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Biological Activity of Natural Sesquiterpenoids containing a gem-Dimethylcyclopropane Unit

Journal:	*Natural Product Reports*
Manuscript ID:	NP-REV-02-2015-000024.R1
Article Type:	Review Article
Date Submitted by the Author:	14-Apr-2015

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REVIEW

Biological Activity of Natural Sesquiterpenoids containing a *gem*-Dimethylcyclopropane Unit

Cite this: DOI: 10.1039/x0xx00000x

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Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

The biological activities of aristolane, aromadendrane, *ent*-1,10-secoaromadendrane, 2,3-secoaromadendrane, *ent*-5,10-cycloaromadendrane, bicyclogermacrane, lepidozane, and maaliane terpenoids which contain the *gem*-dimethylcyclopropyl unit is described. Particular attention is given to their anti-viral, anti-microbial and cytotoxic activities. In the main text there are 119 references covering the literature from 1963-2014. The electronic supplementary information contains tables listing 332 of these terpenoids, their occurrence and biological activity together with the references.

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1 Introduction

Although sesquiterpenes[1-6] and diterpenes[7-11] have been the subject of numerous reviews, sesquiterpenes containing a *gem*-dimethylcyclopropyl subunit need a comprehensive review because of the wide range of their potentially valuable biological activities and broad structural diversity.

These three-membered carbocycles are found in various compounds, particularly terpenoids, which have been isolated from a large number of organisms including plants, liverworts, fungi and marine organisms such as soft corals, sponges or sea slugs.

In this article we provide a comprehensive report of sesquiterpenoid natural products containing a *gem*-dimethylcyclopropyl subunit, which may affect their biological activities. This review, with more than 119 references, covers the literature in this field from 1963 to 2014. Tables containing compounds, the species from which they were isolated, their biological activities and the references where they were described, are included in the SI of this paper.

2 Sesquiterpenoids

There are many natural products that contain a *gem*-dimethylcyclopropane ring as part of a sesquiterpene skeleton including bicyclogermacranes, lepidozanes, aromadendranes, *ent*-1,10-secoaromadendranes, 2,3-secoaromadendranes, *ent*-5,10-cycloaromadendranes, aristolanes and maalianes (Fig. 1).

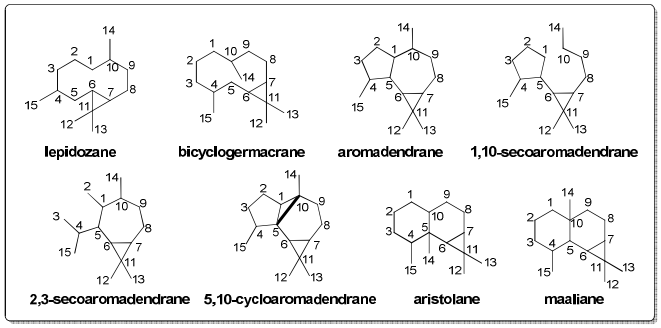


Fig. 1 Sesquiterpene skeleta containing a *gem*-dimethylcyclopropane.

These groups are structurally related sesquiterpenes containing a fused dimethylcyclopropane ring and it has been proposed that they have a possible common biosynthetic origin (Fig. 2).[12,13] These sesquiterpenes are derived from (2*E*,6*E*)-farnesyl pyrophosphate which is converted into bicyclogermacrene by the enzyme bicyclogermacrene synthase after 1,3-deprotonation of the corresponding carbocation. The latter is believed to be the biosynthetic precursor of aromadendranes, aristolanes and maalianes through regiospecific cyclisations followed by either suitable hydride or methyl shifts. An anti-Markovnikov-oriented cyclisation of the most stable conformer of bicyclogermacrene would lead to aromadendranes whereas a Markovnikov-oriented cyclisation yields the maalianes. Finally, an 1,2-migration of a methyl group from the maaliane cation would yield the aristolanes.[14]

On the other hand, 2,3-secoaromadendranes and 5,10-cycloaromadendranes are probably derived from the appropriate cyclisation or bond cleavages of the corresponding aromadendranes. Finally, lepidozanes could be derived by a suitable proton elimination to produce a *trans* cyclopropane ring.[14]

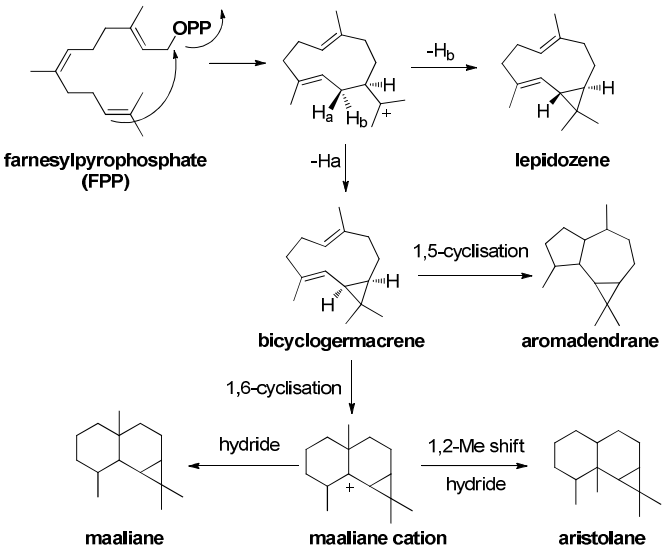


Fig. 2 Proposed common biosynthetic pathway for sesquiterpenes containing a *gem*-dimethylcyclopropane unit.[13]

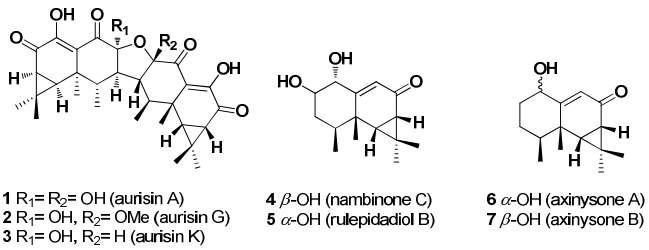
These sesquiterpenes have been isolated from diverse sources and possess a wide variety of biological activities such as cytotoxic, antimicrobial or antifeedant allelopathic activity. The biological activity will be discussed in the context of their different carbon skeleta.

