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REVIEW

Natural disesquiterpenoids

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This review covers the isolation, structural determination, biological activities and biomimetic synthesis of all natural dimeric sesquiterpenoids, along with a detailed discussion of the biogenesis of these metabolites. Syntheses leading to the revision of structures have also been included, and 368 references are cited.

1 Introduction

Natural products, commonly termed as 'secondary metabolites' in contrast to 'primary metabolites', have played a significant role over the last 200 years in treating and preventing diseases, and are continuing to serve as important leads in modern drug discovery.[1–6] As secondary metabolites, these compounds have been elaborated in living organisms by complex enzyme systems developed over a long process of evolution. It is apparent that these natural products present more 'drug-like' or 'biologically friendly' molecular features compared with many purely synthetic compounds. These intrinsic properties provide natural products with an important potential role in modern drug discovery.[7–10]

There are some naturally occurring metabolites that have C_{30} cores, but that originate biosynthetically from two sesquiterpenoid molecules (which may be identical or different) – such metabolites are commonly termed 'disesquiterpenoids' or 'sesquiterpenoid dimers'. Although they have diverse structures, disesquiterpenoids can be classified into three major classes based on their biosynthetic origins, namely *true disesquiterpenoids* (type A), *pseudo-disesquiterpenoids* (type B), and *di-merosesquiterpenoids* (type C). The first two types originate from farnesyl diphosphate, whilst the latter arises from a mixed biosynthetic pathway which is partially derived from a sesquiterpenoid. True disesquiterpenoids refer to structures in which two units of a sesquiterpenoid are linked directly by one or two C–C bonds, which are mainly formed by Diels–Alder,[11] hetero-Diels–Alder, [2 + 2] cycloaddition, or free-radical coupling reactions as shown in Scheme 1. An overview of reports on the true disesquiterpenoids reveals that guaiane dimers and lindenane dimers are mainly formed by Diels–Alder or hetero-Diels–Alder reactions. Conjugated double bonds or α,β-unsaturated ketones that provide dienes and/or dienophiles for these reactions are often found in the parents of these dimers. In contrast, most cadinane and cuparane dimers are formed by the free-radical coupling reaction of two units of the corresponding monomers, as a phenyl group is often present in their structures. From a structural perspective, type B can be easily distinguished since the two units of the sesquiterpenoids are connected by ester, ether or other groups. An overview of the published work on disesquiterpenoids reveals that types A and B are found mainly in the Compositae and Chloranthaceae families, whereas compounds of type C are mainly isolated from microbes and marine organisms.

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Furthermore, the genera *Artemisia* and *Ligularia* are rich sources of guaiane dimers and eremophilane dimers, respectively. Almost all lindenane dimers and sesquiterpenoid alkaloid dimers are found in the genera *Chloranthus* and *Nuphar*, respectively. These metabolites play an important role in chemotaxonomy.

There are many reviews on sesquiterpenoids[12] and on secondary metabolites from a specific family[13] or genus[14,15] that include some of the naturally occurring disesquiterpenoids, but none has provided a complete and in-depth view of this group of natural products. The current review provides extensive coverage of all naturally occurring disesquiterpenoids isolated over the last five decades. The occurrence, distribution and biosynthetic origins of disesquiterpenoids will be discussed in detail. The approaches to the disesquiterpenoid subunits and synthetic efforts towards some of the biologically important examples are also presented.

2 True disesquiterpenoids

2.1 Bisabolane dimers

Diperezone **1**, a symmetrical bisabolane sesquiterpenoid dimer, was obtained from the roots of *Perezia alamani* var. *oolepis*.[16] Definitive structural proof was acquired by direct comparison with a sample prepared by boron trifluoride catalyzed dimerization of perezone.[17] Phytochemical investigation of the aerial parts of *Coreocarpus arizonicus* from Arizona resulted in the isolation of **1** and its 12-(2-methylbutyroxyl) and 12-isovaleroxyl derivatives **2–3**.[18] A novel dimer from an extract of the aerial parts of *Baccharis petiolata* was identified as bacchopetiolone **4**. Biogenetically, it may be formed by an unusual *exo*-[4 + 2] cycloaddition of two molecules of bisabolones.[19] The stereoselective synthesis of the carbocyclic core of **4** was completed in 2006, in which a tandem phenolic

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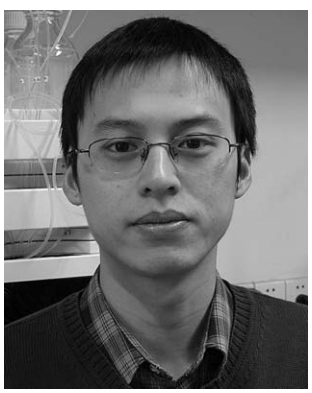
Lie-Feng Ma

Lie-Feng Ma was born in Shaoxin, China, in 1985. He received his B.S. degree from Zhejiang University of Technology in 2008. In the same year, he joined the research group of Professor Wei-Guang Shang as an M.S. student at the same institution, where he is currently carrying out research on the isolation and structural elucidation of bioactive natural products from Traditional Chinese Medicines.

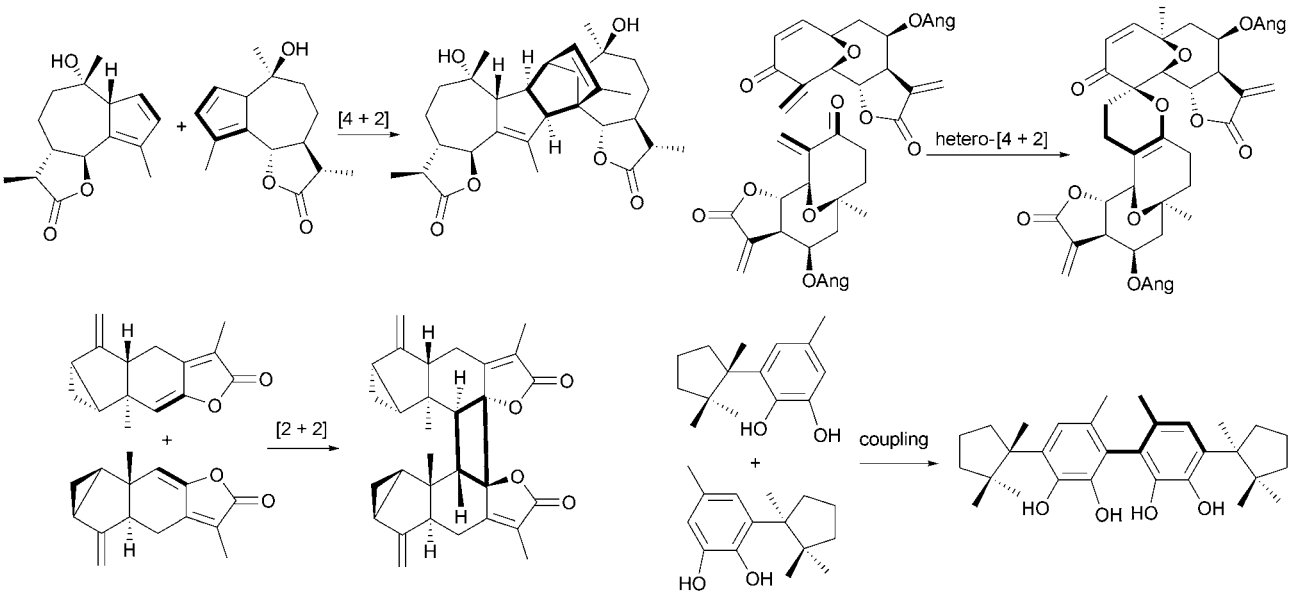


You-Min Ying

You-Min Ying was born in Xianju, China, in 1985. He received his B.S. degree from Zhejiang University of Technology in 2007. In the same year, he joined the research group of Professor Wei-Guang Shang as a Ph.D. student at the same institution, where he is currently carrying out research on the isolation and structural elucidation of bioactive natural products from endophytes.

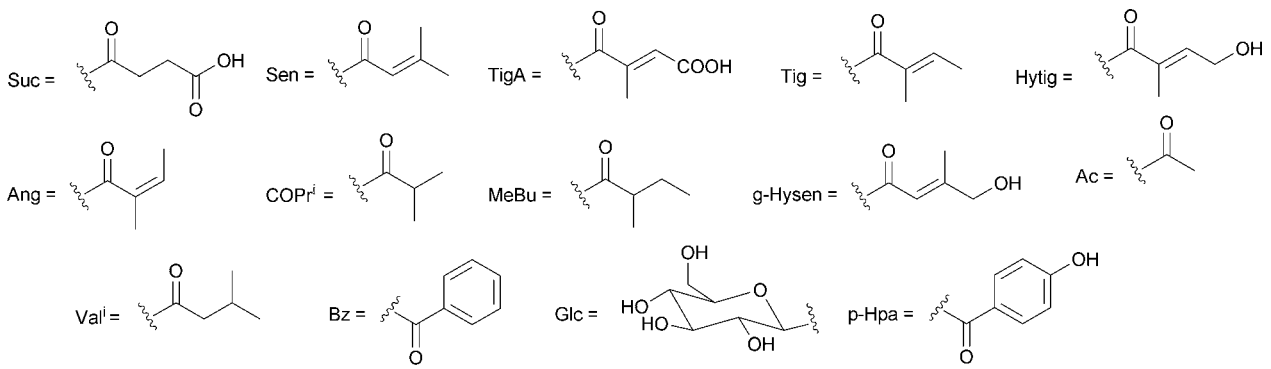
Wei-Guang Shan

Wei-Guang Shan was born in Ningbo, China, in 1961. He received his B.S. degree from Zhejiang University of Technology in 1983, where he remains. In 1998, he received his M.S. degree in Chemistry from Zhejiang University under the guidance of the late Professor Yao-Zhu Chen. During his research career, he has published over 70 scientific papers, book chapters, and patents. His group is actively involved in the isolation, structure determination, and synthetic optimization of natural products, and is currently focused on natural products with activity against infectious diseases, cancer, and neurodegenerative disorders.

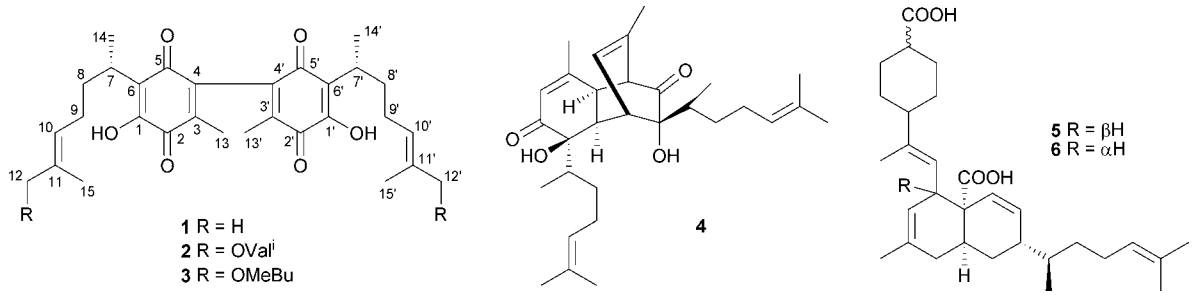


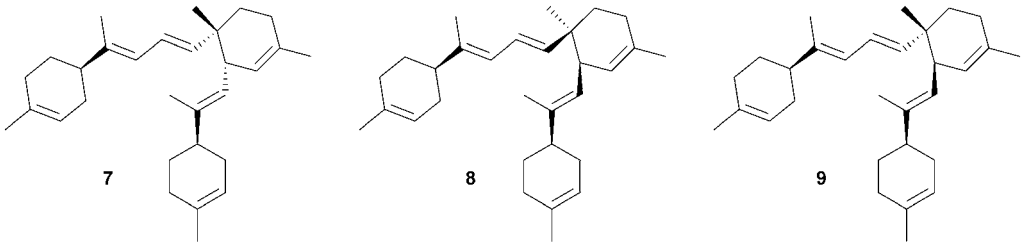
Scheme 1 Four important biosynthetic pathways for true disesquiterpenoids.

oxidation/Diels–Alder reaction was used.[20] A pair of epimers named meiogynins A **5** and B **6** are Diels–Alder-type adducts from *Meiogyne cylindrocarpa*, of which meiogynin A **5** showed potent activity against B-cell lymphoma-extra large (Bcl-xL) and moderate cytotoxic activity.[21] Three diastereoisomeric dimers, *cis*-dimer A **7**, *cis*-dimer B **8** and *trans*-dimer C **9**, were isolated from the South China Sea sponges *Axinyssa variabilis* and *Lipastrotethya ana*, along with dehydrothenonelline, which was their potential precursor. Although the two sponges belong to two different families, the formation of the same metabolite suggests that they may in fact be related.[22]



Structural abbreviations used in this review



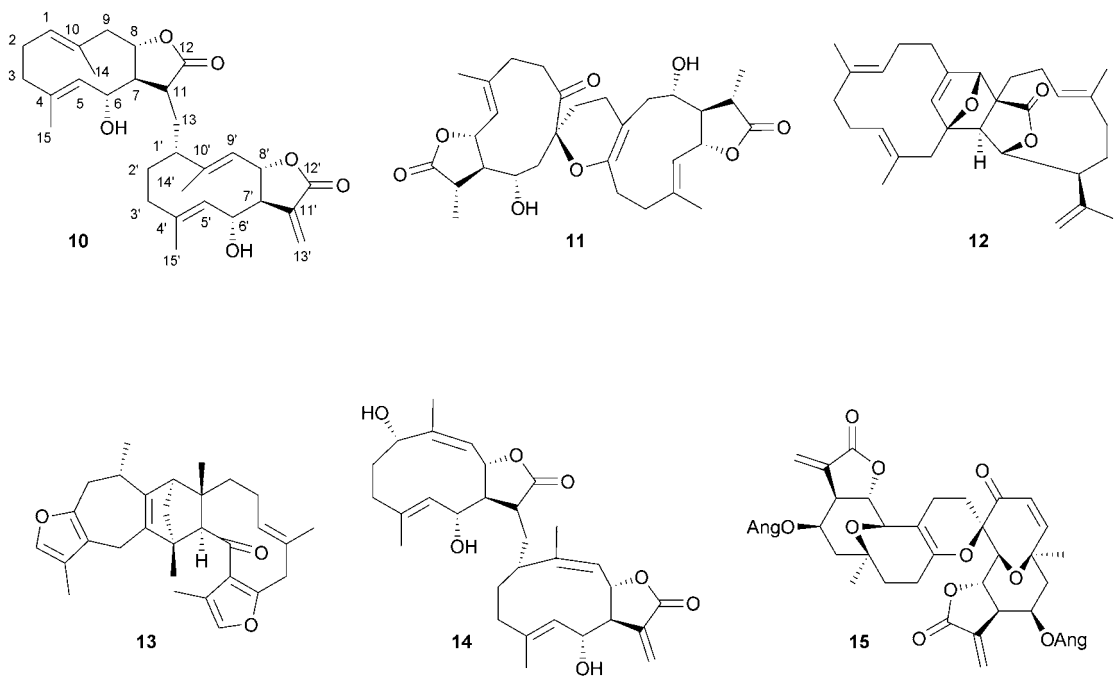


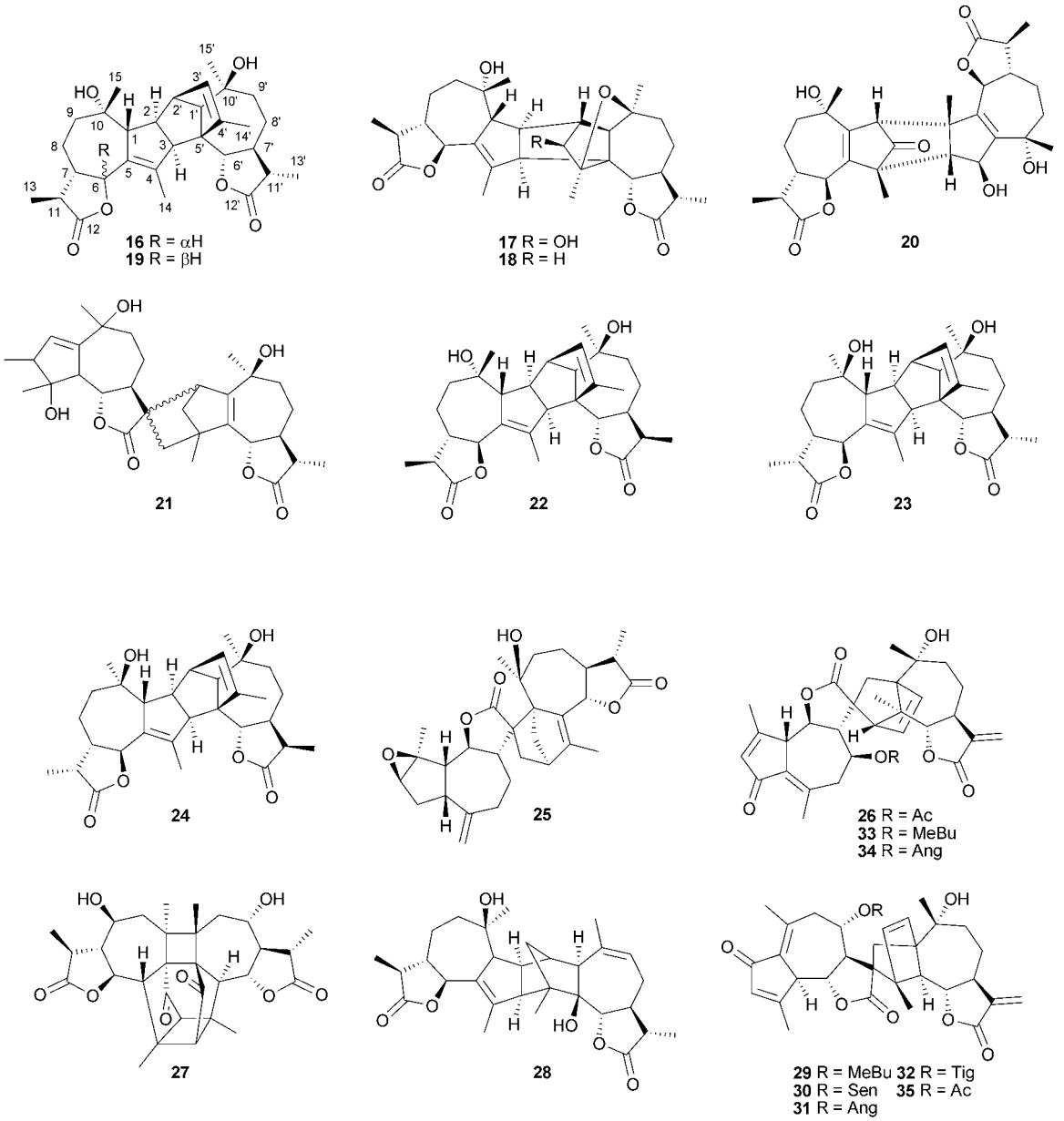
2.2 Germacrane sesquiterpenoid dimers

Investigation of *Mikania goyazensis* afforded a dimer named mikagoyanolide **10**, which was probably formed by dimerization of desacetyl laurenobiolide initiated by proton attack.[23] The metabolite was also found to occur in *Tanacetopsis mucronata*, and its structure was confirmed by X-ray crystallographic analysis.[24] Artebarrolide **11** was isolated from the aerial parts of *Artemisia barrelieri*.[25] Versicolactone D **12** was obtained from *Aristolochia versicolor*.[26] Difurocumenone **13** from *Curcuma zeodoaria*, which is the product of stereoselective Diels–Alder reaction of two sesquiterpenoids, was identified by NMR, CD and X-ray techniques.[27,28] Separation of the EtOH extract of *Gonospermum elegans* resulted in the characterization of elegain **14**.[29] Helivypolide G **15**, in whose structure two monomers are connected through carbons C-15 of each unit and an oxygen bridge to form an enolic oxane ring, was isolated from the medium-polarity and bioactive fractions of the leaves of *Helianthus annuus*.[30] The dimer inhibited the growth of wheat coleoptile 72% and 50% at 1 and 0.1 mM, respectively, which indicated that the dimer may serve as a phytotoxin to protect the plant.

