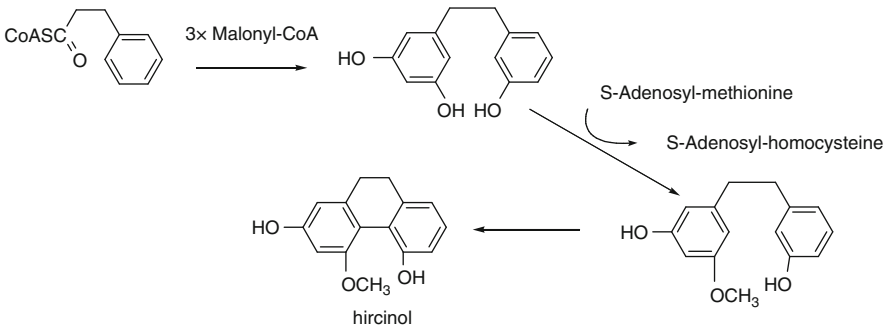


Scheme 62.6

marchantins, riccardins, and plagiochins considers cyclization of open-ring precursors, such as perrottetin E **146**, through intramolecular phenol oxidation, accompanied by C–O or C–C linkage of the terminal *m*-hydroxyphenyl units [109]. Likewise, isoplagiochins A-D might be biosynthesized from isoperrottetin A **150** (Scheme 62.6) [110].

3.4 Biosynthesis of Phenanthrenes

Bibenzyls are regarded as the bicyclic intermediates of 9,10-dihydrophenanthrenes, and the biosynthetic pathway of 9,10-dihydrophenanthrenes was proposed as showed in Scheme 62.7. Oxidative coupling of the bibenzyl intermediate leads to the formation of phenanthrene [2].



Scheme 62.7

4 Biological Activities

4.1 Antitumor Activity

4.1.1 Stilbenes and Oligostilbenes

Resveratrol, as a representative compound of stilbene, possesses diverse pharmacological activities. The antitumor property has taken the spotlight for its cancer preventive effect on skin cancer in a mice model. Subsequently, plenty of in vivo experiments targeting different tumor model were carried out to evaluate its therapeutic effects on tumors [111]. The results definitely show that resveratrol is able to inhibit or possess chemopreventive functions on different tumors, including breast cancer, liver cancer, gastric cancer, colorectal cancer, prostate cancer, leukemia, lung cancer, neuroblastoma, etc. In these experiments, the incidences, tumor volume, and metastasis are improved. Clinical trials of investigating resveratrol's effects on colon cancer and melanoma (skin cancer) are intending to launch.

Combretastatins attract a lot of interests for their potent antitumor properties by inhibiting tubulin polymerization and disrupting the formation of tumoral vasculature. Combretastatin A-4 **5** was proved to be the most potent candidate of combretastatins with GI_{50} of 3.20 nM in an antitumor screening project against the NCI-60 human tumor cell lines, followed by combretastatins A-1 **2** and A-2 **3** [112]. Further studies focused on the antitumor mechanism of combretastatins, and the results suggested that compounds **2**, **3**, and **5** possessed potent antimitotic effect through binding to the tubulin at colchicine site [113]. Combretastatin A-4, its prodrug combretastatin A-4 phosphate (CA-4-P), and other analogues are currently being investigated in the clinical trials. CA-4-P, being developed as vascular targeting agents, in combination with carboplatin has entered into phase III clinical trial for the treatment of anaplastic thyroid cancer.

The seeds of *Iris halophila* (Iridaceae) produced halophilol A, which possesses moderate cytotoxicity against KB cells and human mammary epithelial cells

(HMECs) with IC_{50} values of 17.28 and 22.47 μM [114], respectively. The prenyl stilbenes **30–32** with dimethylchromene ring exhibit cytotoxic activity against Hepa-1clc7 cells with IC_{50} values of 8.5, 13.0, and 7.0 μM [18], respectively. Tested in the NCI-60 cell line human cancer screen, schweinfurthins A **33** and B **34** show significant cytotoxic activity with mean panel GI_{50} of 0.36 and 0.81 μM. Schweinfurthins E-H were isolated from *M. alnifolia* [115] and display potent antiproliferative effect against A2780 human ovarian cancer cell line with IC_{50} values ranging from 0.26 to 5.0 μM, respectively. Lakoochins A and B also possess cytotoxic activity against breast cancer cell line (6.1 and 3.1 μg/mL) and nasopharyngeal carcinoma cell line (20 and 6.1 μg/mL) [116].