2.1 Aristolanes (structures 1-50)

Aristolane sesquiterpenes are rare in nature although they have been isolated both from terrestrial plants and marine organisms[15] as well as from the fungus *Russula lepida*. They have been tested and reveal different biological activities.

2.1.1 Antimicrobial activity

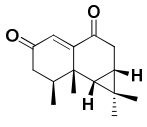
Aurisins A, G, and K (**1**-**3**) are dimeric aristolanes that exhibited antimalarial activity against *Plasmodium falciparum.* The aurisins A (**1**) and K (**3**) also showed antimycobacterial activity against *Mycobacterium tuberculosis*. However, nambinone C (**4**) was not active in any of these assays.[16] Axinysones A-B (**6-7**), and anthracophyllone (**8**) were evaluated for antimalarial activity and activity against *Bacillus cereus* but again they were inactive.[17] Kanshone F (**9**) was examined against *P. falciparum* but it did not show any promising activity.[18] There is a clear difference between the hydrophilic and hydrophobic faces of the dimers.



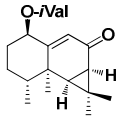
1 R_1= R_2= OH (aurisin A)
2 R_1= OH, R_2= OMe (aurisin G)
3 R_1= OH, R_2= H (aurisin K)

4 β-OH (nambinone C)
5 α-OH (rulepidadiol B)

6 α-OH (axinysone A)
7 β-OH (axinysone B)



8 (anthracophyllone)



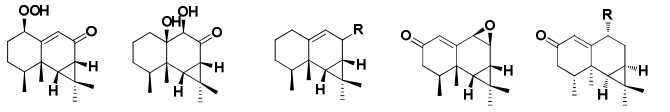
9 (kanshone F)

2.1.2 Cytotoxic activity

Aurisins A, G, and K (**1**-**3**) were evaluated for cytotoxicity activity against KB, MCF-7, NCI-H187, and Vero cells. These three compounds displayed biological activity against KB and NCI-H187. Moreover aurisins A (**1**) and K (**3**) showed cytotoxicity against Vero cell and the cholangiocarcinoma cell lines.[16,17] However, nambinone C (**4**) was evaluated against BC-1, KB, cholangiocarcinoma, and NCI-H187 cell lines showing cytotoxicity against this latter[16] whereas its epimer rulepidadiol B (**5**) was inactive when it was tested for *in vitro* inhibitory activity on the proliferation of A-549, CAKI 1, and WISH cell lines in a 48 h MTT essay.[19] Furthermore, the axinysones A-B (**6**-**7**) were tested against NCl-H187 cell line but only axinysone A (**6**) exhibited specific cytotoxicity against this cell line.[17] These results might indicate an important effect of the stereochemistry of the hydroxyl groups at C-1 and C-2 in the

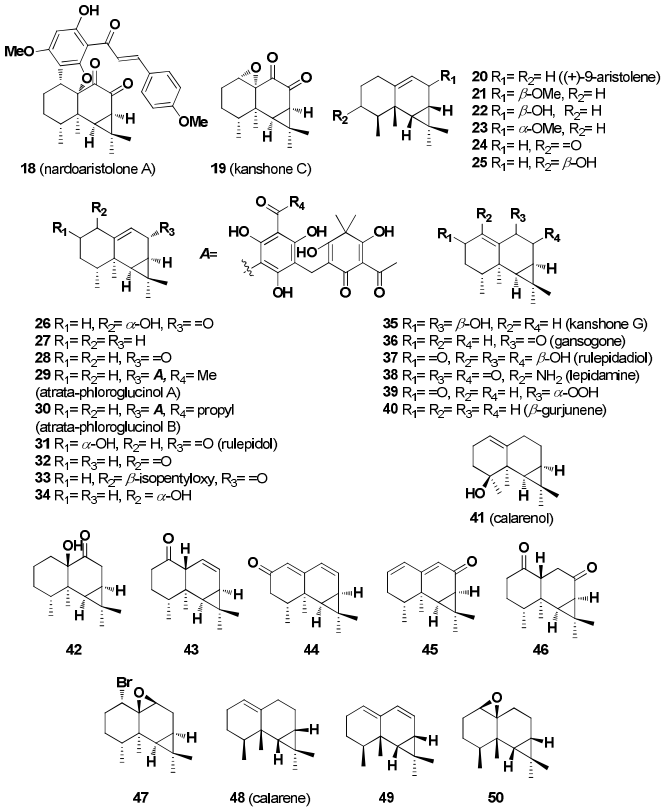
cytotoxic activity. It would appear that the presence of an α-hydroxyl group at C-1 is crucial for the cytotoxicity as in the case of the compounds **4** and **6** since compound **8** with a β-hydroxyl group at C-1 position was inactive. Furthermore, the presence of a vicinal hydroxyl group at the C-2 position should have a *trans* disposition with respect the α-hydroxyl group at C-1 as is the case of nambinone C (**4**). The isomer rulepidadiol (**5**) with the α-hydroxyl group at C-2 was inactive.

The enedione anthracophyllone (**8**) exhibited cytotoxicity against KB, MCF-7, NCI-H187 and Vero cells. However, axinysones A-D (**6**-**7** and **10**-**11**), axinynitrile A (**12**) and (+)-aristolone (**13**) were inactive against the human tumor cell lines MDA-MB-231, A-549, and HT-29.[20] Axinysone E (**14**) was mildly active against the human tumor cell lines A-549 and HT-29[20] and debilon (**15**) showed cytotoxic activity against P-388 cells.[21]



2.1.3 Other activities

Nardoaristolone A (**18**) was evaluated for its protective effects on H_2O_2-induced myocardial injury. This effect was dose-dependent.[22] Kanshone C (**19**) is a highly oxidized aristolane-type sesquiterpenoid[23] that showed a remarkable protective activity against *D*-galactosamine-induced liver damage in rat hepatocytes.[24] Finally, (+)-9-aristolene (**20**) inhibited the metamorphosis of the barnacle *Balanus amphitrite*.[25]

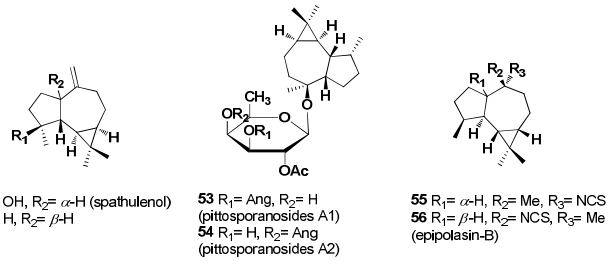


2.2 Aromadendranes (structures 51-190)

Aromadendranes are the most abundant group of compounds containing a *gem*-dimethylcyclopropane ring. They contain a *gem*-dimethylcyclopropane fused to a hydroazulene skeleton (bicycle[5.3.0]decapentane). Aromadendranes have been isolated from the oil or resin of different tree species whereas *ent*-aromadendranes, which have the mirror image carbon skeleta, have been found in liverworts such as *Heteroscyphus planus*, *Mylia nuda* or *Calypogeia azurea*. This large group of compounds are discussed in terms of their biological activities.