2.3 Guaiane and pseudoguaiane sesquiterpenoid dimers

Absinthin **16**, the first dimeric guaianolide, was reported from *Artemisia absinthium*,[31–34] and its structural elucidation was completed in the 1980s by NMR spectroscopy[35] and X-ray crystallographic analyses.[36] To date, a large number of dimers, **17–43**, belonging to this type have been characterized from the genus (listed in Table 1).[37–53] Biosynthetically, all these dimers except **27** from the genus originate from the products of Diels–Alder reaction between dienophile and diene. The retro-Diels–Alder products of these dimers were often observed in the EI and CI mass spectra.[44,48] A study directed towards the biomimetic synthesis of absinthin also partly supports the biosynthetic pathway mentioned above.[54] These metabolites exhibited a wide range of biological activities, such as cytotoxicity,[53] anti-COX-2[53] and anti-HIV-1 protease activity.[51] The most active dimers were arteminolides A–D, which are farnesyl protein transferase (FTPase) inhibitors.[48–50] Specific inhibitors of the FPTase might be interesting chemical leads to develop effective therapeutic agents for the treatment of cancer.[55] These novel dimers could be utilized as lead compounds for modification to provide a better anti-cancer medicine. To address the concern

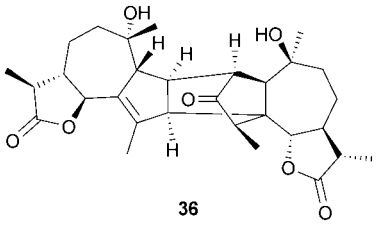




that some of the guaiane dimers isolated from this genus might be artefacts of the isolation procedure, arglabin (a presumed monomeric precursor involved in formation of most of these dimers from the genus of *Artemisia*) was left in $CDCl_3$ solution for several weeks, in an attempt to mimic the extraction process in which plant material is repeatedly extracted with organic solvent. Under these conditions, no observable dimerization occurred, which indicated that these dimers were natural products produced by plants.[52]

Microlenin **44**, microlenin acetate **45** and mexicanin F **46** are antineoplastic constituents of *Helenium microcephalum*.[56–59] Further research demonstrated that DNA synthesis and protein synthesis were significantly inhibited by microlenin **44**. DNA synthesis appeared to be blocked at several sites including DNA polymerase, purine synthesis, and dihydrofolate reductase.[60] A phytochemical study of the polar fractions of *Ambrosia maritima* afforded two new dipseudoguaianolides, and their structures were determined as 11′-epimaritimolide **47** and maritimolide **48**.[61] Two pseudoguaianolide dimers possessing similar structures to **48** were reported from the aerial parts of *Dichrocephala integrifolia*, and showed potent inhibitory effects on lipopolysaccharide induced nitric oxide production in mouse peritoneal macrophages. Chemical and physicochemical evidence revealed their structures to be dichrocepholides D **49** and E **50**.[62] Biennin C **51** was obtained from the dichloromethane extract of the leaves and flowers of *Hymenoxys biennis*.[63]

Pungiolides A–C **52–54** are three 4,5-secoguaianolide dimers isolated from *Xanthium pungens*.[64,65] Chemical investigation of *Salvia nubicola* furnished three dimeric guaianolides, namely



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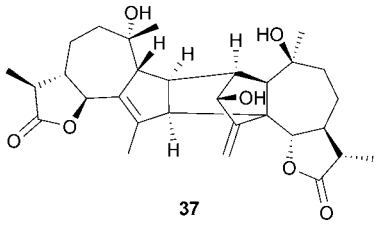

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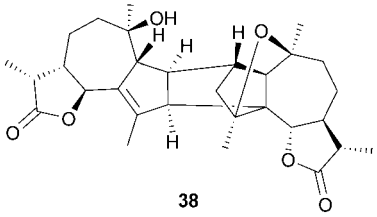

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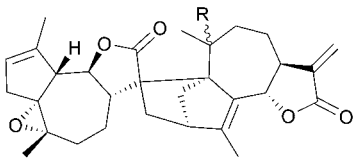
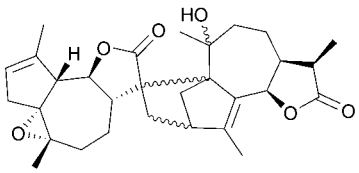


39 R = αOH
40 R = βOH



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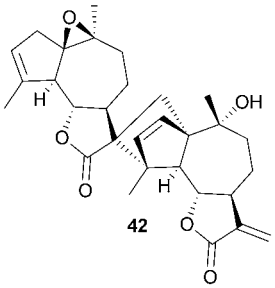

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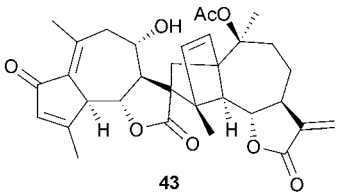

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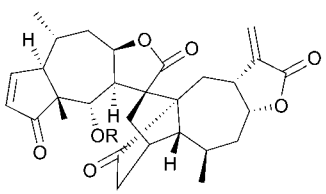
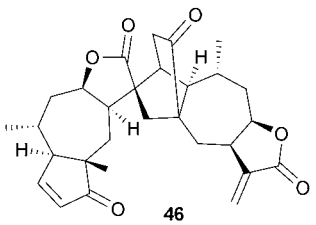
Table 1 Dimeric guaianes from the genus *Artemisia*

No.	Name	Sources	Ref.
17	Anabsin	*A. absinthium*, *A. caruifolia*	37,38,51
18	Anabsinthin	*A. absinthium*, *A. caruifolia*	37,51
19	Isoabsinthin	*A. absinthium*	39
20	Absintholide	*A. absinthium*, *A. caruifolia*	40,41,51
21	Artenolide	*A. absinthium*	42
22	11-*epi*-Absinthin	*A. sieversiana*	43
23	10′,11′-*epi*-Absinthin	*A. sieversiana*	43
24	10′,11,11′-*epi*-Absinthin	*A. sieversiana*	43
25	Artesieversin	*A. sieversiana*	43
26	Artanomaloide	*A. anomala*, *A. sylvatica*	44,50,53
27	Artelein	*A. leucodes*	45
28	Artselenoide	*A. selengensis*	46,47
29	Arteminolide A	*A. sylvatica*, *A. argyi*	48,49
30–32	Arteminolides B–D	*A. argyi*	49
33–34	Artanomaloides A and C	*A. argyi*	49
35	8-Acetylarteminolide	*A. sylvatica*	50,53
36–38	Caruifolins B–D	*A. caruifolia*	51
39–42	Artemyriantholides A–D	*A. myriantha*	52
43	Artanomalide D	*A. anomala*	53



44 R = H
45 R = Ac



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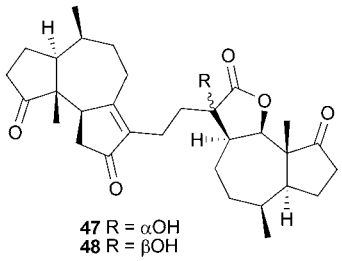
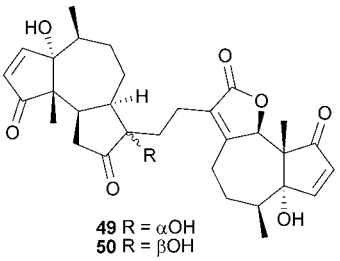
bisnubenolide **55**, bisnubidiol **56** and bistataxacin **57**. Moreover, their biosynthetic precursor, nubenolide, was also found in this species.[66–68] The structures of gochnatiolides A and B were determined as **58** and **59**, respectively. These dimeric sesquiterpenoids were found in the roots of *Gochnatia paniculata*.[69] In addition to **58** and **59**, the aerial parts of *Gochnatia polymorpha* afforded another four new dimers, **60–63**, whereas only **62** and **63** were obtained from the roots of this species.[70] Compounds **64–67**



47 R = αOH
48 R = βOH



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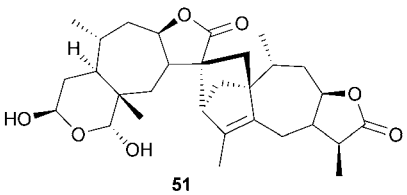
50 R = βOH



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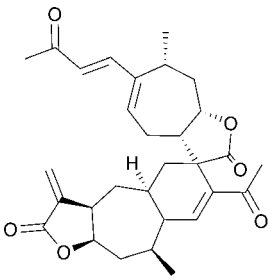

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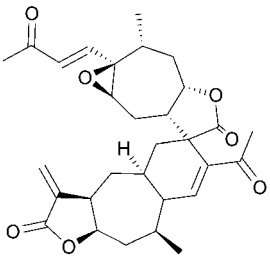

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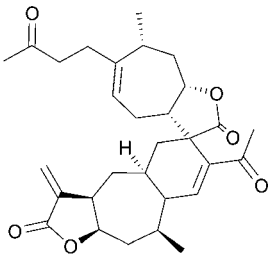

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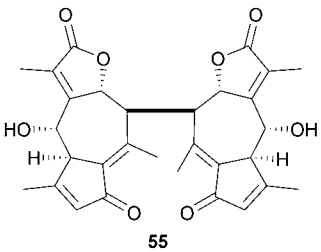

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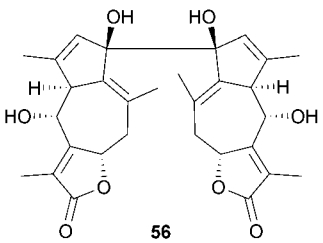

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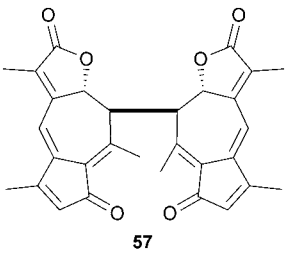

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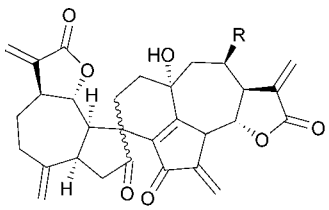

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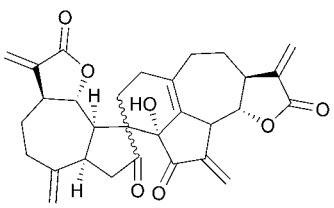
60 R = OH



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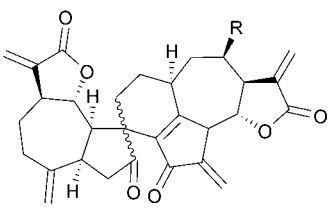
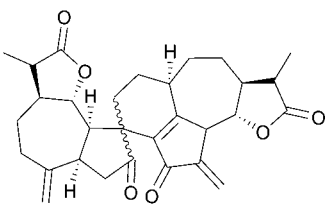


61 R = OH
62 R = H



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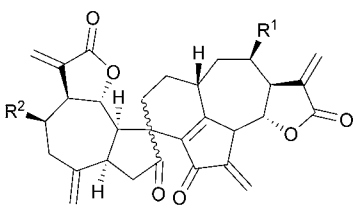
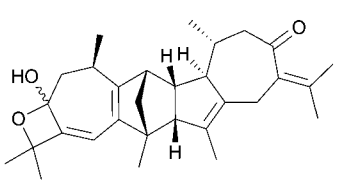


64 R^1 = H R^2 = H **66** R^1 = OH R^2 = H
65 R^1 = H R^2 = OH **67** R^1 = OH R^2 = OH



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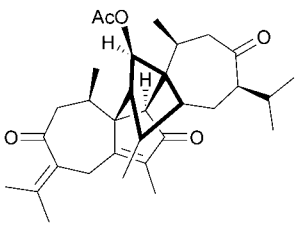

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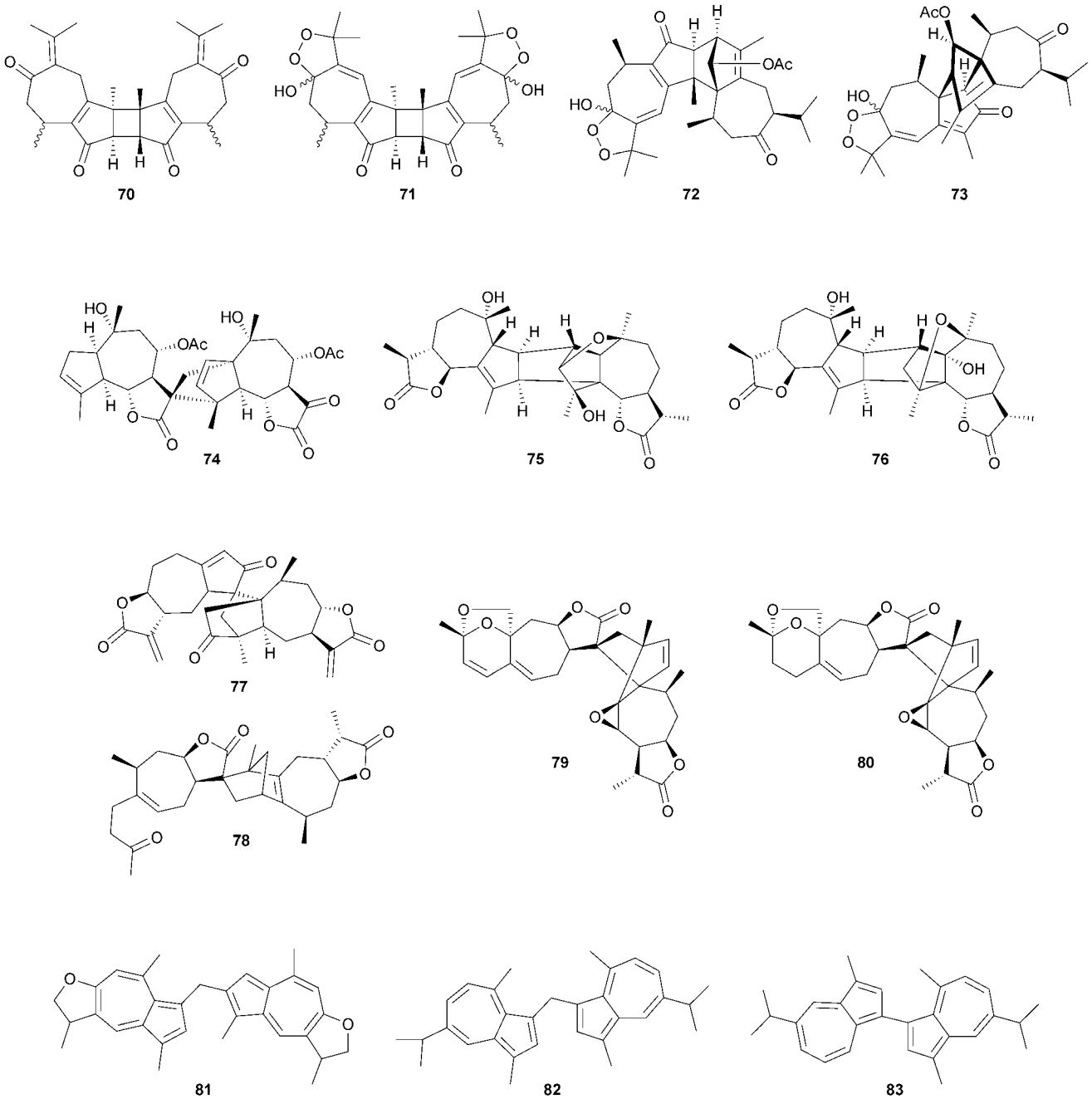
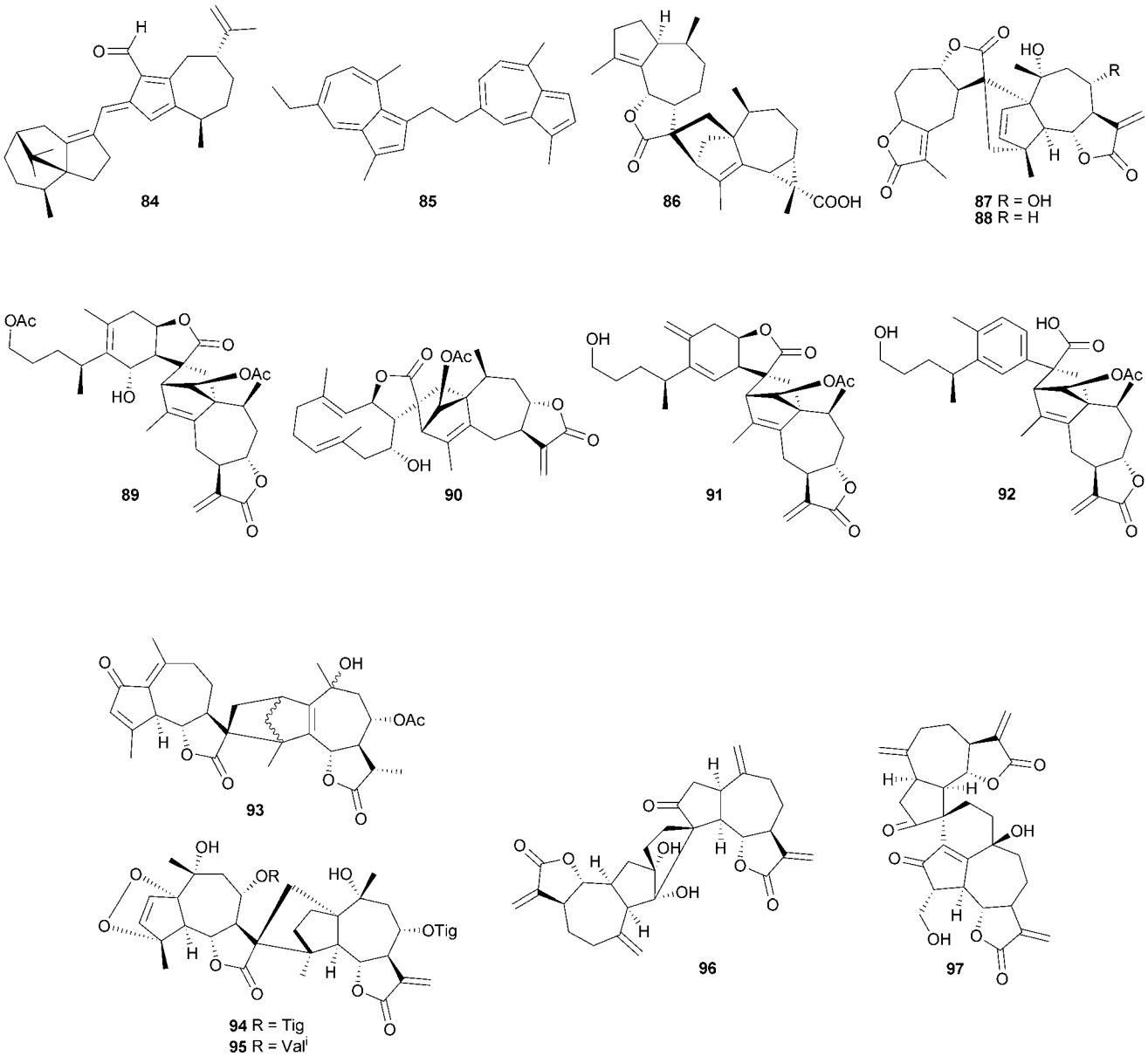


were isolated from the aerial parts of *Gochnatia hypoleuca*.[70] Clearly, dimers **58–67** are formed by cycloaddition of zaluzanin C to 1,2-dihydrozaluzanin C or to its corresponding lactones, and these dimers may be characteristic of the genus. A new guaiane dimer bearing an unusual hemiacetal oxetane ring, **68**, was isolated from the leaves of *Xylopia aromatica*.[71] Five dimeric guaianes, vielanins A–E, were isolated from the leaves of *Xylopia vielana*, and shown to be **69–73**.[72,73] Biogenetically, the bridged rings in **69**, **72** and **73** are constructed from two hypothetical guaiane monomers through Diels–Alder reaction, whereas the symmetric cyclobutanes in **70** and **71** are generated from two equal guaiane moieties by [2 + 2] cycloaddition.