4.1.2 Oligostilbenes

Three trimers nepalensinols A, C, and D and three tetramers nepalensinols B, G, and F were obtained from *Kobresia nepalensis* (Cyperaceae) [117, 118]. The inhibitory effect of the above six oligomers against the decatenation activity of topoisomerase II on kinetoplast DNA is evaluated with IC_{50} values ranging from 0.02 to 10.8 μg mL^{-1}. Among them, nepalensinol B exhibits the strongest activity with an IC_{50} of 0.02 μg mL^{-1}, much better than the clinical antitumor drugs daunorubicin (IC_{50} 4.8 μg mL^{-1}) and etoposide (IC_{50} 70.0 μg mL^{-1}). Vaticanol C is a resveratrol tetramer with dibenzobicyclo[3.2.1]octadiene moiety, is widely distributed in Dipterocarpaceae species, and shows potent growth suppressive activity with IC_{50} values of 5.9 μM against HL60 cells. Upunaphenol A is a hexamer obtained from *Upuna borneensis* and was found to suppress cell growth in HL60 cells through induction of apoptosis with IC_{50} at 9.2 μM [119].

4.1.3 Bibenzyls and Bisbibenzyls

Erianin (also named dihydrocombretastatin A-4), a dihydro derivative of combretastatin A-4 which has been initiated phase II clinical trial as antitumor agent, possessed potent cytotoxicity toward diverse cancer cell lines. It was evaluated against A-549 lung carcinoma, MCF-7 breast carcinoma, HT-29 colon adenocarcinoma, SKMEL-5 melanoma, and MLM melanoma cell lines with ED_{50} ranging from 0.002 to 0.33 μM, respectively [120]. It also showed potent inhibitory activity on the proliferation of HL-60 cells (IC_{50} 38 nM) and was able to alter expression of *bcl*-2 and *bax* genes in HL-60 cells [121].

Bauhinols A **110** and B **111** exhibit significant cytotoxicity against NCI-H187 (small-cell lung cancer) and BC (breast cancer) cell lines with IC_{50} values ranging from 1.1 to 9.7 μg/mL. In addition, bauhinol A **110** is active toward KB cells (IC_{50} 4.5 μg/mL) [64]. 3,5-Dihydroxy-4-methylbibenzyl shows cytotoxic activity, which is able to inhibit the growth rate of P-388 leukemia and hepatoma cell lines by 99.7% and 83.6% at 10 μg/mL, respectively [122].

The bisbibenzyls neomarchantins A **133** and B **134**, marchantin C, and Glaucescens Bis Bibenzyl A and B possess moderate cytotoxicity against P-388 leukemia cells with IC_{50} ranging from 8 to 18 μg/mL [123]. Riccardin C and pusilatins B-C display moderate cytotoxicity against KB cells with ED_{50} of 7.1 to 16.4 μg/mL [79].

Table 62.2 In vitro cytotoxic activity of **181** and **182** with human cancer cell lines (ED_{50} μg/mL)

	Human cancer cell lines											
	A-431	BC1	Col2	HT	KB	KB-V (+VLB)	KB-V (−VLB)	Mel2	LNCaP	Lu1	U373	ZR-75-1
181	11.3	6.9	13.1	5.5	15.0	0.8	3.0	10.0	19.0	6.1	>20	11.2
182	9.4	13.4	>20	3.1	6.4	3.6	5.9	9.2	10.3	19.9	3.2	10.5