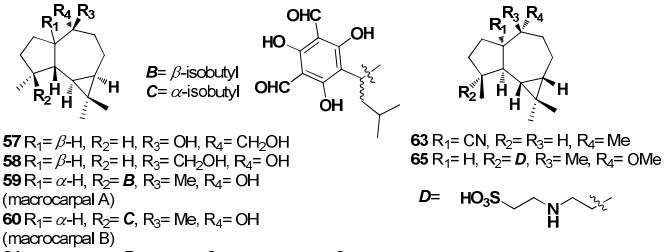
2.2.1 Antifeedant, antifouling and insect repellent activity

Spathulenol (**51**) showed repellent activity against the leaf cutter ant[26] and the compound **52** was toxic to the Southeast Asian termites (*Neotermes* spp.) and played an important role in defence against these insects.[27] Finally, the glycosides pittosporanoside A1 and A2 (**53**-**54**) are active repellent substances against the blue mussel (*Mytilus edulis*) whereas compounds **55** and **56** inhibit the metamorphosis of the barnacle *B. amphitrite*.[25]



2.2.2 Antimicrobial activity

Spathulenol (**51**) showed activity against *Staphylococcus aureus* and *Proteus mirabilis*[28] whereas the *allo*-aromadendranes **57** and **58** displayed antimycobacterial activity against *M. tuberculosis*.[29] Moreover, compound **57** was identified as the sesquiterpenoid responsible for the antibacterial activity of the leaves of *Duguetia grabriuscula*.[30] The macrocarpals A-C (**59**-**61**) are terpenes which were isolated from *Eucalyptus macrocarpa* with structures that are characterized by an isopentyl phloroglucinol dialdehyde fused to an aromadendrane skeleton. They showed activity against Gram-positive bacteria such as *Bacillus subtilis* PCI219 and *S. aureus* FDA209P.[31,32] Additionally macrocarpals A-C (**59**-**61**) exhibited antibacterial effects against not only Gram-positive bacteria, but also Gram-negative periodontopathic bacteria with more than 60% inhibition.[33-35] The sesquiterpenes **62** and **63** are two antimicrobial components of *Acanthella pulcherrima*[36] whereas halichonadin F (**64**) showed antimicrobial activity against *Micrococcus luteus*, *Trichophyton mentagrophytes* and *Cryptococcus neoformans*.[37] Compound **65** inhibits the growth of *B. subtilis* and *M. luteus* but it had no effects on *E. coli*.[38] Both aromadendrane and *ent*-aromadendrane can inhibit the growth of *M. luteus* as is the case of the compounds **64** and **65**.



57 R_1= β-H, R_2= H, R_3= OH, R_4= CH_2OH
58 R_1= β-H, R_2= H, R_3= CH_2OH, R_4= OH
59 R_1= α-H, R_2= ***B***, R_3= Me, R_4= OH
(macrocarpal A)
60 R_1= α-H, R_2= ***C***, R_3= Me, R_4= OH
(macrocarpal B)
61 R_1= α-H, R_2= ***B***, R_3,R_4= $=CH_2$ (macrocarpal C)
62 R_1= β-H, R_2= H, R_3= Me, R_4= NCS
64 R_1= α-H, R_2= H, R_3= NH_2, R_4= Me
(halichonadin F)
63 R_1= CN, R_2= R_3= H, R_4= Me
65 R_1= H, R_2= ***D***, R_3= Me, R_4= OMe

Ledol (**66**), viridiflorol (**67**) and the compounds **68** and **69** are also aromadendranes with antifungal activity. Ledol (**66**) showed activity against *Coriolus ronatus*[39] and *Cladosporium cucumerinum*[40] whereas viridiflorol (**67**) showed weak activity against *C. cucumerinum*[40] and *Pyricularia oryzae*.[41] *Allo*-aromadendrane **68**, isolated from the aerial part of *Ambrosia peruviana*, was a very effective inhibitor of the growth of *Cladosporium herbarium*[42] and compound **69** exhibited anti-*P. oryzae* activity.[43]

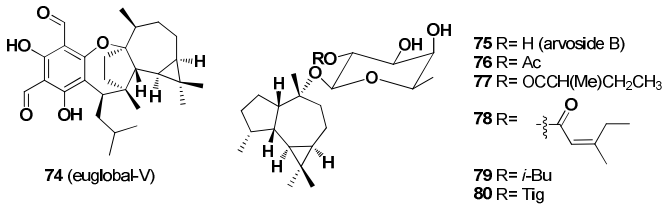
66 R_1= H, R_2= R_3= Me, R_4= OH (ledol)
67 R_1= H, R_2= R_4= Me, R_3= OH (viridiflorol)
68 R_1= R_4= Me, R_2= R_3= OH
69

Millecrone B (**70**) was inactive against *Candida albicans* but inhibited the growth of both *S. aureus* and *B. subtilis*.[44] Finally (-)-cyclocolorenone (**71**) showed antibacterial activity against several Gram-positive bacteria and, at higher concentration, against Gram-negative bacteria and also inhibited the growth of the fungi *Curvularia lunata*, *Chaetomium cochliodes* and *Chaetomium spinosum*, but not of *Aspergillus flavus*.[45] On the other hand, 15-hydroxyspathulenol (**72**) was examined for antimicrobial activity against Gram-positive and Gram-negative bacteria *Pseudomonas aeruginosa*, *E. coli* and the yeast *C. albicans* but it was inactive.[46] Finally, 3-acetoxyspathulenol (**73**) was tested for its antimicrobial activity against two bacteria (*E. coli* and *Bacillus megaterium*), four fungi (*Eurotium repens*, *Fusarium oxysporum*, *Microbotryum violacea* and *Mycotypha microspora*) but again it was inactive.[47] In contrast to spathulenol (**71**), compounds **72** and **73** possess oxygenated substituents either at C-3 or C-15 position which may be involved in a loss of the antimicrobial activity of these compounds. In these compounds, the distance between the hydrophilic group and the hydrophobic dimethylcyclopropane ring appears to affect their antimicrobial activity.