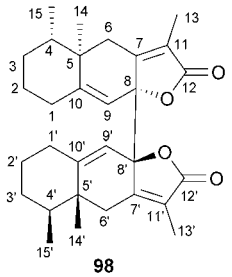
The dimeric guaianolide handelin (which also has the trivial names yejuhua lactone and chrysanthelide) was isolated from *Handelia trichophylla*.[74] On the basis of spectroscopic and chemical characteristics, structure **74** was proposed,[75,76] and this was confirmed by X-ray analyses.[77] The metabolite was also found in *Chrysanthemum indicum* and *C. boreale*.[78,79] Gnapholide **75** was obtained from the chloroform extract of *Pulicaria gnaphalodes*,[80] and seemarin **76** was a constituent of *Daphne oleoides*.[81] It is very interesting that anabsinthin **18**, first reported from *Artemisia absinthium*,[37] was also found in these two species. Decathieleanolide from *Decachaeta thieleana* was shown to be **77**,[82] and helisplendidilactone **78**, containing



a 4,10-secoguaiane unit, was identified from *Helichrysum splendidum*.[83] Ornativolide **79** and dihydroornativolide **80** were separated as minor constituents from the aerial parts of *Geigeria ornativa*.[84]

A condensed guaiazulenoid pigment, gorgiabisazulene **81**, was isolated from a gorgonian, *Acalycigorgia* sp. Its structure was established on the basis of spectroscopic and chemical evidence.[85] In addition to 2,2′-diguaiazulenylmethane **82**, first reported as a synthetic product,[86] 2,2′-biguaiazulenyl **83** was also an antimicrobial constituent of the gorgonian *Calicogorgia granulosa*.[87] Moreover, **82** was also found in a deep-sea gorgonian *Pseudothesia* sp.[88] Recently, two analogues named assufulvenal **84**[89] and 2,12′-bis-hamazulenyl **85**[90] were characterized from the root bark of *Joannesia princeps* and the essential oil of *Ajania fruticulosa*, respectively. Their structures were corroborated by X-ray crystallographic analysis, and the absolute configuration of the former dimer was determined by multiple scattering X-ray experiments.[91] An aromadendrane–guaianolide dimer **86** was isolated from the New Zealand liverwort *Chiloscyphus subporosus*. Its structure was confirmed by the X-ray crystallographic analysis of a derivative of **86**.[92] Two new dimeric guaianolides, named 8α-hydroxyxeranthemolide **87** and xeranthemolide **88**, were identified from the aerial parts of *Anthemis austriaca*.[93]

A bioassay-guided fractionation of the aerial parts of *Inula britannica* var. *chinensis* resulted in the isolation of four new sesquiterpenoid dimers bearing a norbornene moiety, the inulanolides A–D **89–92**.[94] Among them, inulanolides B and D exhibited potent inhibitory activities on the LPS-induced NF-κB activation, and they also strongly inhibited the production of NO and TNF-α in LPS-stimulated RAW264.7 cells. The results provided a partial scientific explanation for the



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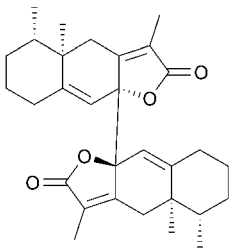

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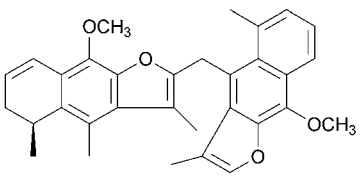

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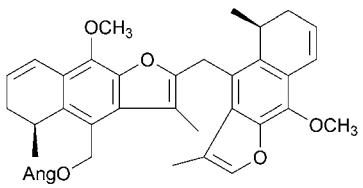

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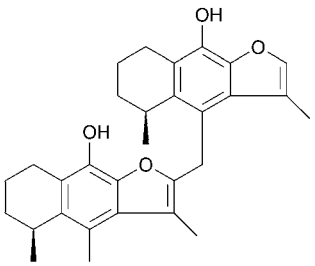

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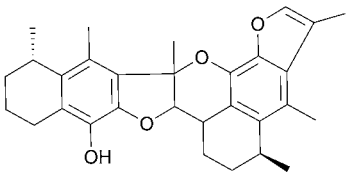

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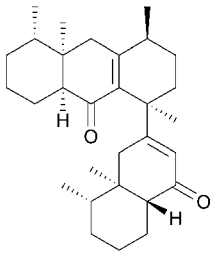

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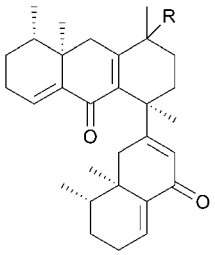
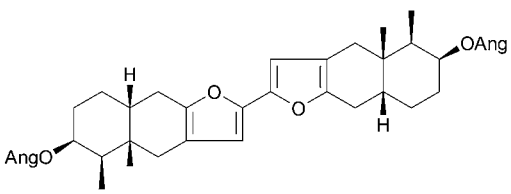


105 R = αH
106 R = OH



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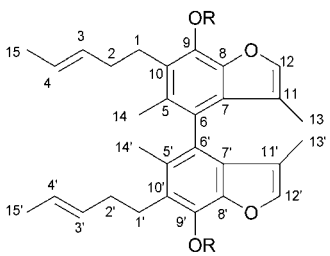
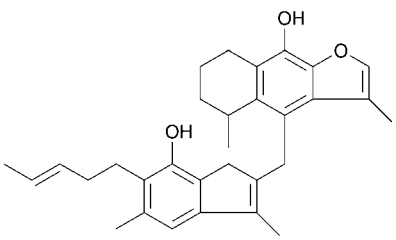


108 R = H
110 R = Me



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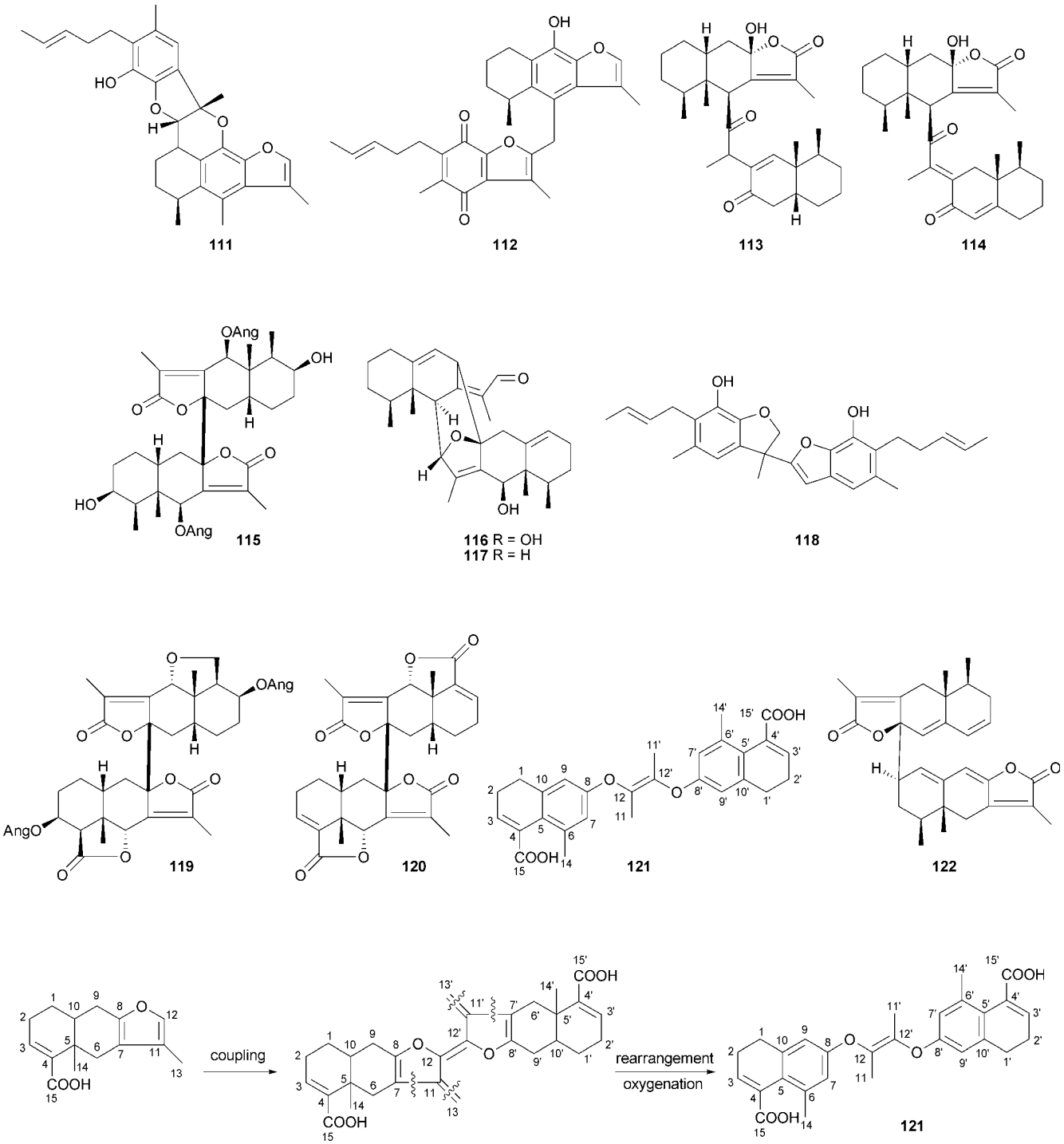
use of this plant in Asia for treating inflammatory diseases.[94] Achicollinolide **93** was found in the flower heads of *Achillea collina*,[95] whilst the distansolides A and B **94–95** were obtained from the flower heads of *Achillea distans*.[96] A phytochemical investigation of *Ainsliaea macrocephala* led to the isolation of ainsliadimer A **96**. Its structure was elucidated by spectroscopic and single-crystal X-ray diffraction analyses. This unusual molecule exerted potent inhibitory activity against the production of nitric oxide in RAW264.7 cells stimulated by LPS.[97] Further research on another species of the genus, *Ainsliaea fulvioides*, resulted in the isolation of ainsliadimer B **97**.[98]

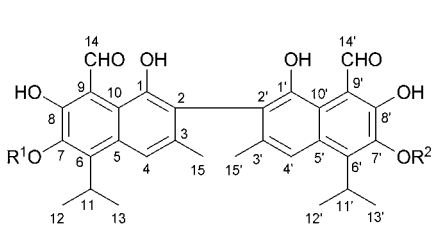
2.4 Eremophilane dimers

Compounds **98–99**, the first natural dimeric eremophilenolides, were reported from *Bedfordia salicina*.[99] Later, these two epimers were also found in the whole plant of *Senecio tsoongianus*. Their absolute stereochemistry were elucidated by NMR techniques and X-ray diffraction studies, along with chemical evidence.[100] Chemical investigation of *Senecio crispus* afforded **100**, a novel rearranged dimeric sesquiterpenoid.[101] A study into the components of *Senecio canescens* led to the isolation of **100** and **101**. Moreover, cacalohastine and 14-(angeloyloxy)cacalohastine, the biosynthetic precursor of **101**, were also found in the same plant.[102] Adenostins A–B **101–103** were obtained from the rhizomes of *Cacalia adenostyloides*.[103] It is interesting that **101–103** also occur in the rhizomes of a plant of a different genus, *Ligularia virgaurea*, which may offer some useful information on the evolutionary relationship between these two genus.[104] Tetrahydromitchelladione **104**, a novel eremophilane dimer with an unusual carbon skeleton, was isolated from the wood oil of *Eremophila mitchelli*.[105] Further research resulted in the isolation of two more dimers, **105–106**, possessing the same skeleton as **104**.[106] A symmetrical eremophilane dimer **107** was identified as a component of the rhizomes of *Farfugium japonica*.[107] The dimers virgaurins A–C **108–110**,[108–111] **111–112**[104] and virgaurols A–B **113–114**[112] were obtained from the same species, *Ligularia*

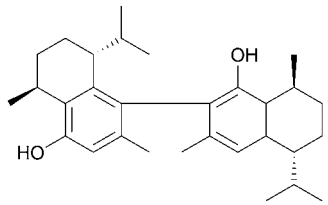


Scheme 2 Biogenetic pathway proposed for **121**.

virgaurea, collected from a different district in China. Bieremoligularolide **115**, which exerts strong cytotoxicity against several cancer cell lines, was obtained from the roots of *Ligularia muliensis*.[113] Three dimeric eremophilanes, namely ligulolide B, ligulolide D and ligularin A **116–118**, were isolated from an extract of the whole plant of *Ligularia virgaurea* spp. *oligocephala*, a traditional folk medicine used for the treatment of stomach ache and nausea.[114–116] A novel bieremophilanolide **119** was found in the roots and rhizomes of *Ligularia lapathifolia*,[117] together with 3β-angeloyloxy-8β-hydroeremophil-7(11)-en-12,8α(14β,6α)-diolide, possibly the parent compound of the dimer.[118] A phytochemical investigation of the roots of *Ligularia atroviolacea* resulted in the isolation of **120** and a rare dimer of a noreremophilanoid, ligulatrovine A **121**.[119,120] The biogenetic pathway shown in Scheme 2 was proposed for **121**. An eremophilenolide dimer, named biligulaplenolide **122**, was obtained from the underground organs of *Ligularia platyglossa*.[121]



123 R^1= H R^2 = H
124 R^1= H R^2 = Me
125 R^1= Me R^2 = Me



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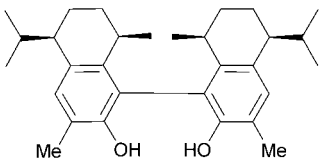

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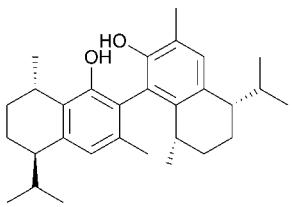

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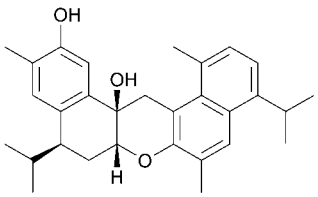

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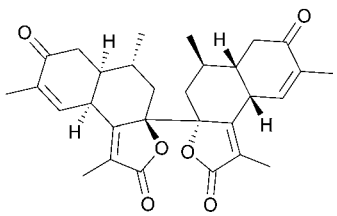

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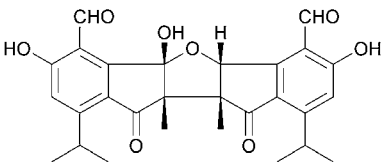

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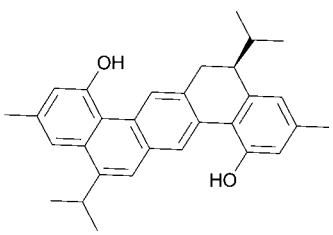

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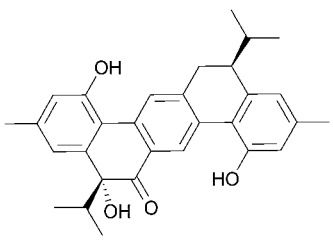

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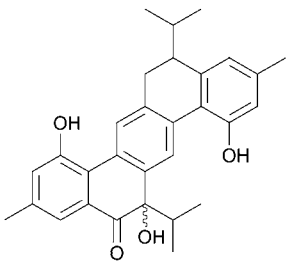

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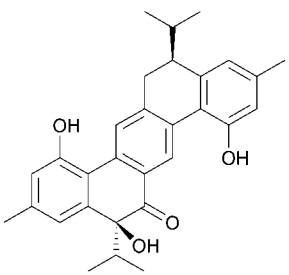

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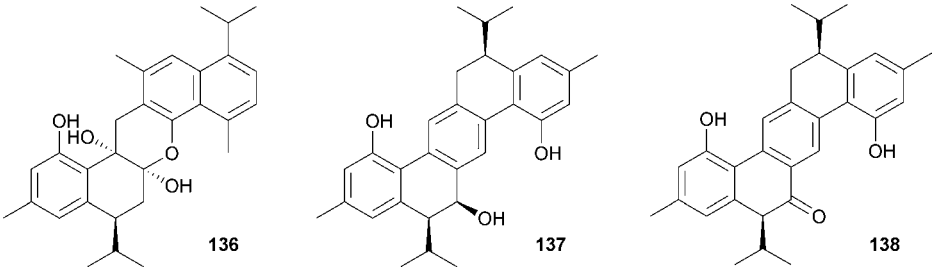
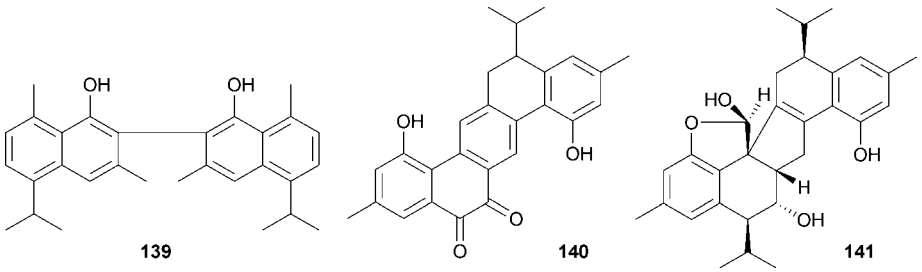
2.5 Cadinane sesquiterpenoid dimers

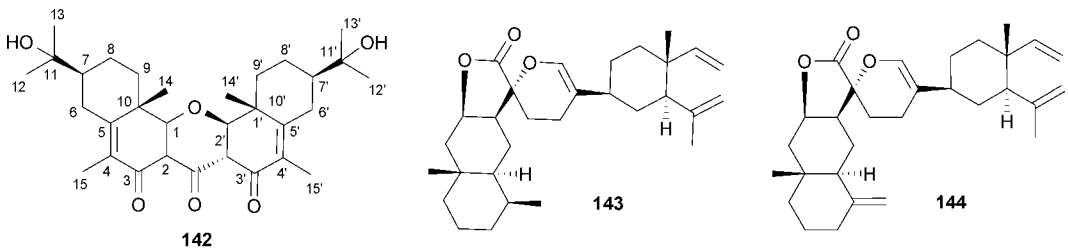
The dimeric sesquiterpenoid gossypol **123**, which occurs naturally in cottonseed and other parts of the cotton plant, possesses many biological properties, including male antifertility and anticancer activities.[122] Gossypol also inhibits the growth of numerous parasitic organisms targeting lactate dehydrogenases,[123,124] and shows antiviral activity against a number of enveloped viruses, including the AIDS virus.[125] It is worth noting that gossypol exists as enantiomers because of the restricted rotation around the central binaphthyl bond. The (−)-enantiomer is toxic to nonruminant animals, while the (+)-enantiomer exhibits relatively weak toxicity, but to plant pathogens they showed the same level of toxicity without any difference.[126] A highlight of an asymmetric synthesis of (*S*)-gossypol was four oxazoline-mediated reactions.[127,128] Two gossypol derivatives, **124** and **125**, were produced by hairy root cultures from *Gossypium hirsutum* and *G. barbadense*.[129]