A-431, human epidermoid carcinoma; BC1, human breast cancer; Co12, human colon cancer; HT, human fibrosarcoma; KB, human oral epidermoid; KB-V(+VLB), drug-resistant KB + vinblastine (1 lag/mL); KB-V(−VLB), drug-resistant KB (no vinblastine); LNCaP, human prostate cancer; Lul, human lung cancer; Mel2, human melanoma; U373, human glioma; ZR-75-1, hormone-dependent human breast cancer

4.1.4 Phenanthrenes

The cytotoxic activities both in vitro and in vivo of lusianthridin and denbinobin isolated from *Dendrobium nobile* are evaluated. Both of them exhibit potent antitumor effects against A549 human lung carcinoma, SK-OV-3 human ovary adenocarcinoma, and HL-60 human promyelocytic leukemia with EC_{50} values ranging from 0.11 to 9.8 μg/mL [124].

Dimeric phenanthrenes denthyrsinol, denthyrsinone, and monomer denthirsinin demonstrate potent cytotoxicity against cervix adenocarcinoma HeLa, K-562, and MCF-7 cells with IC_{50} values from 1.6 to 9.9 μM [125]. A series of phenanthrenes, including 7-hydroxy-2,3,4,8-tetramethoxyphenanthrene, 3-hydroxy-2,4,-dimethoxy-7,8-methylenedioxyphenanthrene, 2-hydroxy-3,5,7-trimethoxyphenanthrene, 2-hydroxy-3,5,7-trimethoxy-9,10-dihydrophenanthrene, and confusarin are evaluated on their antitumor properties against HeLa cell line with IC_{50} values of 0.97–14.21 μM. [126, 127].

3,6-Dihydroxy-l,7-dimethyl-9-methoxyphenanthrene **181** and 3,6-dihydroxy-L-hydroxymethyl-9-methoxy-7-methylphenanthrene **182** are found to demonstrate significant cytotoxic responses against several tumor cell lines (Table 62.2). Compound **181** is more active against drug-resistant KB cells, while **182** is active against HT (fibrosarcoma) and U373 (glioma) cell lines [128].

4.2 Antioxidant Activity

4.2.1 Stilbenes and Oligostilbenes

Lespedezavirgatol was obtained from *Lespedeza virgata* and shows potent antioxidant property. Its oxygen radical absorbance capacity (ORAC) value for Trolox equivalents is 762.96 at 1.5 μM, much better than 164.56 of vitamin C. Inhibitory effects of lespedezavirgatol against lipid peroxidation toward malondialdehyde levels in rat kidney homogenate and plasma are also evaluated with IC_{50} values of 0.16 and 0.18 mM, better than the control vitamin C, with IC_{50} values of 5.54 and 3.05 mM. The above results suggest that lespedezavirgatol is a potent candidate for antioxidants [129]. Tibeticanol **76** was obtained

Table 62.3 Effect of compounds from *V. thunbergii* on $ABTS^+$ scavenging

Compounds	Free-radical scavenging activity (EC_{50} μM)
Vitisinol B	3.6 ± 0.1
Vitisinol C	4.5 ± 0.1
Vitisinol D	4.1 ± 0.1
(+)-ε-Viniferin	2.8 ± 0.1
(−)-Viniferal	4.4 ± 0.1
Ampelopsin C	5.4 ± 1.2
Miyabenol A	6.6 ± 1.2
(+)-Vitisin A	13.8 ± 2.7
(+)-Vitisin C	4.8 ± 0.1
Trolox (positive control)	28.4 ± 5.2

from *Caragana tibetica* and exhibits strong superoxide anion scavenging activity with an IC_{50} of 1.33 μM [46].

A series of oligostilbenes isolated from *Vitis thunbergii* are evaluated on their antioxidant properties based on the radical scavenging effect of the stable $ABTS^{\bullet+}$ free radical. The results are shown in Table 62.3. All of the tested compounds are more active than the positive control Trolox and display free-radical scavenging activity with EC_{50} values from 2.8 to 13.8 μM. Among them, (+)-ε-viniferin shows the most potent radical scavenging potency with EC_{50} of 2.8 μM [23].