70 (millecrone B) **71** ((-)-cyclocolorenone)
72 R_1= H, R_2= CH_2OH (15-hydroxyspathulenol)
73 R_1= OAc, R_2= Me (3-acetoxyspathulenol)

2.2.3 Antiviral activity

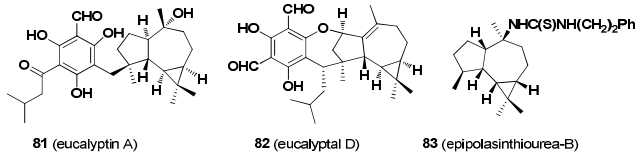
Macrocarpals A-C (**59**-**61**) showed significant inhibitory activity of HIV-RTase[48] whereas 3-acetoxyspathulenol (**73**) was inactive.[47] Euglobal-V (**74**) exhibited remarkable inhibitory effects on the Epstein-Barr virus.[49] On the other hand, arvoside B (**75**) and related ledol glycosides **76**-**80** exhibited antiviral activity against the vesicular stomatitis virus, arvoside B (**75**) being the most effective.[50]



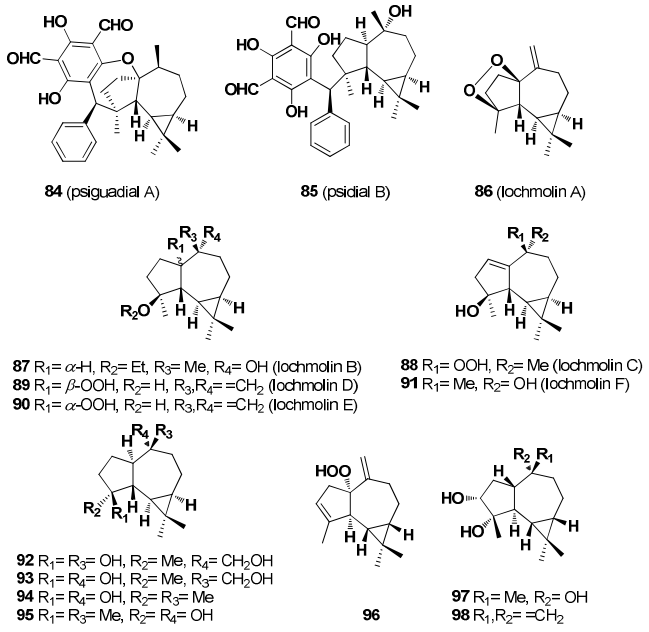
74 (euglobal-V)
75 R= H (arvoside B)
76 R= Ac
77 R= OCCH(Me)CH_2CH_3
78 R=
79 R= *i*-Bu
80 R= Tig

2.2.4 Cytotoxic activity

Allo-aromadendrane-10*β*,14-diol (**57**) was evaluated against Hep2 human larynx carcinoma cells and produced inhibition of cellular growth.[51] For their part macrocarpals A and B (**59**-**60**) and eucalyptin A (**81**) exhibited inhibition on HGF/c-Met axis, eucalyptin A (**81**) showing the most potent inhibition.[52] Furthermore, eucalyptal D (**82**) which is a 3,5-diformyl-isopentyl phloroglucinol-coupled aromadendrane and which possesses an unusual seven-membered ring with an ether bridge between C-2 of the aromadendrane moiety and C-2 of the aromatic unit, exhibited significant *in vitro* cytotoxicity against the human cancer cell lines Huh-7, Jurkat, BGC-823 and KE-97.[53] Epipolasinthiourea-B (**83**) showed moderate cytotoxic activity *in vitro* against L1210 cells[54] and psiguadial A (**84**) exhibited potent inhibitory effects on the growth of human hepatoma cells.[55] Psidial B (**85**) was evaluated against several human cancer cell lines including A-2780, HCT-8, Bel-7402, A-549 and BGC-823.[56] The lochmolins A-D (**86**-**89**) and lochmolins E-F (**90**-**91**) were evaluated against the proliferation of a limited panel of cancer cell lines, including HeLa, SK-Hep1 and B-16 carcinoma cells.[57] The results showed that all these compounds were not cytotoxic toward these three cancer cell lines. The natural products **92** and **93** were evaluated for their cytotoxic effects against A-549 and U-2 OS cell lines[58] whilst the cytotoxicity of compounds **94** and **95** against A-735 and cervical carcinoma HeLa cell lines was also examined as well by an MTT essay.[38] Unfortunately they did not exhibit cytotoxicity. Similarly, the compounds **96**-**98** were not cytotoxic to P-388 and HT-29 cells.[59]



81 (eucalyptin A) **82** (eucalyptal D) **83** (epipolasinthiourea-B)



The vast majority of the cytotoxic aromadendranes (**59-60**, **81-82** and **84-85**) possess a phoroglucinol moiety coupled to an aromadendrane-type skeleton in which the presence of a methyl group at the C-4 and C-10 positions, the *gem*-dimethylcyclopropyl unit and the *β*-hydrogen at C-5 are common in all of them (Fig. 3). These more rigid sesquiterpenes might be acting as biological carriers ensuring that the pharmacophore can cross various barriers and reach the active site. The common substituents of these aromadendranes are highlighted below. To our knowledge, phloroglucinol-coupled *ent*-aromadendranes have not been found in nature.

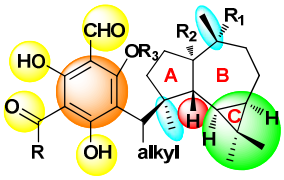


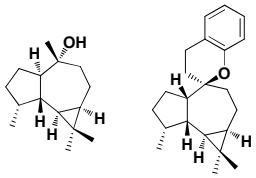
Fig. 3 Common parts of cytotoxic aromadendranes.