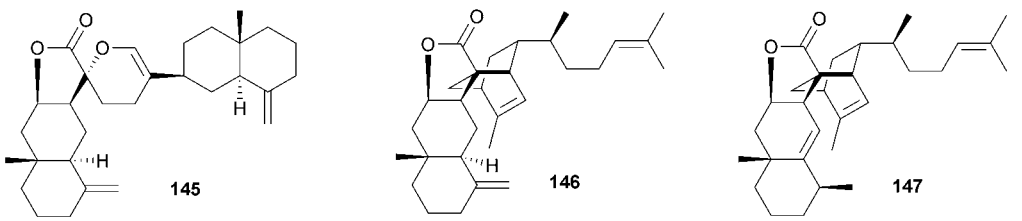
A minor constituent from a Meliaceous plant, *Dysoxylum alliaceum*, was shown to be a novel unsymmetrical dimer of 8-hydroxycalamenene,[130] a co-occurring sesquiterpenoid. Its structure, including the absolute configuration, was established as **126** based on a spectroscopic study and total synthesis.[131] 8,8′-Bis(7-hydroxycalamenene) **127** was found in the hexane and ethyl acetate extracts of the heartwood of *Heritiera ornithocephala*,[132] as well as in the leaves and twigs of the Ecuadorian medicinal plant *Siparuna macrotepala*.[133] In addition to **127**, a new dimeric cadinane **128** was obtained from the hexane extract of the bark of *Ocotea corymbosa*.[134] Dicadalenol **129** was isolated from the aerial parts of *Heterotheca inuloides* and exhibited *in vivo* anti-inflammatory activity when evaluated for inhibition of TPA-induced mouse ear edema.[135] Phytochemical research into the leaves of the invasive plant *Eupatorium adenophorum* resulted in the purification of a dimeric cadinane derivative. Its structure including the absolute configuration was determined as **130** on the basis of spectroscopic data and single-crystal X-ray crystallography.[136] Aquatidial **131**, a new asymmetric bis-norsesquiterpenoid, hypothetically derived from isohemigossypolone, was isolated from the outer bark of *Pachira aquatica* roots.[137] A proposed biogenetic route for aquatidial was also presented in the paper.

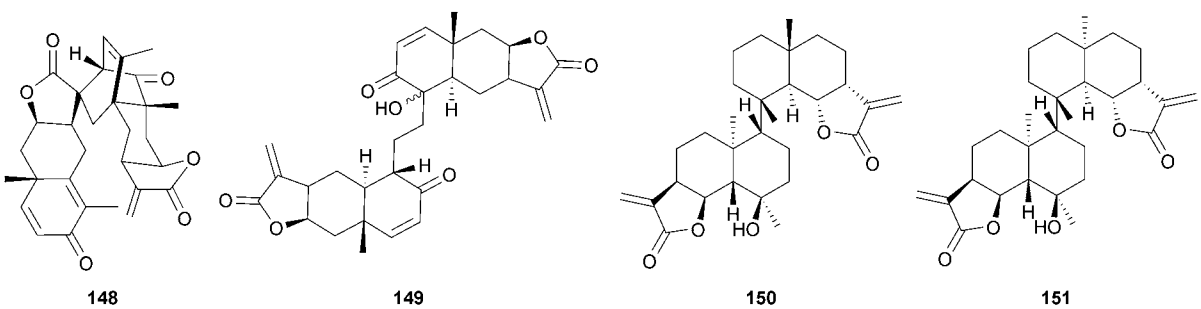
A series of new sesquiterpenoid dimers from *Curcuma parviflora* were identified as parviflorenes A–J **132–141**,[138–141] and the absolute stereochemistry of parviflorenes A, B, D, F and G, was revealed by CD spectroscopic data and chemical means.[140] All



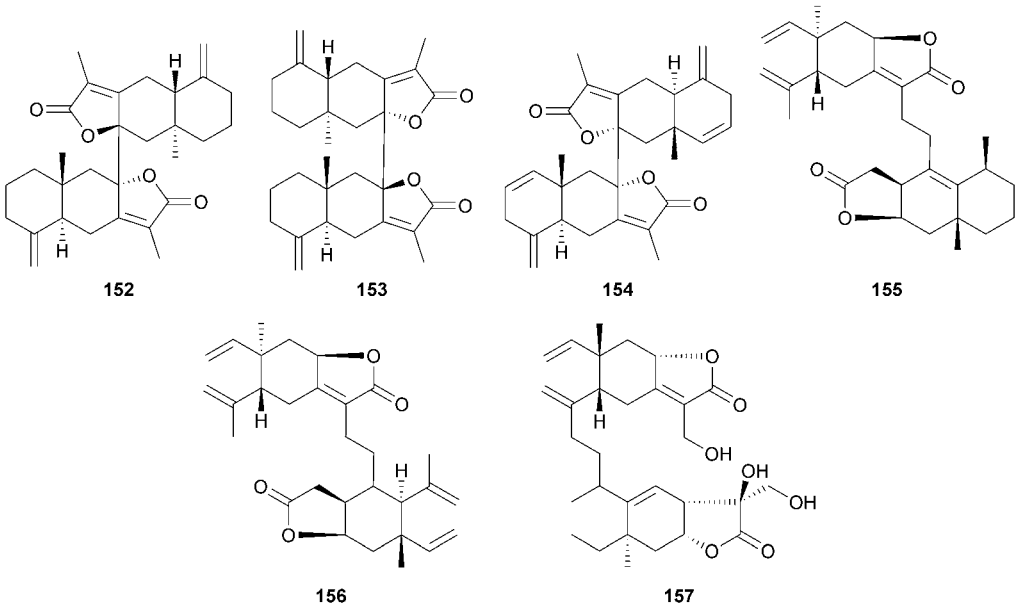


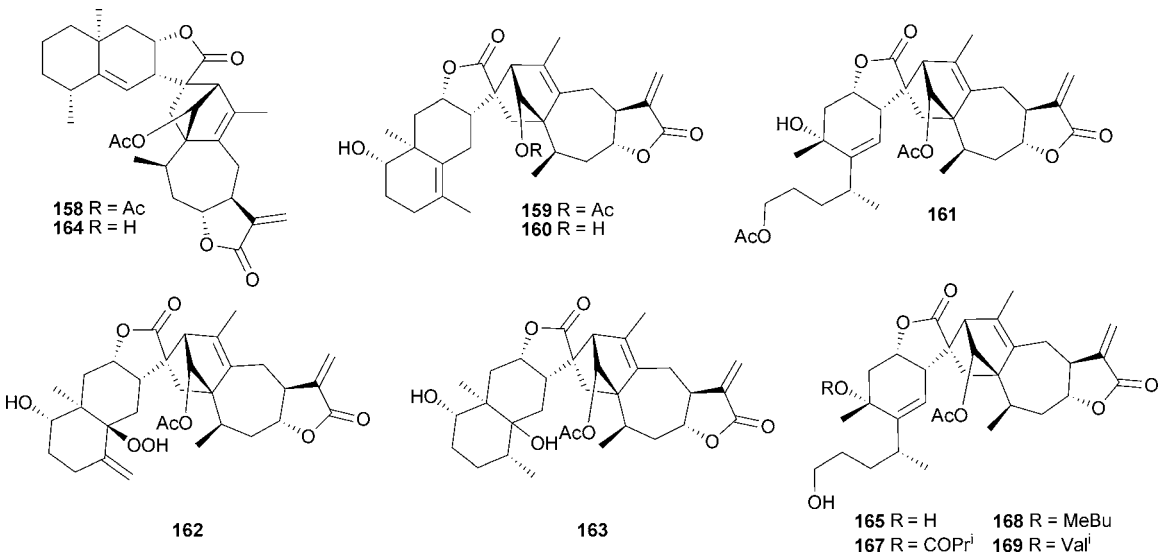






these new dimers, except parviflorene H, showed cytotoxicity against tumor cell lines. Moreover, the major constituent, parviflorene F, enhanced the gene expression and protein production of TRAIL-R2 and augmented the activity of caspase 8 and 3. The research was based on DNA microarray, real-time PCR, and Western blotting studies.[142,143] TRAIL-R2 is one of the death receptors involved in the signaling mechanisms inducing apoptosis. For this reason, parviflorene F may be a useful





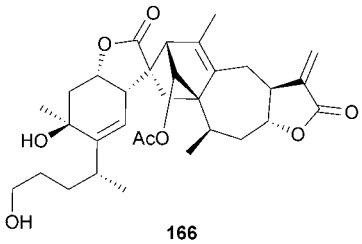
compound for studies on the TRAIL signaling pathway and apoptosis inducement.

2.6 Eudesmane and elemane sesquiterpenoid dimers

Chemical investigation of *Carissa carandas* led to the isolation of a novel type of C_{31} terpenoid, carindone **142**.[144] The authors suggested a possible biosynthetic pathway in which carindone is synthesized in the plant by the condensation of two units of carissone, a major sesquiterpenoid present in the species, and involving incorporation of one extra carbon. Three novel sesquiterpenoid lactone dimers, **143–145**, were Diels–Alder products from a pentane extract of the *Helenium autumnale* roots.[145] Two more dimers, **146–147**, were found in the pentane extract in further research into the same species.[146]

Investigation of the aerial parts of *Ferreyranthus fruticosus* afforded the dimer fruticolide **148**.[147] The metabolite **148** is unlikely to be an artefact, as one of its presumed precursors was not found in the plant, and it would not be a good diene for Diels–Alder reaction to form **148**. The aerial parts of *Montanoa speciosa* yielded a novel dimeric eudesmanolide named hydroxy-bis-dihydroencelin **149**.[148] Two lipophilic constituents of *Frullania muscicolus* were identified as muscicolides A and B **150–151**.[149]

Biatractylolide **152** and biepiasterolide **153** were structurally novel bisesquiterpenoids isolated from *Atractylodes macrocephala*, a Chinese folk medicine used for the treatment of gastroenteric and splenic disorders.[150–152] Structurally, both **152** and



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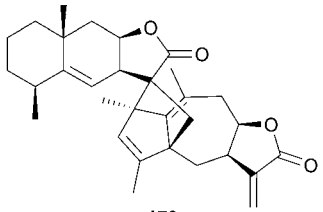

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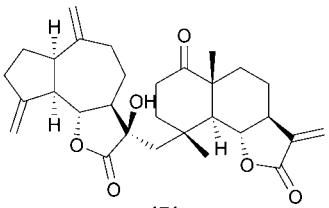

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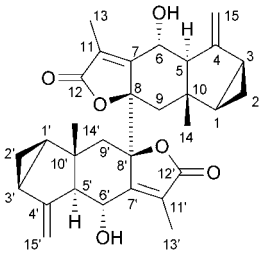

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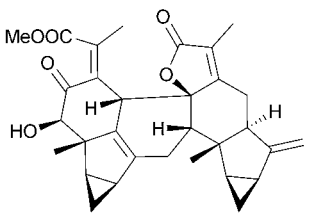

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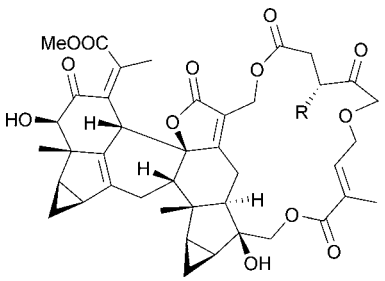
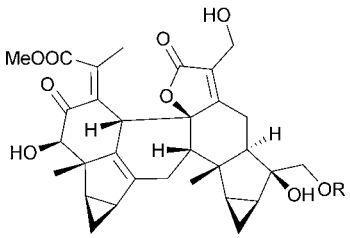
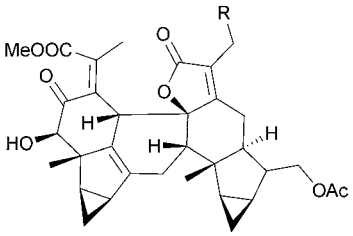


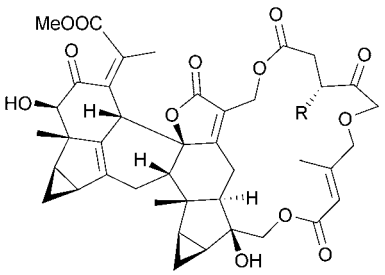
174 R = H 179 R = OH



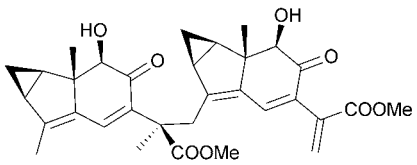
175 R = Tig 184 R = TigA
181 R = g-Hysen 186 R = Ac



176 R = OH
177 R = H



178 R = H 180 R = OH



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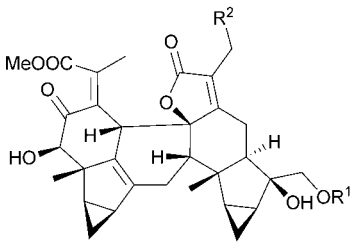
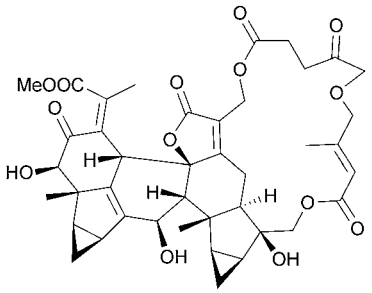


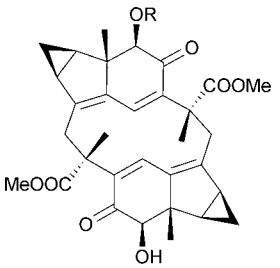
183 R^1 = Sen R^2 = OAc
185 R^1 = g-Hysen R^2 = H
187 R^1 = g-Hysen R^2 = OSuc

153 are dimeric sesquiterpenoid lactones joined at the C_8–$C_{8'}$ bridgehead positions, as proven by X-ray crystallographic analyses.[153] It was interesting that biatractylolide **152** was also found to be present in the resin of *Trattinickia rhoifolia*.[154] Biologically, biatractylolide possesses negative inotropic and chronotropic actions on isolated guinea pig hearts – specifically, it significantly inhibited the contractile force and decreased the heart rate of the isolated right atrium, making it a potential agent for lowering blood pressure.[155] The biomimetic synthesis of these dimers has been reported.[156,157] A new symmetrical bisesquiterpenoid was identified as bilindestenolide **154** from the roots of *Lindera strychnifolia*.[158] Three novel sesquiterpenoid dimers from the bark of *Inula macrophylla* were shown to be macrophyllidimers A–C **155–157**.[159,160]

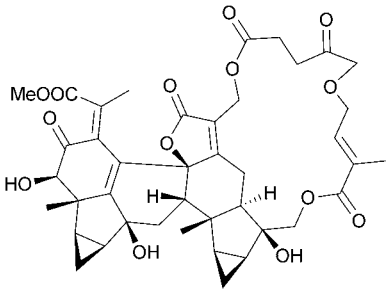
Twelve new dimeric sesquiterpenoid lactones, japonicones A–L **158–169**, comprising eudesmane and guaiane sesquiterpenoids, were isolated from the aerial parts of *Inula japonica*.[161,162] Japonicone A showed potent cytotoxicity against four tumor cell lines, whilst japonicones E–F and G displayed strong inhibitory activity against LPS-induced NO production in RAW264.7 macrophages. Rudbeckiolide **170** was obtained in low yield from *Rudbeckia laciniata*.[163] Bioassay-directed fractionation of *Saussurea lappa* led to the isolation of lappadilactone **171**, which exhibited potent cytotoxicity against several cancer cell lines.[164]



188 189 190a 190b



191 R = H
203 R = Glc



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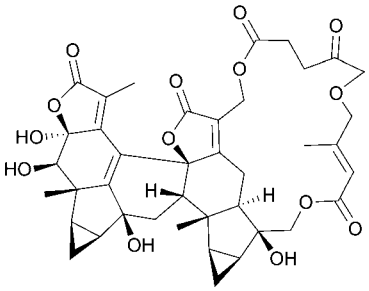

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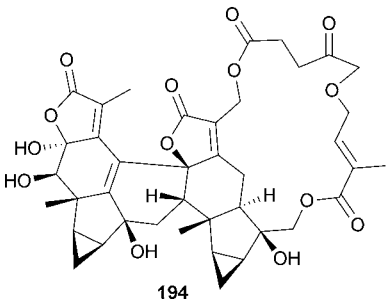

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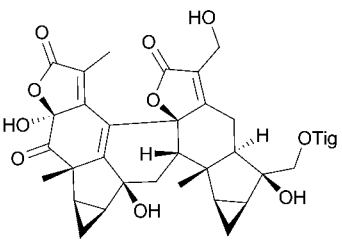

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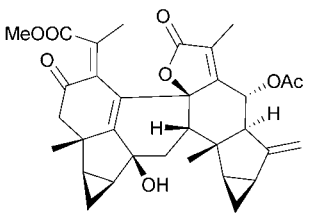

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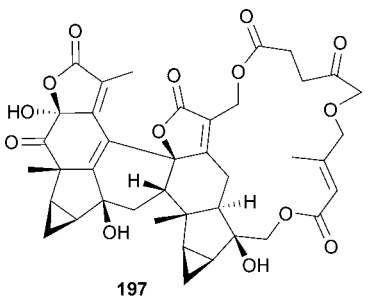

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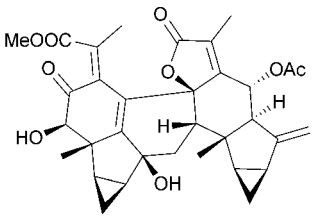

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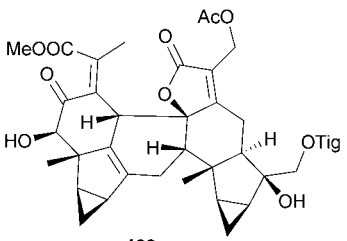

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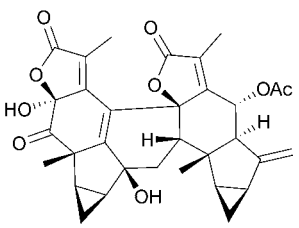

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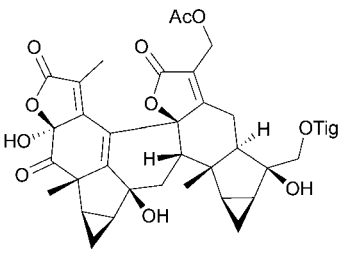