4.2.2 Bibenzyls and Bisbibenzyls

Marchantin H is able to inhibit nonenzymatic iron-induced lipid peroxidation in rat brain homogenates and NADPH-dependent microsomal lipid peroxidation with an IC_{50} of 0.51 and 0.32 μM [130]. It also possesses inhibitory effects of copper-catalyzed oxidation of human low-density lipoprotein. Marchantinquinone exhibits inhibitory effects of Fe^{2+}-induced lipid peroxidation in rat brain homogenates (IC_{50} 15.3 μM) and displays radical scavenging activity [131]. Schwartner et al. reported the antioxidative potential of three macrocyclic bisbibenzyls [marchantins A, B, and D], one acyclic bisbibenzyl (paleatin B) and a prenylated bibenzyl (perrottetin D) by pulse-radiolytic and EPR-spectroscopic techniques. The results confirm that these compounds are effective antioxidants [132]. Isoamoenylin and 5,4′-dihydroxy-3-α-L-rhamnopyranosyl-(1→3)-β-D- xylopyranosyloxybibenzyl showed radical scavenging activity, comparable with the control vitamin C and ascorbic acid [63, 133]. Five prenylated dihydrostilbenes, α,α-dihydro-3,5,3,4-tetrahydroxy-4,5-diisopentenylstilbene, α,α-dihydro-3,5,3,4-tetrahydroxy-5-isopentenylstilbene **183**, α,α-dihydro-3,5,4-trihydroxy-4,5-diisopentenylstilbene, α,α-dihydro-3,5,4-trihydroxy-5-isopentenyl stilbene, and α,α-dihydro-3,5,3-trihydroxy-4-methoxy-5-isopentenylstilbene **184**, from *Glycyrrhiza glabra* were tested for antioxidant effects by measuring the absolute inhibition rate constant (k_{inh}) of the oxidation process. Compounds **183** and **184** display potent antioxidant properties with k_{inh} values of 1.1×10^4 and 0.9×10^4 $M^{-1}s^{-1}$ [134].

Table 62.4 Effect of compounds isolated from *V. thunbergii* on the platelet aggregation induced by AA and U46619

	IC_{50} (μM)	
Compounds	AA	U46619
Vitisinol B	>100	7.8 ± 2.2
Vitisinol C	13.4 ± 2.2	10.5 ± 3.4
Vitisinol D	15.0 ± 4.8	5.7 ± 1.4
(−)-Viniferal	7.0 ± 2.9	3.1 ± 2.5
Ampelopsin C	8.1 ± 1.1	5.9 ± 0.9
Miyabenol A	9.0 ± 1.6	7.5 ± 2.0
(+)-Vitisin A	10.3 ± 1.2	13.3 ± 2.1
(+)-Vitisin C	5.7 ± 1.3	3.9 ± 0.7
Aspirin (positive control)	32.7 ± 6.4	Not detected

4.3 Antiplatelet Activity

Resveratrol prevents platelet aggregation and thrombus formation in vitro. In a hypercholesterolaemic diet-induced rabbit model, administration of resveratrol inhibited the platelet aggregation. This effect was also verified by reducing the atherosclerotic area and the size of the thrombus generated by laser-induced damage to the endothelium in mice.

Vitis thunbergii (Vitaceae), a folk medicine in Taiwan, produced several resveratrol oligomers, including vitisinol C with a tropilene structure in molecule, vitisinols B and D, and some known compounds (−)-viniferal, (+)-ε-viniferin, and (+)-vitisin C, etc. The isolated compounds were evaluated for antiplatelet aggregation activities induced by arachidonic acid (AA) and 9,11-dideoxy-11α,9α-epoxymethanoprostaglandin F2α (U46619). Most of the tested oligomers demonstrate potent antiplatelet aggregation property with IC_{50}<10 μM, more positive than aspirin (EC_{50} 32.7 μM). In the above bioassay, (−)-viniferal and (+)-vitisin C are most effective against aggregation induced by AA and U46619, with IC_{50} values of 5.7 and 3.1 μM, respectively [23]. The results are summarized in Table 62.4.