2.2.5 Other activities

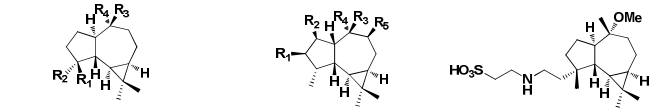
Compounds obtained from plants of the genus *Eucalyptus*, or from microorganisms such as the macrocarpals A-B (**59-60**), isolated from *Eucalyptus globulus*, have been shown to be useful as CNS activity modulators e.g. in the treatment of depression, for lifting mood and/or for increasing other behavioural activities.[60] Macrocarpals A-C (**59-61**) also showed significant inhibitory activity of aldose reductase.[61]

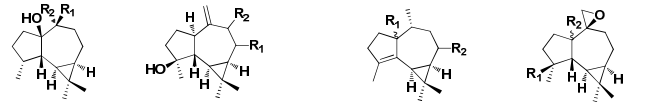
Allo-aromadendrane **68** caused a reduction in the growth of cress seeds and stimulated wood and shoot growth in lettuce at low concentration[42] whereas cyclocolorenone (**71**) showed growth inhibitory activity against etiolated wheat coleoptiles and phytotoxicity against green-house grown corn, bean and tobacco plants.[45] Globulol (**99**) exhibited weak activity against the germination of cress seed.[62]

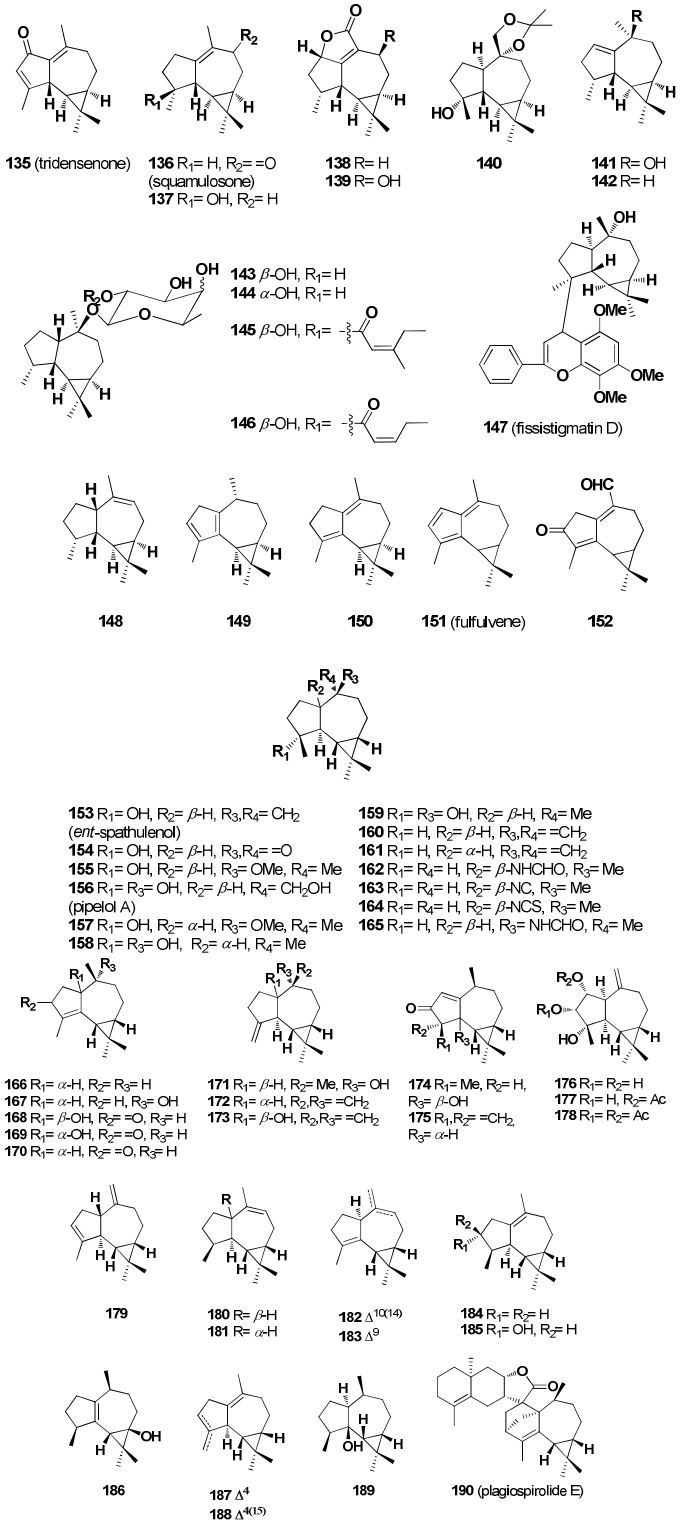
Euglobal-V (**74**) showed granulation inhibition in the fertile egg test indicating anti-inflammatory activity.[63] Psidial B (**85**) showed activity to protein tyrosine phosphatase 1B (PTP1B), inhibition rates of enzyme PTP1B were 61.7% in 10 μM.[56] The anti-inflammatory activities of lochmolins A-D (**86-89**) against the accumulation of pro-inflammatory iNOS and COX-2 proteins in RAW264.7 macrophage cells have been evaluated and all of them were found to inhibit the accumulation of the LPS-induced pro-inflammatory COX-2 protein in RAW264.7 macrophage cells.[57]



3-Acetoxyspathulenol (**73**) was tested for its effects toward a nematode (*Caenorhabditis elegans*), the green alga *Chlorella fusca*, the brine shrimp (*Artemia salina*), and p56lck tyrosine kinase but in all of the applied test systems no positive activities were observed.[47] Furthermore, the anti-inflammatory activities of lochmolins E-F (**90-91**) against the accumulation of pro-inflammatory iNOS and COX-2 proteins in RAW264.7 macrophage cells were evaluated but they did not show activity.[57] Compounds **92** and **93** were evaluated for their antioxidant effects on H_2O_2 production in H9c2 cardiac muscle cells, and their anti-inflammatory effects on lipopolysaccharide-induced nitric oxide production in both RAW 264.7 and BV-2 cells.[58] Tanzanene (**100**) was tested in the growth inhibition essay of *P. falciparum in vitro* but it showed no activity.[64]

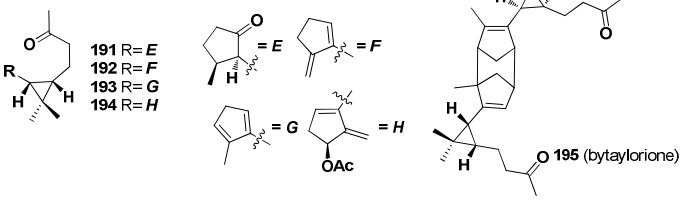






2.3 *ent*-1,10-Secoaromadendranes (structures 191-195)

Although a number of *ent*-1,10-secoaromadendrane-type sesquiterpenes have been isolated from *Mylia* species of liverworts and the liverwort *Lepicolea ochroleuca*,[65-67] the biological activities of these compounds have not been investigated.