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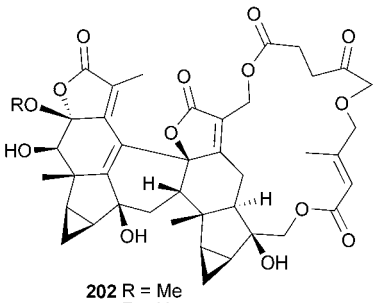
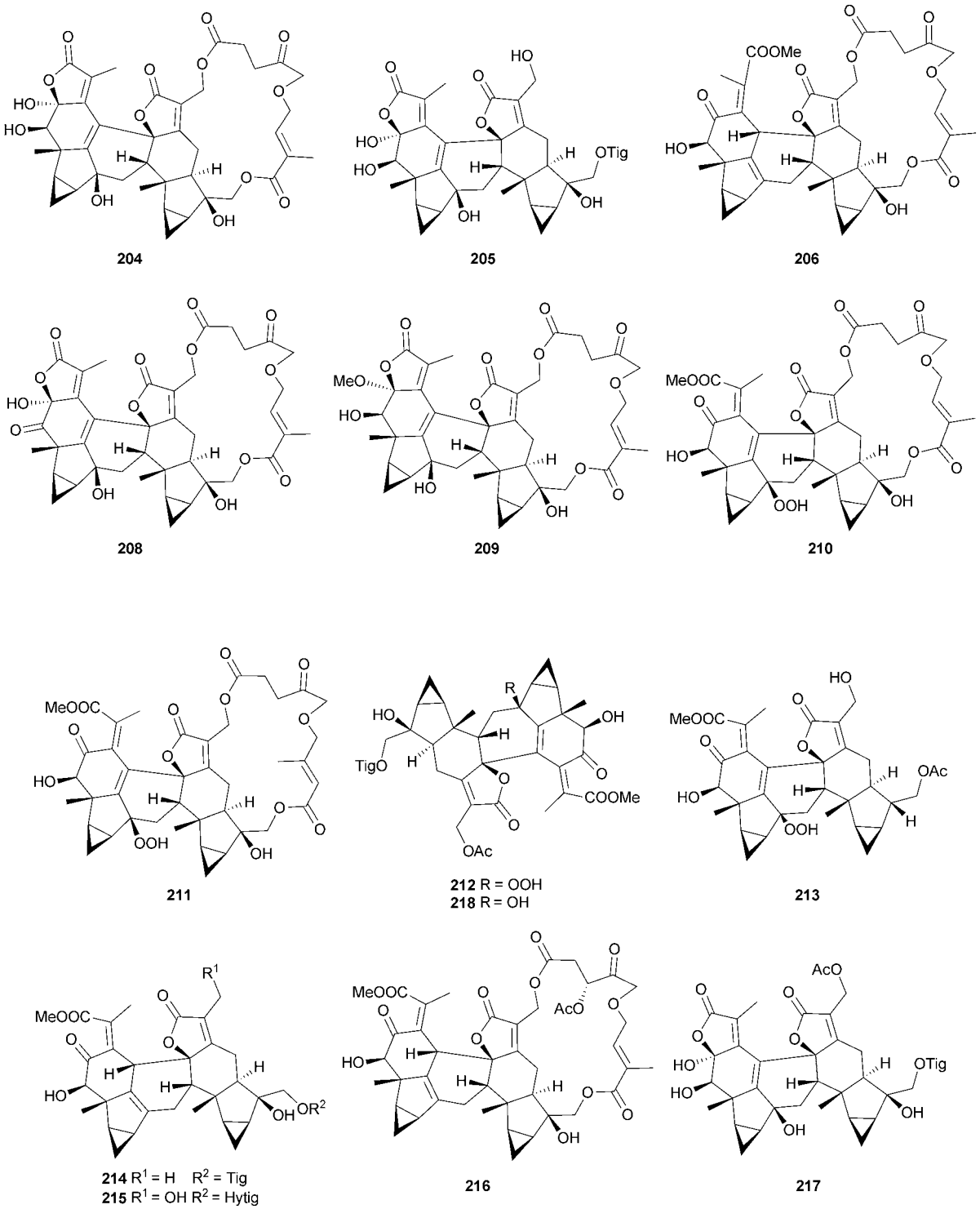


202 R = Me
207 R = H



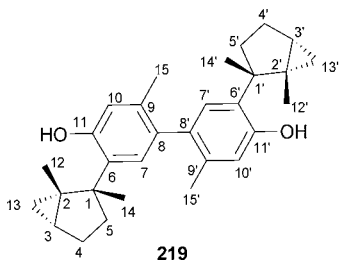
2.7 Lindenane sesquiterpenoid dimers

This skeleton of lindenane differs from that of eudesmane only in its three-membered ring formed by C1, C2, and C3. To date, most lindenane sesquiterpenoid dimers have been isolated from the Chloranthaceae family. The isolation, structural elucidation, and biological activity of these dimers have been reviewed.[12a,15,165–168] Many naturally occurring lindenane sesquiterpenoids have been reported,[169–173] but all lindenane sesquiterpenoid dimers except lindenanolide F **172**[169] have been found only in the Chloranthaceae family. These natural products could be a group of metabolites with possible taxonomic significance for the Chloranthaceae family.

The first isolation of a lindenane sesquiterpenoid dimer, shizukaol A **173**, was reported from *Chloranthus japonicus*.[174] To date, 46 dimers, listed in Table 2, have been characterized from the Chloranthaceae family.[174–195]

Table 2 Dimeric lindenane sesquiterpenoids from the genera Chloranthaceae family (genera *Chloranthus* and *Sarcandra*)

No.	Name	Sources	Ref.
174	Shizukaol B	*C. serratus*, *C. japonica*, *C. henryi*, *S. glabra*	175,178,179,181,195
175	Shizukaol C	*C. serratus*, *C. henryi*, *S. glabra*	175,191,195
176	Shizukaol D	*C. serratus*, *C. fortunei*	175,179
177	Shizukaol E	*C. japonica*, *C. fortunei*, *C. spicatus*, *S. glabra*	176,179,185,195
178	Shizukaol F	*C. japonica*, *C. fortunei*, *C. multistachys*	176,178,179,180,188
179	Shizukaol G	*C. japonica*, *S. glabra*	176,195
180	Shizukaol H	*C. japonica*	176
181	Shizukaol I	*C. japonica*, *C. fortunei*	176,179
182	Shizukaol J	*C. japonica*, *C. fortunei*	177,179
183–187	Shizukaols K–O	*C. fortunei*	179
188	Shizukaol P	*C. fortunei*	180
189	Methyl chloranthadimeric acid acetate	*C. japonica*	181
190b	Chloranthalactone A photodimer	*C. japonica*, *C. glaber*	181,182
191	Cycloshizukaol A	*C. serratus*, *C. japonica*, *C. fortunei*, *C. multistachys*	178,180,183,188,195
192	Chloramultilide A	*C. multistachys*, *C. spicatus*, *S. glabra*	184,185,193
193	Chloramultilide B	*C. spicatus*, *C. fortunei*	180,185
194–195	Chloramultilides C–D	*C. spicatus*	185
196	Chloraholide A	*C. holostegius*	186
197	Chloraholide B	*C. holostegius*, *C. spicatus*, *C. fortunei*	180,185,186
198	Chloraholide C	*C. holostegius*	187
199	Chloraholide D, CHE-23C, henriol D	*C. holostegius*, *C. henryi*	179,187,190,191
200–201	Chloraholides E–F	*C. holostegius*	187
202	Yinxiancaol, 8-*O*-methyltianmushanol	*C. japonica*, *C. fortunei*, *C. tianmushanensis*	180,189,192
203	9-*O*-β-Glucopyranosylcycloshizukaol A	*C. fortunei*	180
204–206	Henriols A–C	*C. henryi*	191
207	Tianmushanol	*C. tianmushanensis*	192
208–209	Spicachlorantins A–B	*C. spicatus*	193
210–213	Spicachlorantins C–F	*C. spicatus*	194
214–218	Sarcandrolides A–E	*S. glabra*	195



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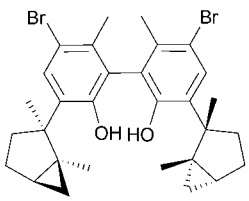

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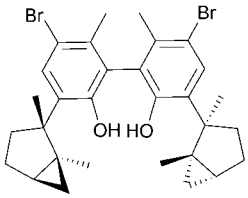

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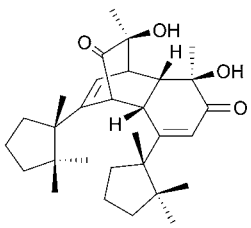

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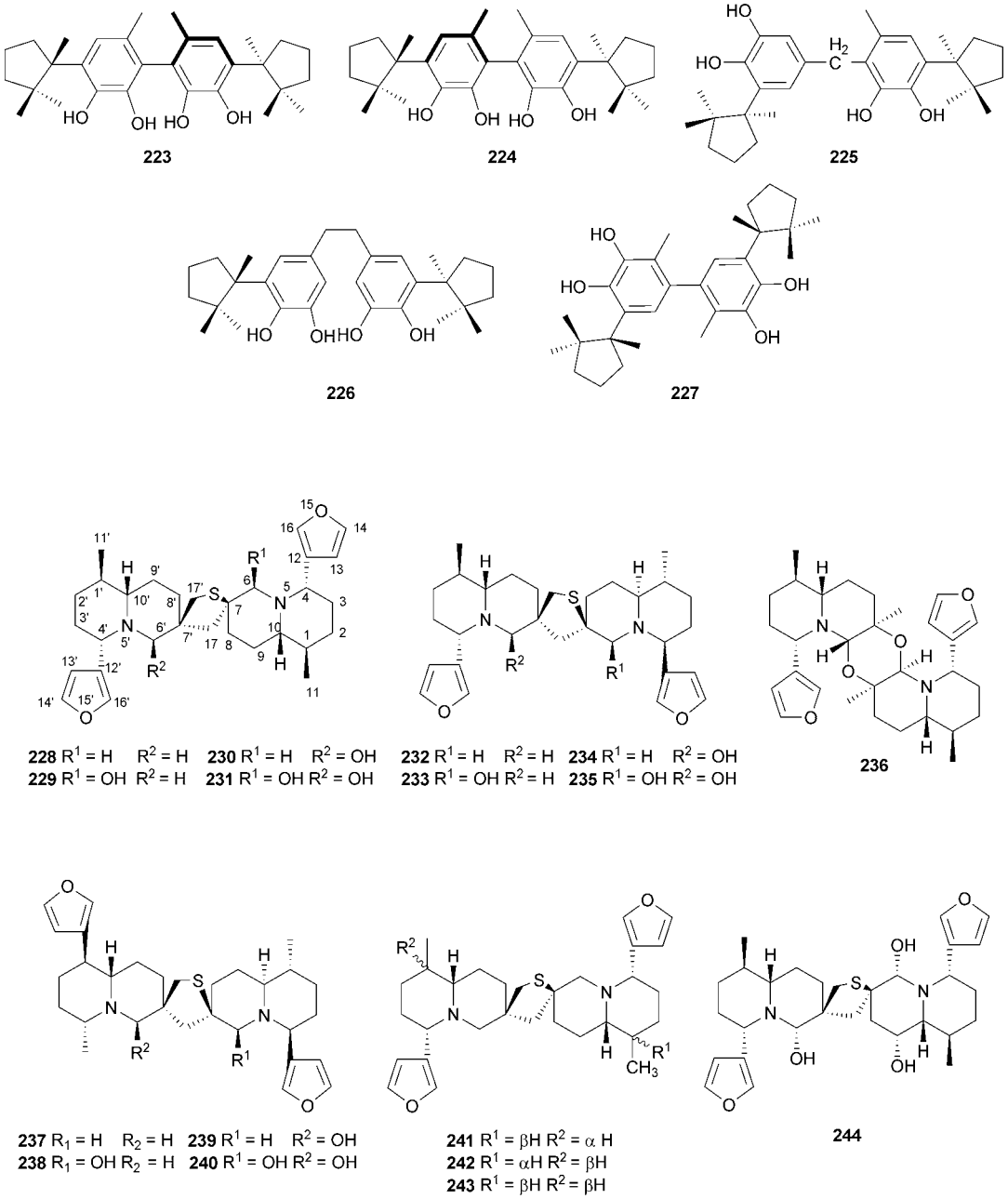
The structure of chloranthalactone A photodimer from *Chloranthus japonicus* shown as **190a**[181] was revised to **190b** mainly on the basis of NOESY spectra and chemical methods.[182] It is worth mentioning that compounds named as chloraholide D, CHE-23C and henriol D from different species share the same structure, **199**.[187,190,191] The reader should also note that yinxiancaol and 8-*O*-methyltianmushanol have the same structure, **202**.[189,192] A phytochemical study of *Chloranthus spicatus* cultivated in Japan resulted in the isolation of four new lindenane dimers, spicachlorantins C–F **210–213**, possessing a hydroperoxy group at the C4 position. These compounds were considered to be biogenetic precursors of the corresponding hydroxyl derivatives of dimeric lindenane sesquiterpenoids distributed in *Chloranthus* plants.[194] Interesting biological activity was shown by these novel dimers, such as cell adhesion inhibition,[178] inhibition of the delayed rectifier K^+ current,[186,187] antifungal,[185,190] cytotoxicity,[191] and tyrosinase inhibitory activity.[192] In their biogenetic pathway, an intermolecular [2 + 2],[181,182] Diels–Alder,[184] or [6 + 6] cycloaddition[183] of two molecules of lindenane sesquiterpenoids leads to the underlying the dimeric core. A wide range of lindenane dimers can then be formed through oxidation, rearrangement and/or acylation of the dimeric core. Assignments of the two sets of methylene signals in the succinate unit commonly occurring in dimeric lindenane sesquiterpenoids was made by steady-state and transient $^{13}C\{^1H\}$ NOE experiments.[196]

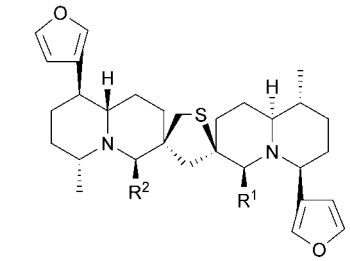
2.8 Cuparane, laurane, cyclolaurane and herbertane sesquiterpenoid dimers

The oily extract of the red alga *Laurencia nidifica* was repeatedly separated by column chromatography to yield a symmetrical cyclolaurane dimer, laurebiphenyl **219**.[197] Biogenetically, it was proposed that the metabolite was formed from two molecules of debromolaurinterol or laurinterol, two naturally occurring sesquiterpenoids from the same genus, by the oxidative coupling at the *para*-position of the phenol groups.[198] Another species of the genus, *Laurencia microcladia*, contained a new dimeric

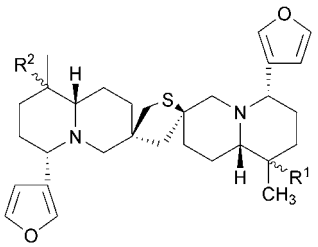


sesquiterpenoid of the cyclolaurane type, **220**. These algae were collected from coastal rocks of Serifos in the Aegean Sea.[199] An investigation of the same specimens collected off the coast of Chios Island resulted in the isolation of a cytotoxic constituent **221**, an isomer of **220**.[200] The structure of a novel sesquiterpenoid dimer was determined as aquaticol **222** by spectroscopic methods and finally confirmed by X-ray diffraction. This dimeric sesquiterpenoid was isolated from a traditional Chinese medicine, *Veronica anagallis-aquatica*.[201,202] A biomimetic total synthesis of (+)-aquaticol was accomplished in 2006. An *ortho*-quinol derivative was used as a key intermediate to form (+)-aquaticol through an intermolecular Diels–Alder reaction.[203]

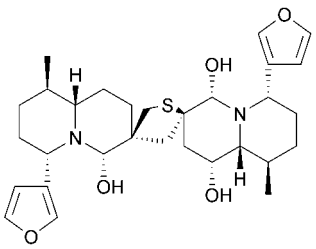
Four dimeric herbertane-type sesquiterpenoids, mastigophorenes A–D **223–226** from the liverwort *Mastigophora diclados*, were assigned on the basis of detailed spectroscopic analyses.[204–206] Herbertenediol, a co-metabolite in this plant, may be the biosynthetic precursor through radical-initiated phenolic oxidation to form mastigophorenes A–D. Mastigophorenes A–C were also reported from the crude extract of *Herbertus sakuraii*. This indicated that the genus *Herbertus* is closely related chemically to *Mastigophora*, although the two genera are classified in two different families.[207] The axial chirality of mastigophorenes A and B was determined as *P* and *M* respectively by HPLC-CD.[208] It was interesting that mastigophorenes A, B and D possessed neurotrophic properties, and resulted in accelerated neuritic sprouting and network formation in the primary neuritic cell culture derived from the foetal rat hemisphere, whereas mastigophorene C suppressed neuritic differentiation. It is noteworthy that two



237 R_1 = H R_2 = H **239** R^1 = H R^2 = OH
238 R_1 = OH R_2 = H **240** R^1 = OH R^2 = OH



241 R^1 = βH R^2 = α H
242 R^1 = αH R^2 = βH
243 R^1 = βH R^2 = βH



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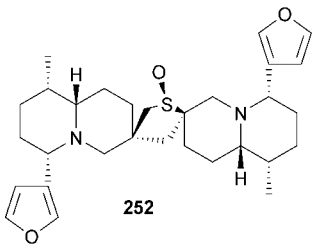

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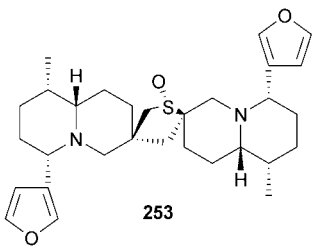

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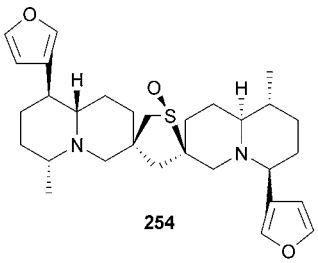

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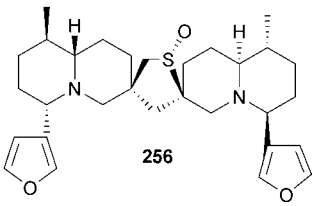
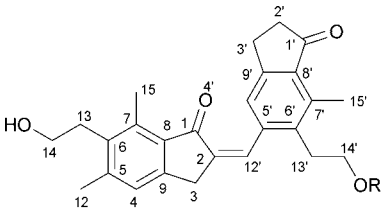


256

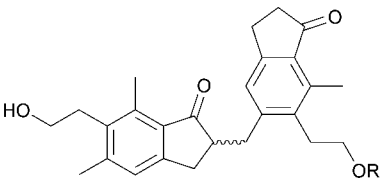
Table 3 Dimeric C_{30} alkaloids from the genus *Nuphar*