Marchantinquinone displays potent inhibitory activity on the aggregation of washed rabbit platelets induced by thrombin, arachidonic acid (AA), collagen, U46619, and platelet-activating factor (PAF) [135, 136]. It inhibits thromboxane B_2 (TxB_2) formation induced by thrombin, PAF, and collagen. In addition, marchantinquinone is able to inhibit the rising intracellular Ca^{2+} concentration stimulated by five inducers mentioned above [136]. Gigantol exhibits antiplatelet aggregation activity on SD-rat platelet aggregation [137]. 3-Methylgigantol possesses significant inhibitory effects against aggregation induced by AA, collagen, and PAF [138]. Among them, 3-methylgigantol is most potent effective against AA-induced aggregation (IC_{50} 30 μM). Moscatilin is able to inhibit AA- and collagen-induced platelet aggregations [139]. Perrottetin E **146** shows inhibitory activity of thrombin (IC_{50} 18 μM) [140].

The phenanthrenes, erianthridin, and denbinobin display potent antiplatelet activity on washed rabbit platelets against aggregation induced by either thrombin, arachidonic acid (AA), collagen, or PAF at a dose of 100 μg/mL. Erianthridin is proved to be the most potent compound with an IC_{50} of 9 μM against AA-induced aggregation [138].

4.4 Antidiabetic Activity

5,4′-Dihydroxystilbene-3-*O*-α-arabinopyranoside, named rumexoid, was found in *Rumex bucephalophorus* (Polygonaceae). This compound and resveratrol display potent α-glucosidase inhibitory activity even better than the commercial antidiabetic agent acarbose [141]. 2′-*O*-Demethylbidwillol B and addisofurans A-B were prenyl-substituted arylbenzofurans isolated from *Erythrina addisoniae*. Those compounds are inhibitors of type II diabetes target protein tyrosine phosphatase 1B with IC_{50} values of 13.6–15.7 μM. The linear prenyl chain was responsible for its inhibitory activity, and the cyclization of prenyl group decreased this effect [142]. In a bioassay-guided fractionation against α-glucosidase, 13-hydroxykompasinol A and scirpusin C were obtained from the seeds of *Syagrus romanzoffiana* and possess potent inhibitory activity against α-glucosidase type IV from *Bacillus stearothermophilus* with the IC_{50} value of 6.5 and 4.9 μM [143].

4.5 Antimicrobial Activity

4.5.1 Stilbenes and Oligostilbenes

Machaeriol B, a compound with hexahydro-6*H*-benzo[c]chromene system, was obtained from *Machaerium multiflorum* (Leguminosae), and it demonstrates potent antimalarial activity (IC_{50} 0.12 μg/mL) against *Plasmodium falciparum* [144]. Preracemosols A and B exhibit moderate antimalarial activity with EC_{50} of 18.0 and 3.0 mg/mL, respectively [145]. *Trans*-4-isopentenyl-3,5,2′,4′-tetrahydroxystilbene was discovered in *Artocarpus integer* (Moraceae) and possesses antimalarial activity against *Plasmodium falciparum* ($EC_{50} = 1.7$ μg mL^{-1}) [146]. This is the first report of antimalarial activity of stilbenes.

A series of arylbenzofuran-type stilbenes, guided by bioautographic assay for antifungal activity against *Cladosporium herbarum*, have been isolated from the root of *Stemona collinsae* (Stemonaceae) and tested in microwells against another four microfungi *Alternaria citri*, *Fusarium avenaceum*, *Pyricularia grisea*, and *Botrytis cinerea* [22]. Among them, stemofuran B shows the highest antifungal potency against above four parasitic fungi with EC_{50} values of 1.4 μg/mL. Stemofuran E exhibited antifungal property against *C. herbarum* with EC_{50} of 0.09 μg/mL.