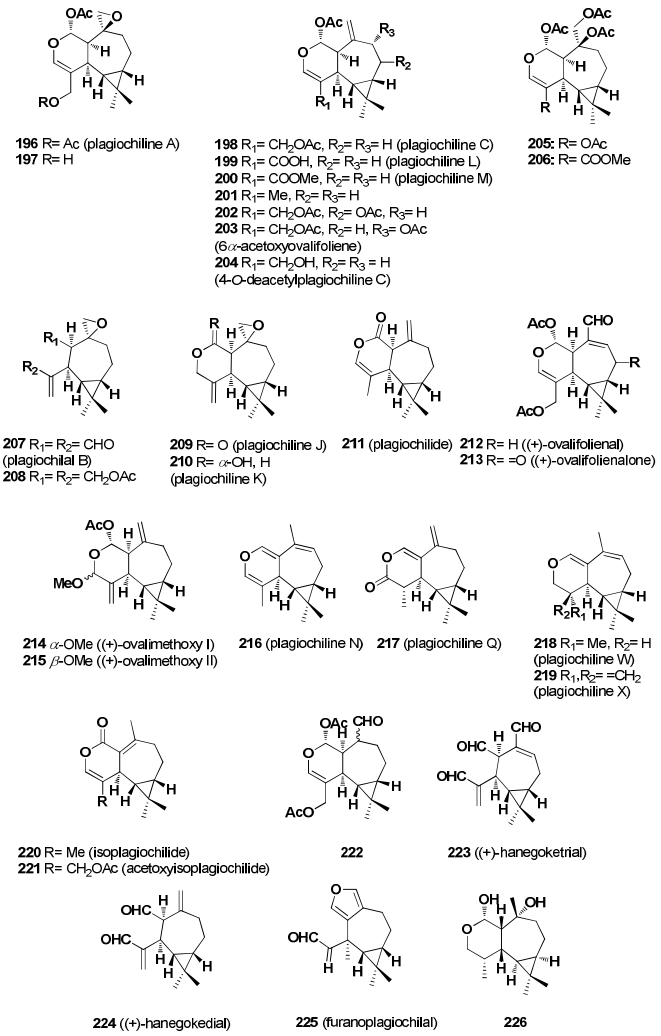


2.4. 2,3-Secoaromadendranes (structures 196-226)

The *ent*-2,3-secoaromadendrane-type sesquiterpenes are widely distributed in liverworts such as members of *Plagiochilaceae* and *H. planus*.[68,69] The presence of (-)-bicyclogermacrene in a *Plagiochila* species led to the proposal of a possible route for the biosynthesis of *ent*-2,3-secoaromadendrane lactones and hemiacetals from this metabolite.[70] The pungent substances of the *Plagiochilaceae* are *ent*-2,3-secoaromadendrane-type sesquiterpenes which have shown different biological activities.

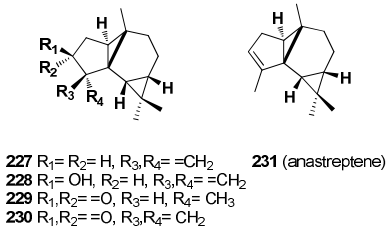
Plagiochiline A (**196**) is an *ent*-secoaromadendrane-type sesquiterpene hemiacetal which was isolated from *Plagiochila* species[71-73] that showed cytotoxic activity against P-388 murine leukemia tumor cells,[74] KB cells[75] and which exhibited strong antifeedant activity against the African army worm *Spodoptera exempta*.[76] Plagiochiline C (**198**) showed significant antiplatelet effects on the arachidonate and collagen induced aggregations of washed rabbit platelets.[77] When plagiochiline A and M (**196** and **200**) were incorporated into the larval diet they reduced the larval growth of *Spodoptera frugiperda*. Compound **205** underwent rapid decomposition after incorporation into the larval diet of *S. frugiperda*, its effects could not be evaluated.[71] Treatment with plagiochiline M (**200**) also produced abdomen and wing malformation in adult insects preventing mating.[71] Plagiochilal B (**207**) showed neurotrophic properties. It exhibits not only acceleration of neurite sprouting but also enhancement of choline acetyltransferase activity on a neuronal cell culture of fetal rat cerebral hemisphere However, plagiochilines J, K and plagiochilide (**209**-**211**) showed no neurotrophic activity.[70] This fact could be explained by the presence of a rigid six-membered ring instead of the corresponding open chain dialdehyde. The biological activity of dialdehydes is often associated with the formation of rings with amines.

On the other hand, plagiochiline A (**196**) inhibited the germination of rice and wheat[78] whereas plagiochiline C (**198**), ovalifolienal (**212**), ovalifolienalone (**213**) and ovalimethoxy I and II (**214**-**215**) inhibited the growth of the leaves and roots of rice seedlings.[79] Finally compound **226** is the first compound with a 2,3-secoaromadendrane-type skeleton which has been isolated from the culture of basidiomycete *Agrocybe salicacola*. However the biological activity has not been tested to our knowledge.[80]



2.5 *ent*-5,10-Cycloaromadendranes (structures 227-231)

ent-5,10-Cycloaromadendranes are fused tetracyclic sesquiterpenes with two cyclopropane rings in conjugation which have only been isolated from liverworts of the *Calypogeia*, *Saccogyna* and *Mylia* species.[66,81-83] As far as we know the biological activities of these compounds have not been investigated.