No.	Name	Sources	Ref.
228	Thiobinupharidine, thionuphlutine A	*N. luteum*	225–227,231
229	6-Hydroxythiobinupharidine, thionupharoline	*N. luteum*, *N. pumilum*	235,236,238,246
230	6′-Hydroxythiobinupharidine	*N. luteum*	236,236
231	6,6′-Hydroxythiobinupharidine, nuphleine	*N. luteum*, *N. pumilum*	228–230,246
232	Thionuphlutine B	*N. luteum*	231,234
233	6-Hydroxythionuphlutine B	*N. luteum*, *N. pumilum*	235,236,246
234	6′-Hydroxythionuphlutine B	*N. luteum*, *N. pumilum*	235,236,246
235	6,6′-Dihydroxythionuphlutine B	*N. luteum*	230
236	6,7β-Oxidodeoxynupharidine dimer	*N. luteum* subsp. *macrophyllum*	232
237	Neothiobinupharidine	*N. luteum*, *N. pumilum*	226,231,233,246
238	6-Hydroxyneothiobinupharidine	*N. luteum*	235,237
239	6′-Hydroxyneothiobinupharidine	*N. luteum*	235,237
240	6,6′-Dihydroxyneothiobinupharidine	*N. luteum*	235
241	1-*epi*-Thiobinupharidine	*N. luteum*	239
242	1′-*epi*-Thiobinupharidine	*N. luteum*	239
243	1-*epi*-1′-*epi*-Thiobinupharidine	*N. luteum*	239
244	Thionupharodiolone	*N. luteum*	240
245	*syn*-Thiobinupharidine sulfoxide	*N. luteum*, *N. pumilum*	241,246
246	*syn*-6-Hydroxythiobinupharidine sulfoxide	*N. lutea*	242
247	*syn*-6′-Hydroxythiobinupharidine sulfoxide	*N. lutea*	242
248	*syn*-6,6′-Dihydroxythiobinupharidine sulfoxide	*N. lutea*	242
249	*anti*-Thiobinupharidine sulfoxide	*N. lutea*, *N. pumilum*	242,246
250–253	Nupharpumilamines A–D	*N. pumilum*	243
254	Neothiobinupharidine β-sulfoxide	*N. luteum*, *N. pumilum*	244,246
255	Thionuphlutine B β-sulfoxide	*N. luteum*, *N. pumilum*	245,246
256	Thionuphlutine B α-sulfoxide	*N. luteum*	245

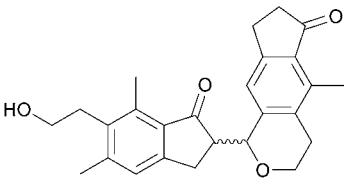
simplified analogs of mastigophorene exerted similar neurotrophic effects on mesencephalic dopaminergic cells in primary culture, showing that the diphenyl core may be a key functional group for the retention of its bioactivity, and providing simplified lead compounds for further investigation.[209] The remarkable neurotrophic activity of these dimers has attracted considerable attention from synthetic chemists. Several synthetic groups have accomplished the total synthesis of these dimers and their corresponding precursor, herbertenediol.[210–219] Mastigophorenes A and B can be obtained from the biotransformation of herbertenediol by *Penicillium sclerotiorum*.[220] A related dimer aquaticenol from *Lejeunea aquatica* has the structure **227**.[221]



257 R = H
260 R = Me



258 R = H
261 R = Me
262 R = Glc



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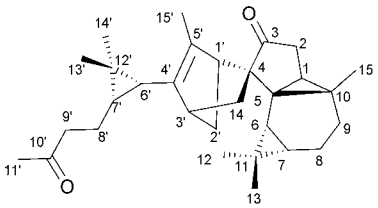

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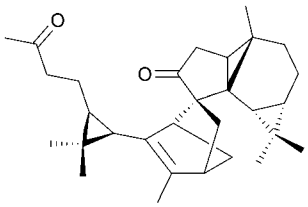

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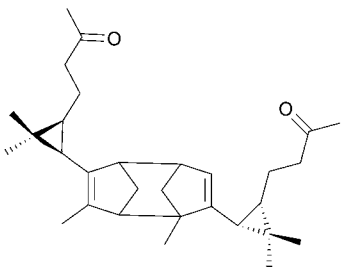

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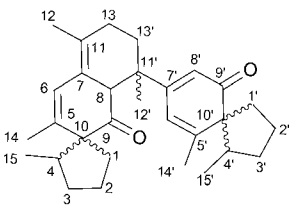

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2.9 Sesquiterpenoid alkaloid dimers

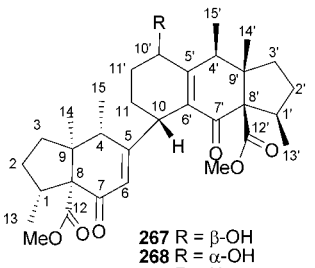
Aquatic macrophytes of the genus *Nuphar* produce a series of alkaloids possessing a 3-furyl group attached to quinolizidine or piperidine ring systems.[222–224] These structural features are all incorporated within a regular sesquiterpenoid framework. Among the alkaloids discovered to date, the structurally interesting ones are the compounds that consist of two C_{15} (3-furyl)quinolizidine units fused in a somewhat symmetrical fashion through carbon and a third heteroatom-sulfur. They are commonly termed C_{30} *Nuphar* alkaloids, and are listed in Table 3.[225–246] These dimers display potent immunosuppressive,[247,248] anti-metastatic[249] and apoptosis-inducing activities.[250] For more detailed information, the reader is referred to three recent reviews.[251–253]

2.10 Miscellaneous sesquiterpenoid dimers

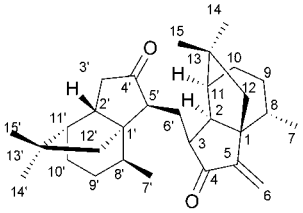
Monachosorins A–C **257–259** and methylmonachosorin A **260**, novel dinorsesquiterpenoid dimers, were obtained from *Monachosorum arakii*, *M. flagellare* and *Dennstaedtia distenta*, respectively.[254,255] Among the isolates, **257–259** were also found in three other *Monachosorum* species (*M. flagellare*, *M. henryi*, and *M. maximowiczii*) and *Dennstaedtia scandens*. Two derivatives of monachosorin B, namely methylmonachosorin B **261** and distentoside **262**, were constituents of the Mexican fern, *Dennstaedtia distenta*.[256] The isolation of three novel dimeric sesquiterpenoids named myltayloriones A–B **263–264** and bitaylorione **265** from the leafy liverwort *Mylia taylorri* has been reported. They were shown by spectroscopic analysis to be Diels–Alder-type adducts of the sesquiterpenoids myliol and taylorione.[257] The aerial parts of *Cineraria fruticulorum* afforded a bisesquiterpenoid **266**, but the relative configuration was not assigned. It was suggested that **266** is a Diels–Alder adduct of cinera-5,7,11-trien-9-one, a co-occurring sesquiterpenoid.[258]

The ether extract of the liverwort *Porella acutifolia* subsp. *tosana* furnished three novel dimeric pinguisane sesquiterpenoids, namely bisacutifolones A–C **267–269**. Their structures were established by a combination of 2D-NMR, X-ray crystallographic analysis, modified Mosher's method, CD spectra, and chemical degradation.[259,260] Recently, the biomimetic synthesis of bisacutifolones A–B was reported by the Nishiyama research group.[261] In this work, a Mukaiyama aldol reaction was used as the key step in the synthesis of acutifolone A. An intermolecular Diels–Alder reaction of the monomeric sesquiterpenoid then led to stereoselective dimerization, furnishing bisacutifolones A and B. Bioassay-guided fractionation of the organic extract of the gorgonian *Alertigorgia* sp. yielded a known tricyclic sesquiterpenoid, suberosenone, and alertenone **270**, a dimer of suberosenone.[262] Since **270** was unstable and lacked cytotoxicity, the authors speculated that alertenone may serve as a nontoxic, nonvolatile storage form of suberosenone, which, in turn, may be a chemical defensive agent of the gorgonian.[262] A tandem free-radical cyclization–rearrangement sequence was designed and executed in the total synthesis of suberosenone.[263]

A novel sesquiterpenoid quinine, **271**, was obtained from the EtOAc-soluble portion of the dried powdered root of *Helicteres angustifolia*.[264] A plentiful constituent (1.5% by weight), officinalic acid **272**, was obtained from the ether extract of the ground mycelium of *Fomes officinalis*, a wood-rotting fungus.[265] The assignment of the metabolite was achieved by NMR data, chemical methods, and single-crystal X-ray diffraction analyses,[266] and its absolute configuration was determined by chemical transformation.[267] Though officinalic acid was first reported as a triterpene, biosynthetically the natural product may not be derived from squalene – it is most likely that it is formed *via* cycloaddition dimerization of a drimane sesquiterpenoid



267 R = β-OH
268 R = α-OH
269 R = H



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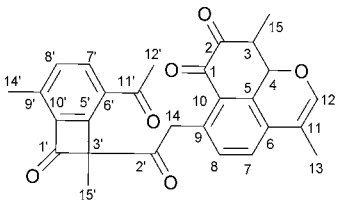

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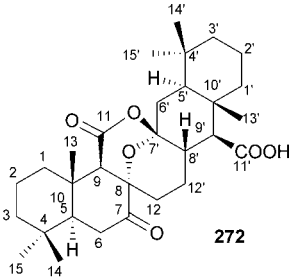

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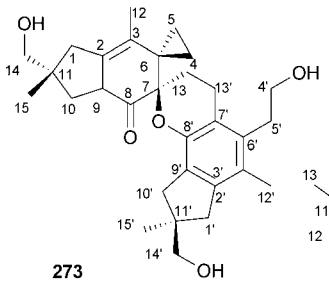

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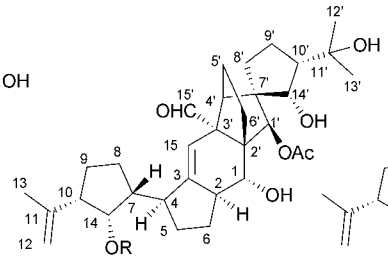
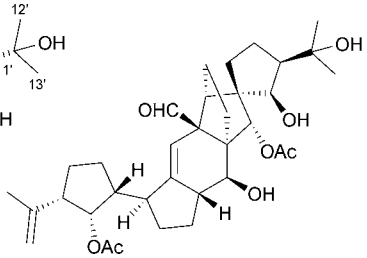
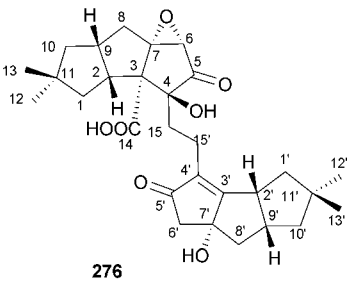


274 R = H
275a R = Ac



275b



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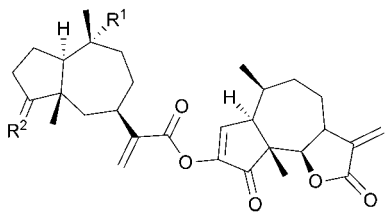
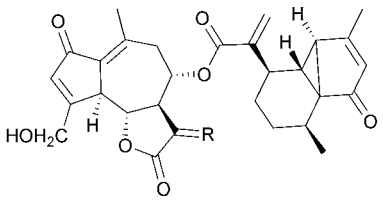
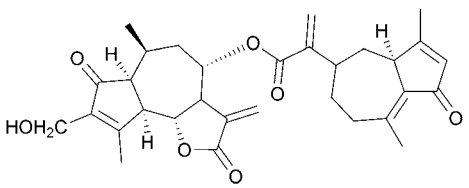


277 R^1 = H R^2 = O
284 R^1 = OH R^2 = H_2



278 R = CH_2
279 R = βH, αCH$_3$



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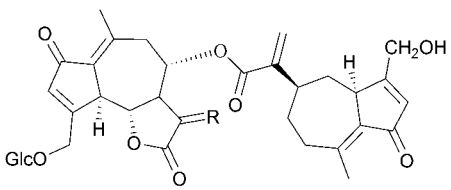
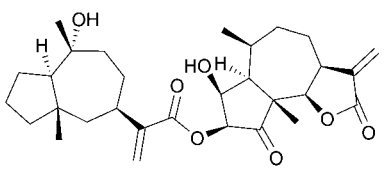


281 R = CH_2
282 R = H, αMe



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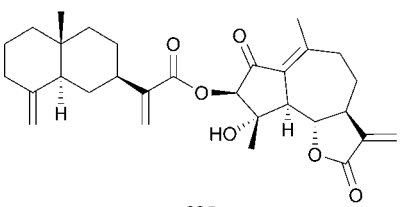

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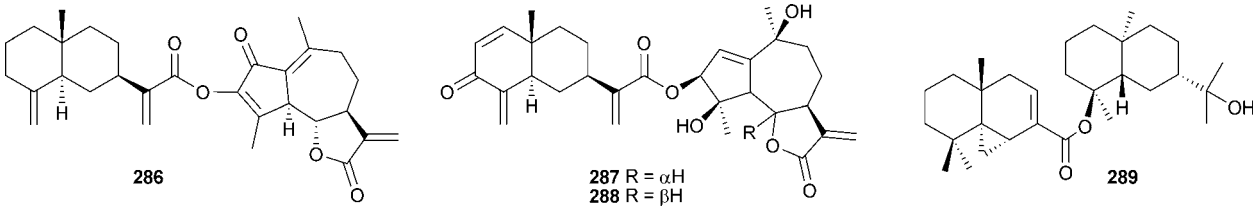
containing an α,β-exomethylene cyclohexanone moiety. Furthermore, laricinolic acid (LCA, $C_{15}H_{24}O_3$), which is easily converted into a key intermediate for the biosynthetic precursor of **272**, was found to co-exist in *Laricifomes officinalis*, demonstrating that the hypothesis is correct.[267] The biomimetic synthesis of officinalic acid was completed with the guidance of this biosynthetic hypothesis.[267,268] In the synthesis, the naturally occurring LCA was used as the starting material, which was oxidized to the rather unstable crystalline enone. The mixture, without purification, was refluxed in toluene to offer the desired product **272**. The extract of the basidiomycete *Bovista* sp. 96042 yielded a novel hexacyclic metabolite bovistol **273**, which displayed weak antibacterial and antifungal activity, but pronounced cytotoxic activities.[269] Vannusals A **274** and B **275a** were found in tropical strains of *Euplotes vannus* morphospecies.[270] At first, these compounds were believed to arise from a modification of the squalene pathway to triterpenes, but their biosynthesis is better explained in terms of a nucleophilic dimerization of two molecules of hemivannusane sesquiterpenoid.[271] Recently, the latter structure was revised to **275b** by total synthesis.[272–274] A triquinane sesquiterpenoid dimer from *Xeromphalina* sp. was identified as xeromphalinone E **276**.[275]



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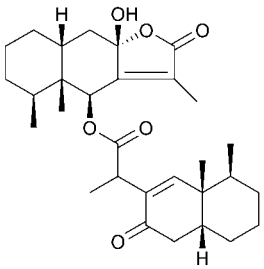
287 R = αH
288 R = βH

289



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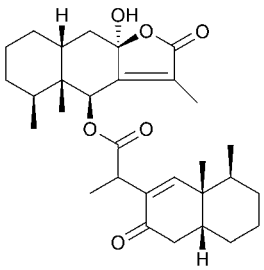

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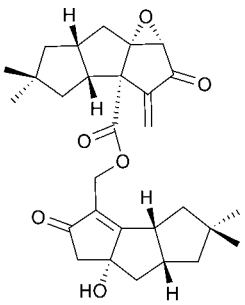

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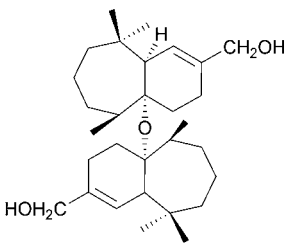

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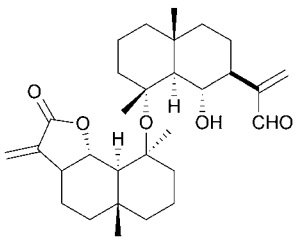

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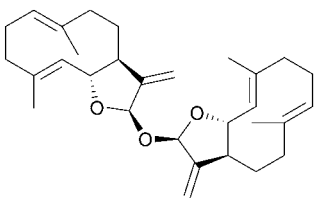

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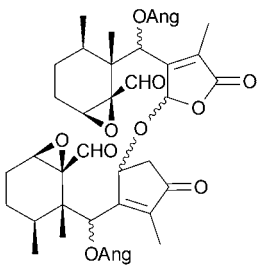
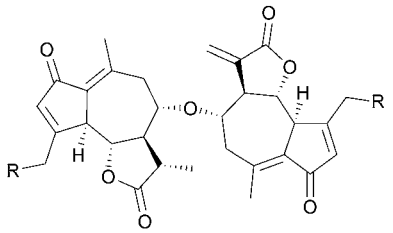


296

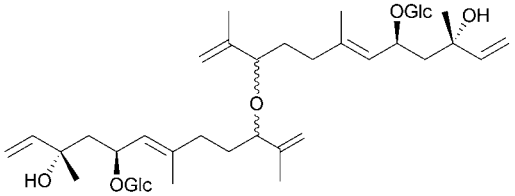
3 Pseudo-disesquiterpenoids

3.1 Ester linkage

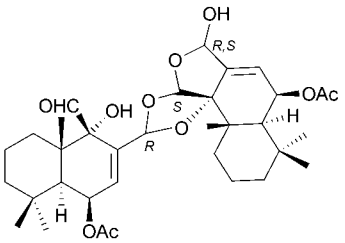
A phytochemical study of *Ambrosia hispida* in the vegetative state led to the isolation of an unusual ester of damsinic acid and 2-hydroxyambrosin, **277**.[276] Lactucin-8-*O*-hypoglabrate **278** and 8α-hypoglabroyloxyjaquinelin **279**, in which guaianolides were esterified with the same sesquiterpenic acid respectively, were reported from *Hypochoeris glabra*.[277] Further investigation of another species of this genus, *Hypochoeris oligocephala*, afforded an 1α,10α-dihydrolactucin 8-*O*-isohypoglabrate **280** and its corresponding free acid.[278] Careful separation of the polar fraction of the methanolic extract of *Picris hieracioides* var. *japonica* yielded two novel dimeric sesquiterpenoid glycosides named picriosides A and B **281–282**.[279] Two novel pseudoguaianolide esters, arrivacins A and B **283–284**, were isolated from the dichloromethane extract of *Ambrosia psilostachya*. They inhibited angiotensin II by binding to receptors from bovine adrenal cortex.[280] The structure of podachaenin **285** from the aerial parts of *Podachaenium eminens* was determined by spectroscopic data and hydrolysis. It was formed by esterification of an hydroxyguaianolide by costic acid.[281] The dimer possessed a strong inhibitory activity against human neutrophil elastase,[282] an important pathogenic factor in several inflammatory diseases, such as rheumatoid arthritis and cystic fibrosis.[283] Further study of the same species resulted in the isolation of 3-costoyloxydehydroleucodin **286**, which inhibits the transcription factor for NF-κB activity.[284] Two disesquiterpenoids, **287–288**, were separated from the leaves of *Warionia saharae*, a traditional medicine used in Morocco to treat inflammatory diseases.[285] These dimers showed a strong cytotoxicity similar in potency in HeLa, Jurkat T and human peripheral blood mononuclear cells. Furthermore, **287–288** possessed potent inhibition of NF-κB activity, which explains the use of the plant in traditional medicine for the treatment of inflammatory diseases. The chemical investigation of *Chamaecyparis obtusa* resulted in the isolation of a novel sesquiterpenoid dimer **289** formed between cryptomeridiol and hinokiic acid,[286] two compounds that are found to co-occur with **289**.[287] Virgaurols C–D **290–291**, two novel eremophilane sesquiterpenoid dimers, were found in the roots of *Ligularia*



297 R = H
298 R = OH
299 R = Op-Hpa



300 (10*R*,10'*R*) or (10*S*,10'*S*)
301 (10*S*,10'*S*) or (10*R*,10'*R*)