Stilbene derivatives were obtained from *Calligonum leucocladum*, and the structures were determined as (*E*)-resveratrol 3-(6-galloyl)-*O*-β-D-glucopyranoside.

Although ineffective when tested alone, it is able to restore oxacillin's effectiveness against oxacillin/methicillin-resistant *Staphylococcus aureus* when used in combination. The galloyl group may play a role in this synergistic activity [147].

Hopeanolin was obtained from the stem bark of *Hopea exalata* and exhibits potent antifungal properties against six types of pathogenic fungi *Alternaria attenata*, *Alternaria solani*, *Colletotrichum lagenarium*, *Fusarium oxysporum f.* sp. *vasinfectum*, *Pyricularia oryzae*, and *Valsa mali* with MIC values ranging from 0.10 to 22.5 μg mL^{-1} [148].

4.5.2 Bibenzyls and Bisbibenzyls

Bryophytes normally grow in humid habitats; however, they are seldom damaged by fungi. It indicates that bryophytes are able to elaborate constitutive and inducible antifungal natural products against adverse effects. A large amount of bibenzyls and bisbibenzyls with antifungal activity have been found in plants, primarily in bryophytes (Table 62.5), which provided important sources for research and development of antifungal agents. The antifungal effects of bibenzyls and bisbibenzyls were summarized in Table 62.5.

The bibenzyls 4-hydroxy-3′-methoxybibenzyl, 2,4,6-trichloro-3-hydroxybibenzyl, 2, 4-dichloro-3-hydroxylbibenzyl, 2-chloro-3-hydroxybibenzyl, together with bisbibenzyls neomarchantins A **133** and B **134**, and marchantin C show antimicrobial activity against the gram-positive bacterium *Bacillus subtilis* [60, 123, 150]. In addition, 4-hydroxy-3′-methoxybibenzyl is active toward *Escherichia coli* [150].

4.6 Anti-inflammatory Activity

Anti-inflammatory properties of resveratrol have been confirmed, which is an effective inhibitor of cyclooxygenase (COX) in vitro. It is also found that resveratrol significantly reduces acute and chronic chemically induced edema, lipopolysaccharide-induced airway inflammation, and osteoarthritis. Resveratrol could also present as an alternative, instead of aspirin, for treatments of chronic inflammation because of the latter's side effect on the stomach. Resveratrol derivatives displayed similar anti-inflammatory effects. For instance, resveratrol (*E*)-dehydrodimer 11-*O*-β-D-glucopyranoside and resveratrol (*E*)-dehydrodimer from *Vitis vinifera* show significant inhibitory activity against cyclooxygenase-1 (COX-1) with IC_{50} of 5.2 and 4.3 μM and against cyclooxygenase-2 (COX-2) with IC_{50} of 7.5 and 3.7 μM. From the above results, these two compounds seem to be the worthy candidates for further research to find application in anti-inflammatory treatment [151].

(+)-Vitisifuran A and heyneanol A were found in *Vitis* genus and display potent inhibition on biosynthesis of LTB_4 with inhibitory rate of 72% and 76% at a concentration of 10 μM [152]. A tetramer named gnetuhainin R **73** was obtained from the same species (*G. hainanense*) and shows potent histamine receptor antagonism (IC_{50} 0.1 μM) [44]. Aiphanol exhibited significant inhibitory activities against COX-1 (IC_{50} 1.9 μM) and COX-2 (9.9 μM) [153].