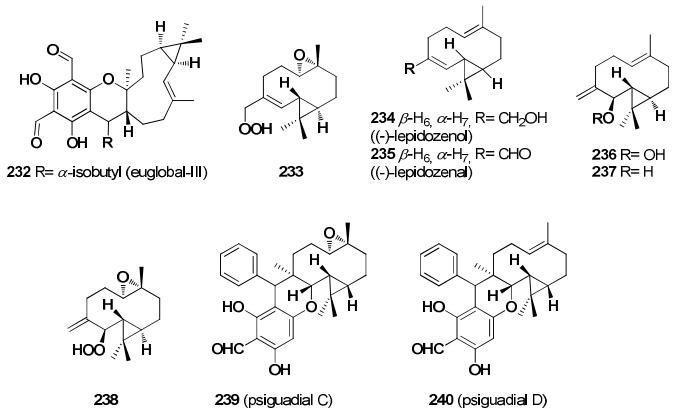


2.6 Lepidozanes and bicyclogermacranes (structures 232-283)

The bicyclogermacranes, which are found in higher plants, have a *cis*-fused cyclopropane ring whereas the stereoisomeric lepidozanes are found in liverworts and marine organisms, which possess a *trans*-fused cyclopropane ring.[15] This stereochemistry seems to determine the biological activity shown for these compounds. Whereas the fungistatic, allelopathic, cytotoxic and inhibitory activity of acetycholinesterase have been described for the bicyclogermacrenes, only cytotoxic activity has been reported for the lepidozanes.

2.6.1 Cytotoxic activity

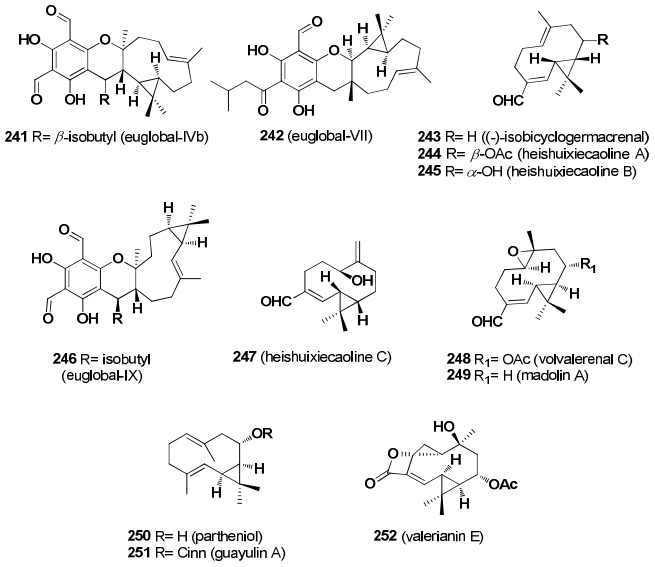
The phloroglucinol-terpene adducts are a group of secondary metabolites with interesting bioactive structures that are unique in plants of the Myrtaceae family, especially *Eucalyptus* species.[84-86] Thus the euglobals are acylphloroglucinol-terpene. Euglobal III (**232**) is one of the most active of them and it has a wide variety of biological activity. Among them it exhibited remarkable antitumor promoting effects on mouse skin tumor in an *in vivo* carcinogenesis test.[87,88] On the other hand, lepidozanes **233**-**238** exhibited cytotoxicity against murine melanoma cells. The compounds **233** and **236** have an allylic hydroperoxymethylene group which is rare in natural products and they exhibited the strongest activity.[89] Finally, bicyclogermacrenes **239** and **240** showed significant cytotoxicity toward HepG2 and HepG2/ADM cells.[90]



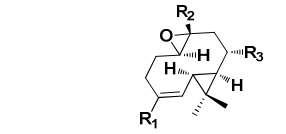
2.6.2 Other activities

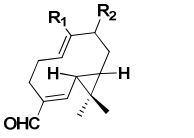
Euglobal-III (**232**), euglobal-IVb (**241**) and euglobal-VII (**242**) possessed a potent granulation inhibition activity[91,92] whereas (-)-isobicyclogermacrenal (**243**), isolated from the liverwort *Lepidozea vitrea*, inhibited the growth of rice.[93] Euglobal-III (**232**) has also shown strong inhibitory effects on the activation of the Epstein-Barr virus.[49] The essential moiety for this activity was considered to be the presence of acylphoroglucinol structure. Thereby, euglobal-IX (**246**) inhibited the catalytic activity of CYP3A4.[94] On the other hand, the protective effect of heishuixiecaoline A-C (**244**-**245** and **247**) and volvalerenal C (**248**) was investigated on the neurotoxicity of PC12 cells induced by amyloid-beta ($A\beta_{25-25}$), respectively. They were seen to afford protection against Aβ-induced toxicity in PC 12 cells.[53] Finally, the bicyclogermacrane madolin A (**249**) showed

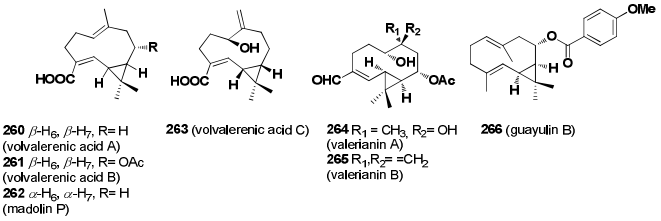
inhibitory activity on acetylcholinesterase[95,96] whereas partheniol (**250**),[97] guayulin A (**251**)[98] and valerianin E (**252**)[99] showed fungistatic activity against the growth of *Aspergillus niger*, allergenic activity and antidepressant activity, respectively.

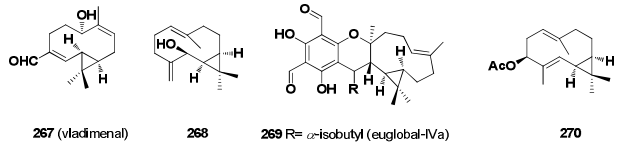


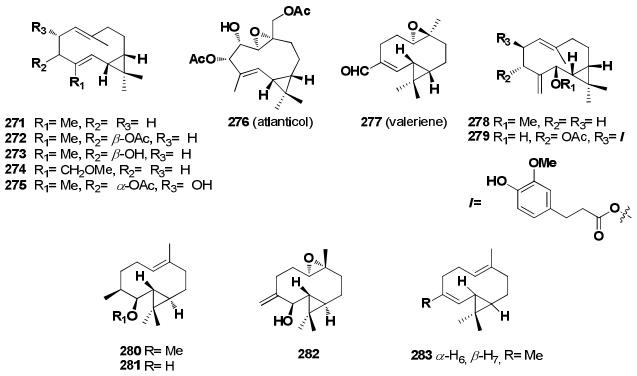
Volvalerenals A-B (**253-254**), volvaleranals D-E (**257-258**) and volvalerenic acids A-C (**260**-**261** and **263**) were examined for acetylcholinesterase inhibitory activity, but all were inactive at 100 μM unlike madolin A (**249**).[95] The presence of an epoxide between C-1 and C-10 and the absence of functionality at C-14 might be key features for the acetylcholinesterase inhibitory activity of madolin A (**249**). On the other hand, valerianins A-B (**264-265**) were evaluated for their antidepressant activity based on recording the total duration of immobility of mice in a forced swim test. In contrast to compound **252**, they showed no antidepressant activity.[99] The lactone ring of the compound **252** might be involved in the biological activity because the greater rigidity it imposes enables the compound to cross the barriers and reach the site of activity. Finally, guayulin B (**266**) does not exhibit significant allergenic activity on the contrary that guayulin A (**251**).[98] This suggests that the substituent at C-8 might play a crucial role in the biological activity of these compounds.