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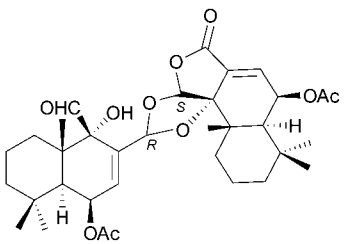

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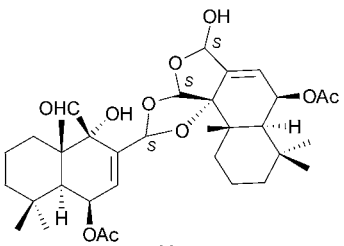

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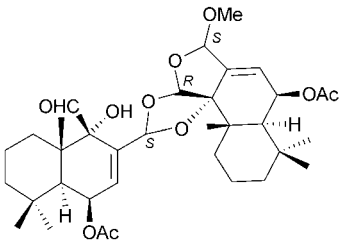

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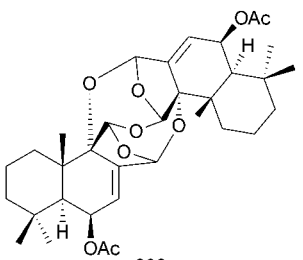

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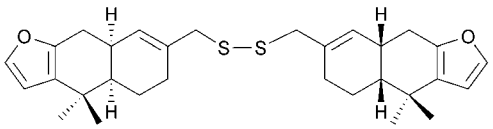

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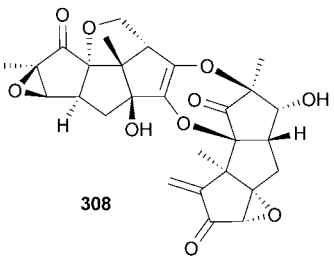

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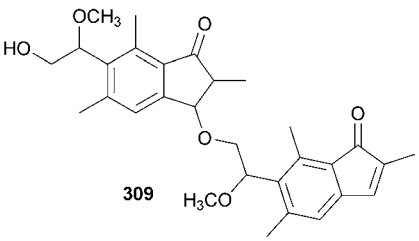


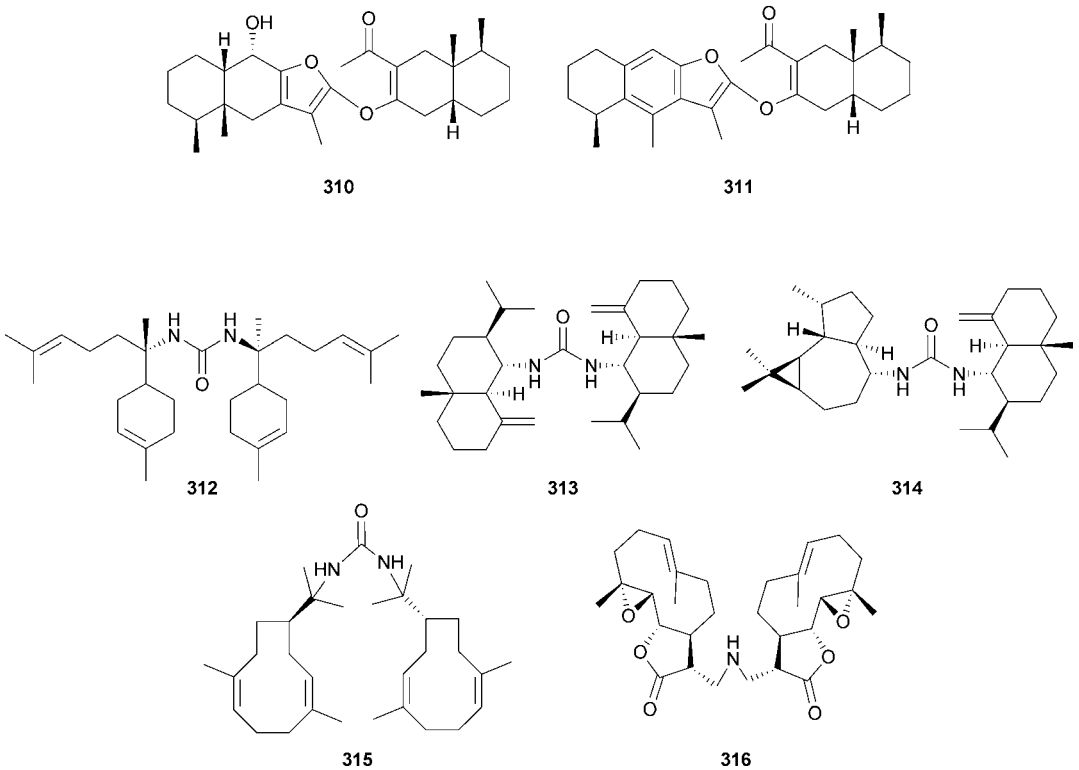
309

virgaurea.[288] A triquinane sesquiterpenoid dimer from *Xeromphalina* sp. was shown to be xeromphalinone F **292**.[275]

3.2 O- or S-ether linkage

Chinensiol **293**, a new dimeric himachalane-type sesquiterpenoid, was found in the roots of *Juniperis chinensis*[289] as well as in the heartwood of *Juniperis chinensis* var. *tsukusiensis*.[290] Chemical investigation of the ether extract of *Frullania tamarisci* subsp. *obscura* furnished a dimeric eudesmane-type sesquiterpenoid **294**.[291] Its structure including absolute configuration was elucidated by spectroscopic methods and chemical evidence. The structure of costunolact-12β-ol dimer **295** from the southern evergreen plant *Magnolia virginiana* was established by spectroscopic methods and single-crystal X-ray diffraction.[292] Ligumacrophyllal **296**, constructed by the joining two identical 8,9-secoeremophilanolide units through an ether linkage, was obtained from the roots of *Ligularia macrophylla*.[293,294]

Bioactivity-guided chromatographic fractionation of the acetone extract of *Lactuca indica*, which possessed significant antidiabetic activity, led to the isolation and characterization of three novel sesquiterpenoid lactones, lactucains A–C **297–299**.[295] A pair of diastereoisomers, amarantholidosides VI–VII **300–301**, formed by dimerization of amarantholidoside II,[296] were



characterized from *Amaranthus retroflexus*.[297] These were tested on *Taraxacum officinale* to evaluate the role of this weed in the habitat, and on the seed of *A. retroflexus* to verify the potential autotoxic effect of the plant. In further bioactivity screening, **300–301** were found to possess strong radical-scavenging capacity.[298] The structure of cytotoxic capsicodendrin **302**, isolated first from *Capsicodendron dinisii* and tentatively suggested to be a tetramer of cinnamodial,[299] was revised to a mixture of C12′-epimers of 12′-hydroxycinnafragrin B by extensive 2D NMR analyses and X-ray crystallography of its oxidized product, cinnafragrolide **303**.[300]

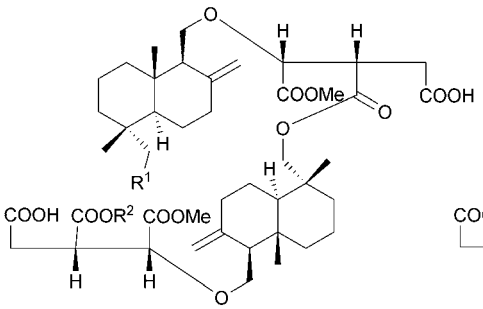
Three new dimeric drimane sesquiterpenoids named cinnafragrins A–B and D **304–306** were obtained from the Malagasy medicinal plants *Cinnamosma fragrans* and *C. macrocarpa*.[300,301] Dithiofurodysinin disulfide **307** containing two symmetrical furanosesquiterpenoid parts linked by disulfide was isolated from an Australian nudibranch (*Ceratosoma brevicaudatum*). This may be an artefact arising from oxidative coupling of the corresponding thiol.[302] The metabolite can be used to treat helminthiasis.[303] A dimeric norhirsutane sesquiterpenoid neocreolophin **308** is an artefact formed from creolophin E upon warming during isolation and purification.[304] A dimer **309** constructed by two units of illudalane sesquiterpenoids *via* an ether bond was obtained from *Pteris oshimensi*.[305] Ligulamulienins A–B **310–311**, two novel asymmetric sesquiterpenoid dimers containing a 12-norer-ermophilane subunit, were reported as constituents of the rhizomes of *Ligularia muliensis*. These compounds exhibited moderate cytotoxic activity against several cancer cell lines.[306]

3.3 Nitrogen or urea linkage

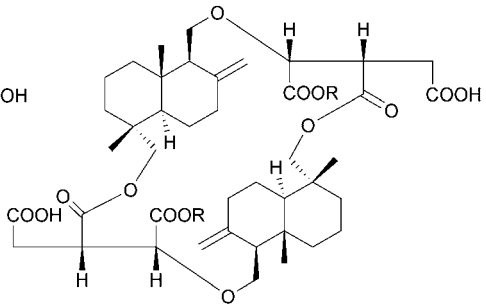
An antimicrobial constituent, (6*R*,7*S*)-7-amino-7,8-dihydro-α-bisabolene, together with its corresponding symmetrical urea **312**, was obtained from the marine sponge *Halichondria* sp., and its structure and absolute configuration was elucidated by an X-ray crystallographic study combined with chemical conversion to (6*R*,7*E*)-α-bisabolene.[307] Later, two new related dimeric sesquiterpenoids with a urea group, halichonadin A **313** and halichonadin E **314**, were reported from two different species of *Halichondria*, respectively.[308,309] The latter isolate showed moderate cytotoxicity against two cancer cell lines *in vitro*.[309] Metabolites including sesquiterpenoid isothiocyanates, isonitriles, and formamides are thought to have key roles in maintaining ecological systems, *e.g.* as allomones of the browser–prey relationship.[310,311] The isolation of a dimeric sesquiterpenoid **315** formed by two germacrane skeletons with a urea linkage from a sponge, *Axinyssa* n. sp., was reported.[312] The natural occurrence of sesquiterpenoid isocyanates[313,314] and carbamates[308] suggested that sesquiterpenoid isocyanates may play an important role in the biosynthesis of sesquiterpenoid dimers with a urea functionality in marine sponges. A model study with a menthyl-derived isocyanate supported the hypothesis.[315] Bisparthenolidine **316**, presumably derived in the plant from two molecules of parthenolide and ammonia, was found in *Paramichefia baillonii*, and demonstrated significant cytotoxicity in the KB cell culture assay.[316] The same dimer was also found in *Michelia rajaniana*.[317]

3.4 Isocitric acid linkage

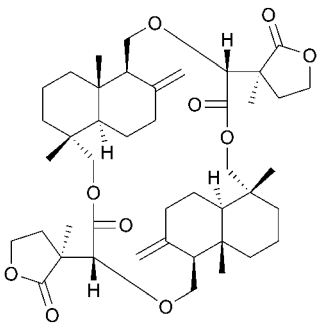
The characteristic of this group of sesquiterpenoid dimers lies in the way in which two drimane sesquiterpenoid subunits are linked by isocitric acid *via* ether and/or ester bonds. The isolation of cryptoporic acids C–G **317–321** from the fungus *Cryptoporus volvatus* was the first report of the characterization of these metabolites. Their structures including absolute configurations



317 R^1 = H R^2 = Me **320** R^1 = H R^2 = H
319 R^1 = OH R^2 = Me **321** R^1 = OH R^2 = H



318 R = Me
322 R = H



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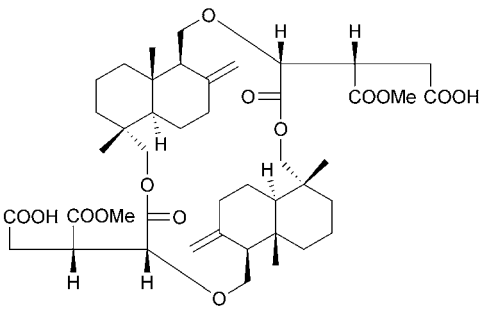

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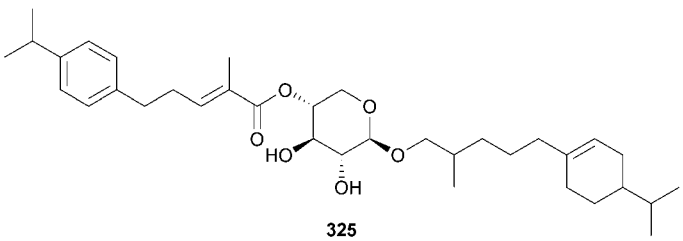

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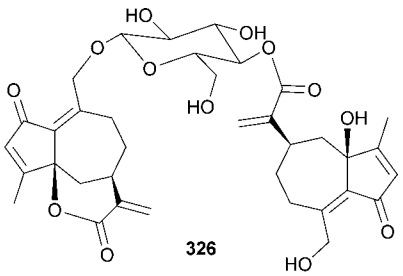

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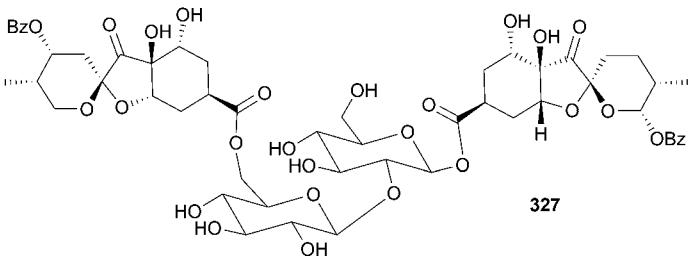

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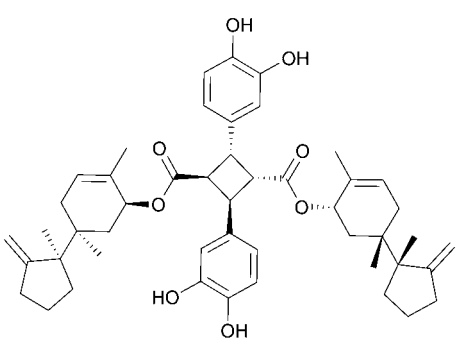
were established by spectroscopic methods, chemical transformations and X-ray analysis.[318,319] Of the five compounds, cryptoporic acids C and E inhibited the release of superoxide anions from guinea pig peritoneal macrophages induced by the O_2^- stimulant FMLP (formyl-methionyl-leucyl-phenylalanine) with IC_{50} of 0.07 and 0.05 μg ml^{-1}, respectively. Cryptoporic acid C also inhibited the release of O_2^- from rabbit polymorphonuclear leucocytes induced by the O_2^- stimulant FMLP with an IC_{50} of 2 μg ml^{-1}.[318,320] Further research demonstrated that orally administered cryptoporic acid C could inhibit the development of colon cancer in both rats and mice.[321] A dicarboxylic acid, cryptoporic acid D **322**, was characterized as the chemical constituent of *Cryptoporus volvatus* infected by *Paecylomyces varioti*.[322] Roseolide A **323** was purified from the chloroform extract of the fruiting bodies of *Roseoformes subflexibilis*, a wood-rotting fungus, and the structure elucidation of **323** was made on the basis of 2D NMR spectroscopy, structural transformation to a known compound, and X-ray crystallographic



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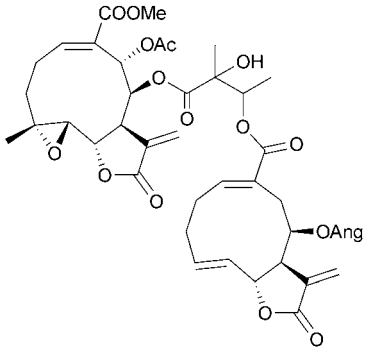

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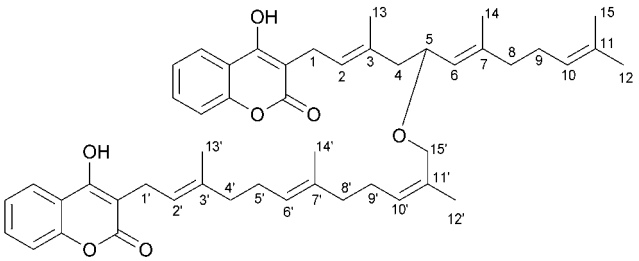

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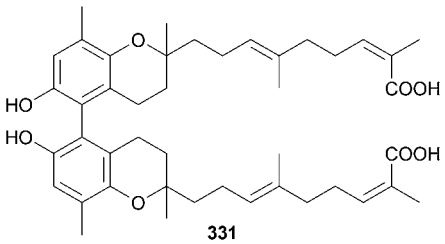

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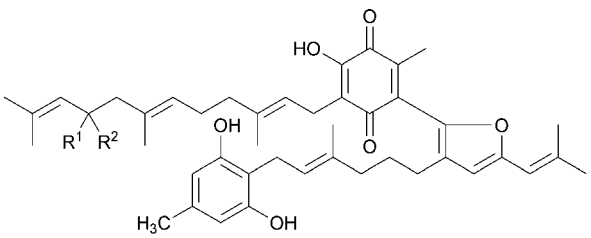
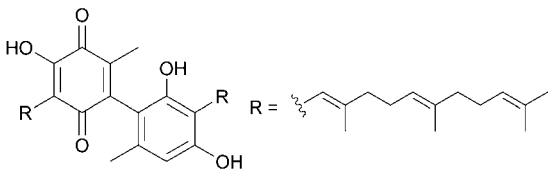


332 R^1,R^2 = O
333 R^1,R^2 = H,H
334 R^1,R^2 = OH,H



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analysis.[323] Haploporic acid A **324** was isolated from *Haploporus odorus*, a wood-rotting fungus growing mainly on willow trees.[324]