Table 62.5 Antifungal bibenzyls and bisbibenzyls

Compound	Fungi	Dose	References	Compound	Fungi	Dose	References
Bauhinol B	*Candida albicans*	28.9[a]	[64]	2,4-Dichloro-3-hydroxy bibenzyl	*Candida albicans*	2[f]	[60]
Bazzanin B	*Botrytis cinerea*	18.9[a]	[149]		*Cladosporium resinae*	2[f]	
	Cladosporium cucumerinum	17.5[a]			*Trichophyton mentagrophytes*	12[f]	
	Pyricularia oryzae	3.9[a]		Dihydropinosylvin	*Botrytis cinerea*	69[b]	[91]
	Septoria tritici	23.5[a]			*Cladosporium herbarum*	32[b]	
Bazzanin S	*Cladosporium cucumerinum*	30.8[a]	[149]		*Fusarium avenaceum*	56[b]	
	Phythophthora infestans	29.2[a]			*Pyricularia grisea*	44[b]	
	Pyricularia oryzae	2.6[a]		Isoplagiochin D	*Botrytis cinerea*	7.6[a]	[149]
	Septoria tritici	4.5[a]			*Cladosporium cucumerinum*	13.0[a]	
2-Chloro-3-hydroxybibenzyl	*Candida albicans*	2[f]	[60]		*Pyricularia oryzae*	4.0[a]	
	Trichophyton mentagrophytes	3[f]			*Septoria tritici*	15.9[a]	
Riccardin H **136**	*Candida albicans*	0.4[c]	[80]				

[a]IC_{50} (μg/mL)
[b]EC_{50} (μg/mL)
[c]MID (μg)
[d]LC_{90} (ppm)
[e]MIC (μg/mL)
[f]Width of the zone of inhibition (mm) at 30 μg/disk

Stemofurans B, D, G, and J and stilbostemin G were reported possessing anti-inflammatory effects with IC_{50} values ranging from 3.7 to 26.3 μM by inhibiting leukotriene formation [154]. The inhibition of lipopolysaccharide-induced nitric oxide synthase (NOS) by 19 bisbibenzyls in RAW 264.7 macrophages has been reported, and marchantin A is most effective with IC_{50} values of 1.44 μM. The structure-activity relationship (SAR) is discussed, and the phenolic hydroxyl groups and diarylether bonds play important roles in its inhibitory effect [155]. Pusilatins B-C exhibit selective DNA polymerase-β inhibitory activity with IC_{50} of 13.0 and 5.16 μM [79]. Bauhinol B **111** and 3,5-dihydroxy-2-(3-methyl-2-butenyl)bibenzyl are potent inhibitors of COX-1 and COX-2 with IC_{50} ranging from 1.3 to 9.0 μg/mL [134].

Phenanthrenes obtained from the *Stemona* species were evaluated on their leukotriene biosynthesis inhibition property using human neutrophile granulocytes in vivo. Stemanthrenes A **162** and D **165** display inhibitory activity in a dose-dependent manner, with IC_{50} values of 8.5 and 4.8 μM. Stemanthrenes B **163** and C **164** possess 100% inhibition against leukotriene biosynthesis at 25 μM. The phenanthrenes might be responsible for the anti-inflammatory and antiasthmatic principles of the *Stemona* species [154]. Denbinobin, a phenanthraquinone from *Dendrobium moniliforme*, shows in vitro anti-inflammatory activity. It inhibits the formation of tumor necrosis factor and prostaglandin E2 induced by lipopolysaccharide in RAW 264.7 and N9 cells at a dose of 1 μM [100].

4.7 Neuroprotective Activity

In vivo pharmacological studies have indicated that resveratrol has a neuroprotective effect, including reduced lipid, peroxidation and neurological cell destruction, attenuation of induced lesion areas, induced tolerance to brain injury, reduced frequency of seizures, impairment of motor coordination, and enhancement of learning [111].

Stilbostemin B 3′-β-D-glucopyranoside, stilbostemin H 3′-β-D-glucopyranoside, and stilbostemin I 2″-β-D-glucopyranoside possess significant neuroprotective activity against 6-hydroxydopamine-induced neurotoxicity in human neuroblastoma SH-SY5Y cells [156]. Hopeahainol A from *Hopea hainanensis* contains an unprecedented carbon skeleton and shows potent acetylcholinesterase inhibitory effect with an IC_{50} value of 4.33 μM, comparable even to that of huperzine A (IC_{50} 1.6 μM) [157]. The tetramer neohopeaphenol A from the same species also displays significant inhibitory action against AChE with an IC_{50} value of 7.66 μM [158].

4.8 Hepatoprotective Activity

Acer mono (Aceraceae), a Korean folk medicine for hemostasis, produces two potent hepatoprotective stilbene glycosides, 5-*O*-methyl-(*E*)-resveratrol 3-*O*-β-D-glucopyranoside and 5-*O*-methyl-(*E*)-resveratrol 3-*O*-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside [16]. Those two compounds significantly prevent the depletion

of glutathione (GSH) in H_2O_2-injured primary cultured rat hepatocytes and potently restore the level of GSH depleted by buthionine sulfoximine or diethylmaleate in the presence or absence of H_2O_2. In addition, they preserve the effects of antioxidant enzymes such as superoxide dismutase, glutathione reductase, and glutathione peroxidase reduced by H_2O_2 insults. Therefore, it is concluded that both compounds exerted significant hepatoprotective effects against H_2O_2-induced hepatotoxicity by maintaining the antioxidant defense system [159].

4.9 Cardioprotective Activity

It is well known that drinking wine and grape juices will reduce cardiovascular, cerebrovascular, and peripheral vascular risks due to the presence of resveratrol. As a natural antioxidant, resveratrol is able to prevent LDL oxidation, scavenge intracellular reactive oxygen species, lower the oxidative stress, and induce NO synthesis. Resveratrol modulates various aspects of cardiovascular diseases and is effective against atherosclerosis, hypertension, ischemia reperfusion injury and heart failure, and many other cardiac dysfunctions [111].

4.10 Phytotoxicity

The phenanthrenes, ephemeranthol-A and fimbriol A from *Epidendrum rigidum*, together with erianthridin from *M. densa* demonstrated phytotoxicity against *Amaranthus hypochondriacus* with IC_{50} values of 0.12, 5.9, and 58.2 μM [160]. The phenanthrenes from the *Juncus* genus show growth inhibitory effects against the green alga *Selenastrum capricornutum* with IC_{50} values ranging from 11.1 to 19.9 μM [161].

Bibenzyls are elaborated to confer the producing plants' selective advantage against the competition from the other plants and microbial attack. Gigantol, batatasin III, 2,3-dimethoxy-9,10-dihydrophenathrene-4,7-diol, and 3,4,9-trimethoxyphenanthrene-2,5-diol from the orchid *Epidendrum rigidum* inhibit radicle growth of *Amaranthus hypochondriacus* with IC_{50} of 0.65, 0.1, 0.12, and 5.9 μM [160].

5 Conclusion

Stilbenoids represent a group of important natural products in the plant kingdom. The developments of modern analytical methods accelerate the discovery of these compounds, and to this day more than 1,000 stilbenoids have been isolated. For the stilbenes, bibenzyls, and phenanthrenes, these three groups shared the feature of their nucleus with hydroxyls, methyl, methoxy, prenyl, geranyl, glycosyl, etc., substituents. The oligostilbenes and bisbibenzyls are formed by polymerization of stilbene and bibenzyl units, and the diverse polymerized patterns produced their

diverse structures. They display diverse biological activities and have the potential to be developed as new drugs, especially in the field of antitumor, anti-inflammation, and cardioprotective drug research. The representative compounds resveratrol and combretastatin A-4 phosphate are currently being evaluated as drugs for the treatment of Alzheimer's disease and tumors in clinical trials and have shown satisfactory therapeutic effects. Furthermore, resveratrol displays developing prospects as a cardioprotective drug.

There are problems that need to be noted. Concerning the oligostilbenes, they commonly possess large molecules, intricate structures, and complex stereochemistry, and these characteristics cause troubles in structure identification and chemical total synthesis, therefore, limiting the probability to be developed to new drug. The bisbibenzyls are mainly distributed in the bryophytes, which are very small terrestrial spore-forming green plants, and different for collections. Therefore, getting enough plant materials for phytochemical investigation and new drug research is really a Gordian knot and resorts to the chemical synthesis for resolving the resource problems.

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