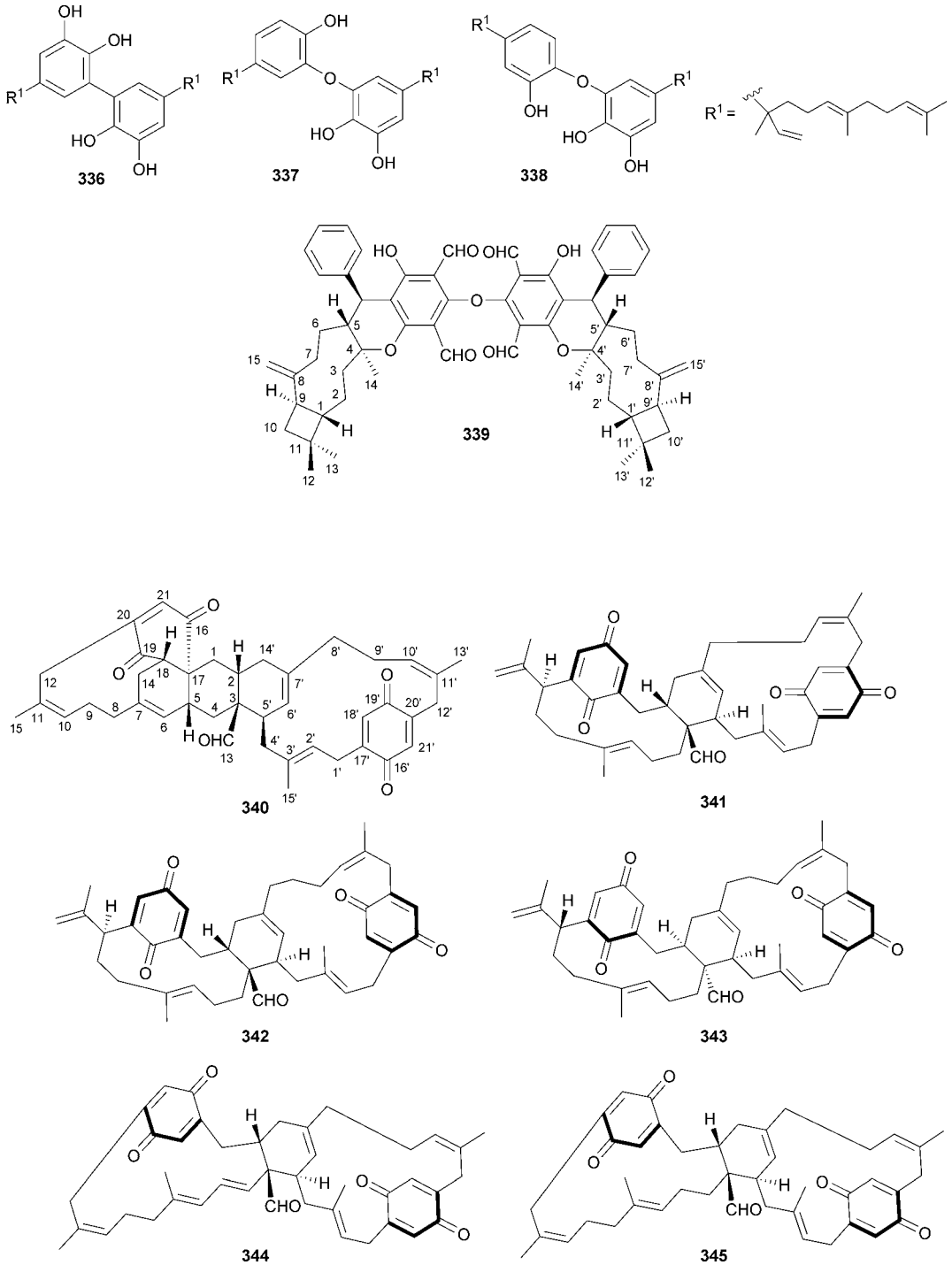
3.5 Others

An investigation of *Conyza aegyptica* afforded conyaegyptin **325**, in whose structure two sesquiterpenoid moieties are linked by xyloside.[325] The dichloromethane extract of the whole plant of *Leontodon hispidus* afforded 14-hydroxyhypocretenolide-β-D-glucopyranoside-4′-14″-hydroxyhypocretenoate **326**.[326] Phyllaemblicin F **327** was identified as a norsesquiterpenoid dimer from the roots of *Phyllanthus emblica*, and is presumably formed from phyllaemblic acid and phyllaemblicin B through an ester linkage between C6 of phyllaemblicin B and C13 of phyllaemblic acid.[327] A novel dimer from *Bazzania pompeana* was shown to be **328**.[328] A novel dimeric melampolide from the leaves of *Smallanthus sonchifolius* was established as **329**.[329]

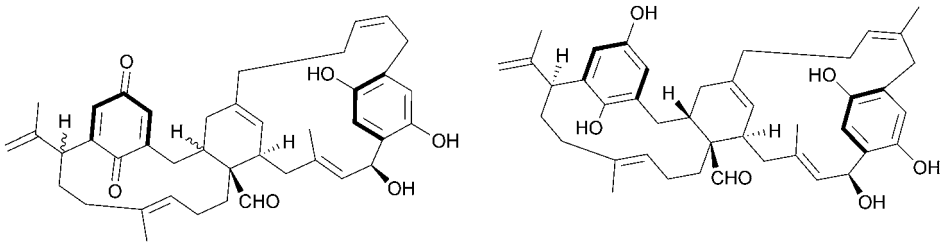
4 Merosesquiterpenoid dimers

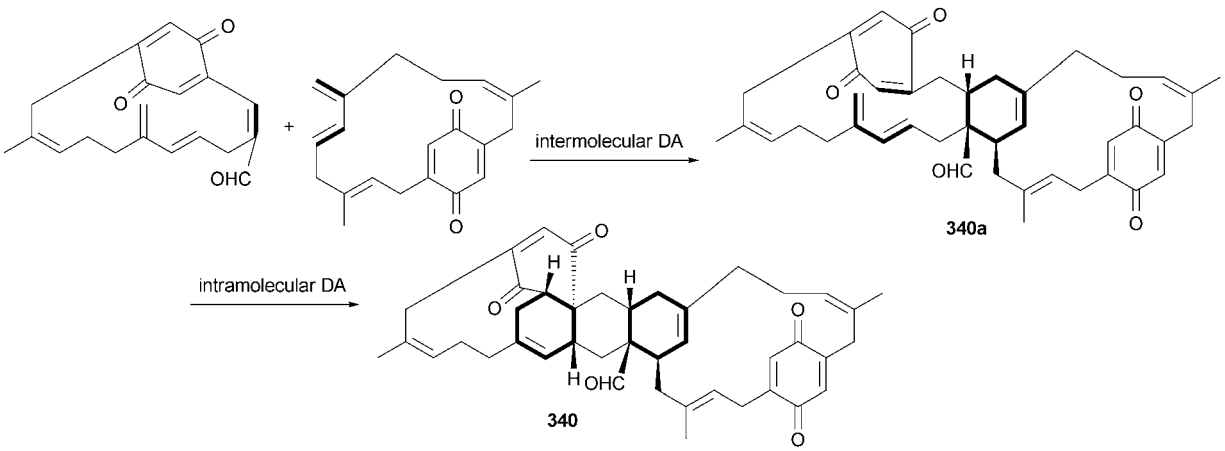
The term meroterpenoid refers to natural products of mixed biosynthetic origins which are partially derived from terpenoids. These natural products are most frequently isolated from fungi and marine organisms, but higher plants can also produce meroterpenoids. In addition to their wide occurrence, meroterpenoids display a vast range of structural diversity and important biological activities.[330] Although diverse in structure, meroterpenoids can be grouped into two major classes based on their biosynthetic origins: polyketide–terpenoids, exemplified by **358**, and non-polyketide–terpenoids, exemplified by **330**.[331] In this review, we have restricted to ourselves to naturally occurring dimeric merosesquiterpenoids, including their biological activities and total synthesis.

A dimeric prenylated coumarin named ferulenoloxyferulenol **330** was isolated from the root sap of *Ferula communis* var. *genuina*. Structurally, **330** arises from the etherification of

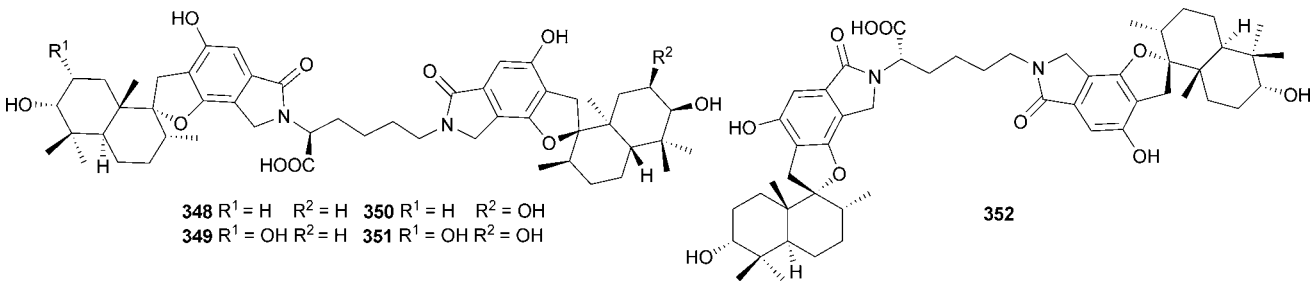


ε-hydroxyferulenol by ω-hydroxyferulenol, which were also found in the species.[332] A new benzosesquiterpenoid dimer, 3″,3‴-bispolycerasoidol **331**, along with its monomer, polycerasoidol, was isolated from the leaves of *Polyalthia cheliensis*.[333,334] A series of new farnesyl phenols dimers, grifolinone B **332**,[335] albatrellin **333**,[336]16-hydroxyalbatrellin **334**[336] and grifolinone C **335**,[337] were found in the mushrooms *Albatrellus caeruleoporus*, *A. flettii* and *A. confluens*, respectively. Total synthesis was used to confirm the structure of albatrellin **333**.[336] Grifolin[337,338] and cristatin,[339] two components also present in the genus, may be key intermediates in the biosynthesis of these novel dimers. Grifolinone B **332** exhibited inhibitory activity against nitric oxide production stimulated by lipopolysaccharide in RAW 264.7 cells,[335] whilst albatrellin **333** exhibited moderate cytotoxic activity against HepG2 human lung carcinoma cells.[337] Three new prenylated catechol dimers, peltatols A–C **336–338**, and their corresponding monomer were isolated from the tropical shrub *Pothomorphe peltata*.[340] Peltatols A–C inhibited





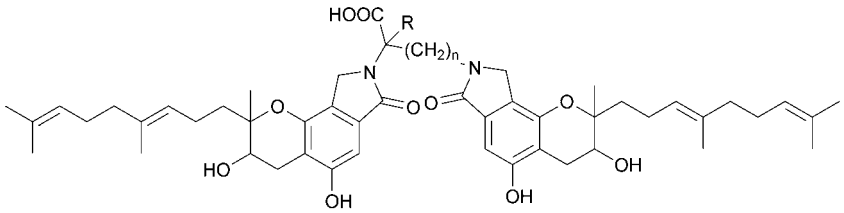
Scheme 3 Biogenetic pathway proposed for longithorone A (**340**).



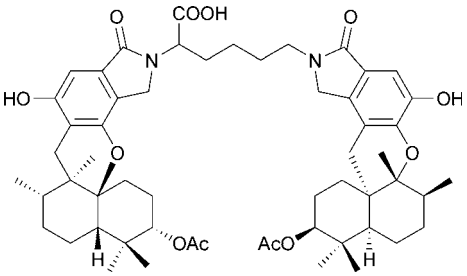
cytopathic effects of HIV-1 infection in a human T-lymphocytic cell line at subcytotoxic concentrations of 1–10 μg ml^{-1}, whereas the monomer was inactive. Moreover, it was very interesting that the diphenyl ethers, peltatols B and C, were interconvertible in solution (MeOH, DMSO) at room temperature. Diguajadial **339**, a homodimeric ether with two guajadial units,[341] was identified from the leaves of *Psidium guajava*.[342] A biomimetic synthesis of guajadial suggested that guajadial was formed biosynthetically *via* a hetero-Diels–Alder reaction between caryophyllene and an *o*-quinone methide.[343]

An unprecedented dimeric prenylated quinone from the tunicate *Aplydium longithorax* was elucidated as longithorone A **340** by spectral data and single-crystal X-ray diffraction.[344] A possible biogenesis of **340** is shown in Scheme 3. In this pathway, the farnesyl units first bridge the 2- and 5-positions of a benzoquinone to form a macrocycle, then an intermolecular Diels–Alder reaction affords **340a**. A similar intermolecular Diels–Alder reaction in **340a** results in the formation of longithorone A. This hypothesis was verified *via* the biomimetic synthesis of longithorone A.[345] Further analyses of *A. longithorax* led to the isolation of a number of related cyclofarnesylated quinones, longithorones E–I **341–345**[346] and longithorols A–B **346–347**.[347]

Four novel endothelin antagonists, stachybocins A–D **348–351**, were isolated from the culture filtrate of *Stachybotrys* sp. M6222. Clearly, stachybocins A–D consist of two spirobenzofuran units each fused to a substituted drimane sesquiterpenoid, which are connected by a lysine residue.[348–350] Later, an analogue, spirodihydrobenzofuranlactam VI, was reported from the same genus,[351,352] and structurally revised to **352**.[353] It showed similar bioactivity to **348–351**. SMTP-7 **353** and SMTP-8 **354**, two novel pseudosymmetric merosesquiterpenoid dimers, were isolated from cultures of *Stachybotrys microspora* IFO



353 R = αH, n = 2 **355** R = βH, n = 2
354 R = αH, n = 3 **356** R = βH, n = 3



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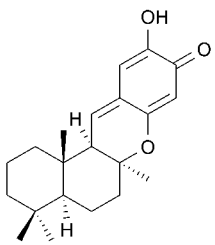

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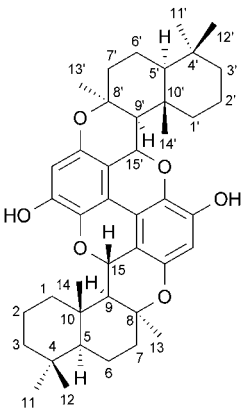

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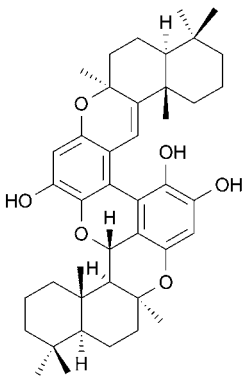

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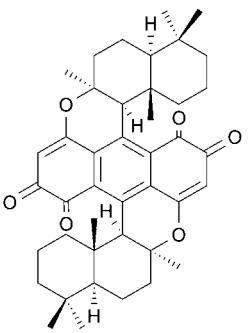

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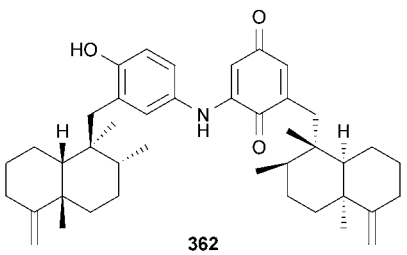
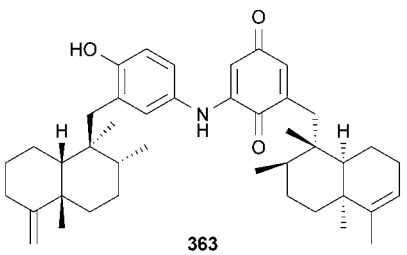
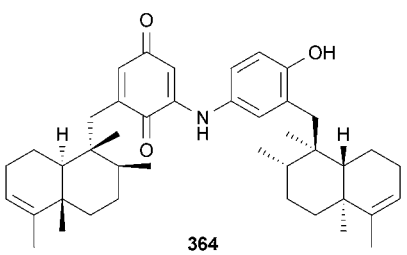


362



363



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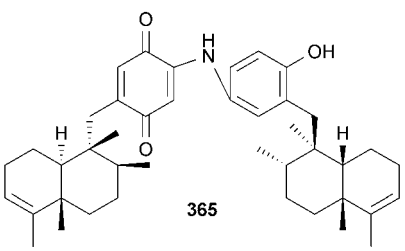

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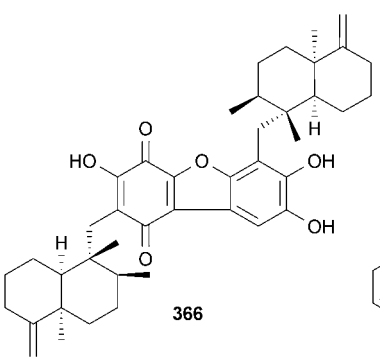

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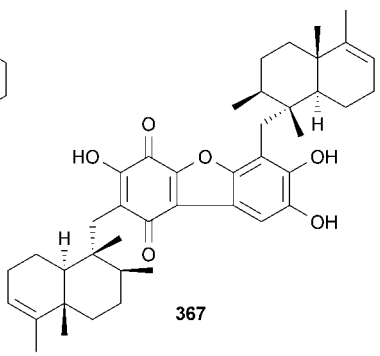

367

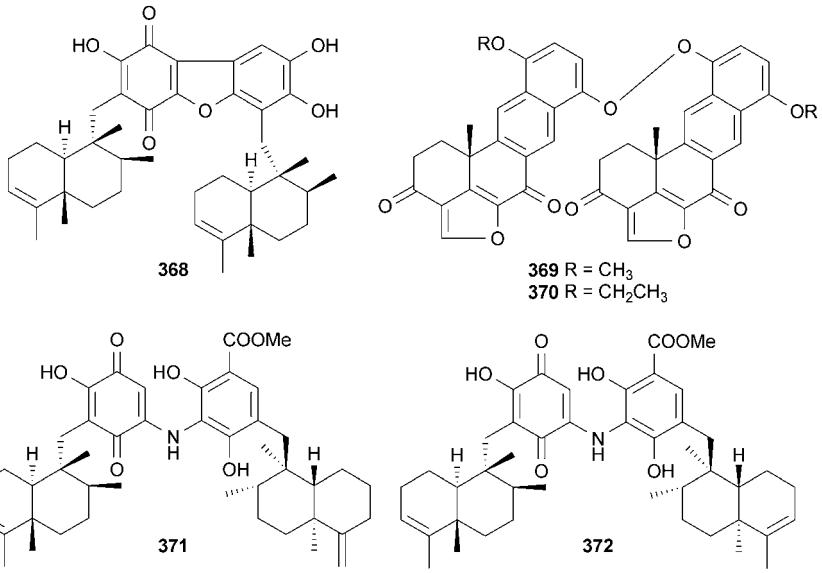

Table 4 Natural dimeric puupehenone derivatives

No.	Name	Sources	Ref.
359	Bispuupehenone	*Hyrtios eubumma*	357
360	Dipuupehetriol	*Hyrtios* sp.; genus unidentified	358,364
361	Dipuupehedione	*Hyrtios* sp.	359
362	Popolohuanone A	*Dysdea* sp.	360
363	Popolohuanone B	*Dysdea* sp.	360
364	Popolohuanone C	*Dysdea* sp.	361,365
365	Popolohuanone D	*Dysdea* sp.	361
366	Popolohuanone E	*Dysdea* sp.	362
367–368	No trivial name given	*Dysdea* sp.	363
369–370	Dihalenaquinolides A–B	Genus unidentified	366
371–372	Nakijiquinones E–F	Genus unidentified	367

30018. Structurally, the SMTP-7 molecule consists of two identical staplabin core structures and L-ornithine which bridges the two partial structures, whereas in the SMTP-8 molecule, the bridging unit is L-lysine.[354] More interestingly, when D-ornithine and D-lysine were added to medium containing this microbe, the corresponding epimers **355–356** were obtained as the main metabolites.[355] Feeding DL-lysine to a culture of *Stachybotrys* sp. RF-7260 in solid-state fermentation condition induced the formation of SQ-02-S-L1 **357**.[356]

Puupehenone **358** and its derivatives, which are biogenetically derived from sesquiterpenoid and C_6-shikimate moieties, were isolated from marine sponges and brown algae. Bispuupehenone **359**, the first dimeric puupehenone, was reported from the marine sponge *Hyrtios eubumma*.[357] Later, an array of novel dimeric puupehenone derivatives, listed in Table 4, were found in marine sponges.[357–367] Furthermore, some exciting bioactivities were displayed to these dimers, such as cytotoxicity, immunomodulatory, antimalarial,[364] and topoisomerase-II inhibitory activity.[362] Most of these compounds are structurally derived from dimerization of puupehenone by oxidation. On biosynthetic grounds, the sesquiterpene moieties within them should have the same absolute stereochemistry as puupehenone, which showed the same absolute configuration as (−)-drimenol.[368]

5 Conclusions

In general, dimeric sesquiterpenoids are hybrid complex natural products, and they often have biological and pharmacological activities that differ from their corresponding monomers. Compared with sesquiterpenoid monomers, dimeric sesquiterpenoids have a relatively limited distribution. The survey of published literature reveals that most of the type A and B disesquiterpenoids occur in higher plants, especially dicotyledons, and only a few are reported from higher fungi and ferns. These metabolites may be used as chemomarkers in the evolution of the plant kingdom. Though some efforts have been made in the biomimetic syntheses of these complex natural products, their total synthesis and elucidation of their biogenetic routes remain a challenge for researchers.

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