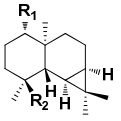




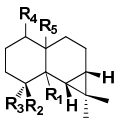


2.7. Maalianes (structures 284-305)

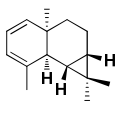
Although the maalianes have been isolated from a range of plants, liverworts, marine sponges, soft corals and bacteria, they are not abundant in nature. Furthermore, to our knowledge little biological activity it has been reported. Compound **284** and epipolasin-A (**285**), isolated from *Cadlina luteomarginata*, were toxic to the fish *Carussius auratus* at 10 μg/mg in a food pellet.[100] Epipolasin-A (**285**) showed *in vitro* antimalarial activity.[101] Epipolasinthiourea-A (**286**) showed moderate cytotoxic activity *in vitro*[54] whereas (1*R*)-bromo-*ent*-maaliol (**293**) is a cytotoxic halogenated maaliane isolated from the calcareous green algae *Neomeris annulata*. The cytotoxic activity of the *ent*-maaliane **293** was indicated by its toxicity to brine shrimp.[102] Finally, the maaliane (**294**) isolated from *Acanthella pulcherrima* has been described as an antimicrobial compound.[36] This compound is enantiomeric to epipolasin-A (**285**), and thus provides the first reported occurrence of an enantiomorphic pair of maalianes.[36]



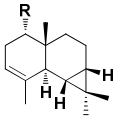
284 R_1= H, R_2= NC
285 R_1= H, R_2=NCS (epipolasin-A)
286 R_1= H, R_2= NHC(S)NH$(CH_2)_2$Ph (epipolasinthiourea-A)
287 R_1= H, R_2= OH (maaliol)
288 R_1= OGlc, R_2= OH
289 R_1= NC, R_2= H
290 R_1= NCS, R_2= H
291 R_1=HNCHO, R_2= H
292 R_1= R_2= OH



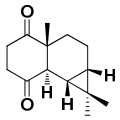
293 R_1= α-H, R_2= Me, R_3= OH, R_4= β-Br, R_5= β-Me ((1*R*)-bromo-*ent*-maaliol)
294 R_1= R_4= H, R_2= Me, R_3= NCS, R_5= β-Me
295 R_1= α-H, R_2,R_3= =CH_2, R_4= H, R_5= β-Me
296 R_1= α-H, R_2= Me, R_3= OH, R_4= H, R_5= β-Me
297 R_1= β-H, R_2= H, R_3= Me, R_4= α-OH, R_5= α-Me (avermitilol)
298 R_1= R_4= H, R_2= OH, R_3= Me, R_5= β-Me (*ent*-4-*epi*-maaliol)
299 R_1= α-OH, R_2= Me, R_3= R_4= H, R_5= β-Me
300 R_1= α-H, R_2,R_3= =CH_2, R_4= α-OH, R_5= β-Me



301



302 R= H
303 R= OAc
304 R= OH



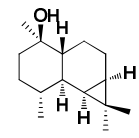
305 (madolin F)

2.8 Miscellaneous sesquiterpenoids (structures 306-332)

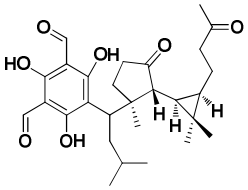
This section contains other sesquiterpenes that are not encompassed by any of the above groups and their biological activities.

2.8.1 Antimicrobial activity

Prostantherol (**306**) is an antimicrobial sesquiterpene which inhibits the Gram-positive *Streptomyces scabies*[103] and eucalyptone (**307**) has showed antibacterial activity against cariogenic bacteria *Streptococcus* species.[104]



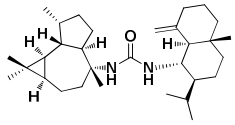
306 (prostantherol)



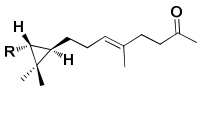
307 (eucalyptone)

2.8.2 Cytotoxic activity

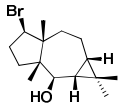
Halichonadin E (**308**) is an unusual dimeric sesquiterpenoid with eudesmane and aromadendrane skeleta linked through a urea fragment. It showed activity against L1210 murine leukaemia and KB human epidermoid carcinoma cells *in vitro*.[105] Anthoplalone (**309**) and noranthoplone (**310**) showed cytotoxic activity against B-16 murine melanoma cells[89] whilst neomeranol (**311**) is a cytotoxic halogenated sesquiterpene isolated from the algae *Neomeris annulata*.[102] Finally, compound **312** was assessed for its potential cytotoxicity against selected cancer cells. Unfortunately it was not cytotoxic to P-388 and HT-29 cells.[59]



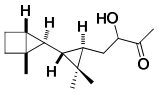
308 (halichonadin E)



309 R= CHO (anthoplalone)
310 R= H (noranthoplone)



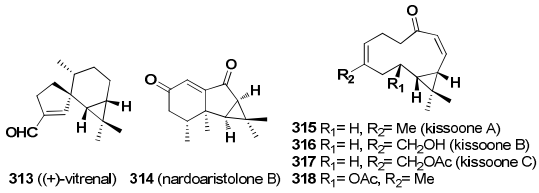
311 (neomeranol)



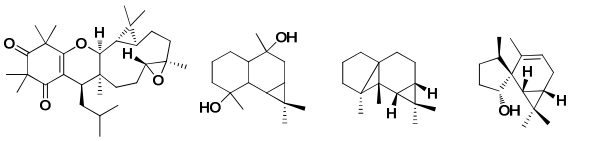
312

2.8.3 Other activities

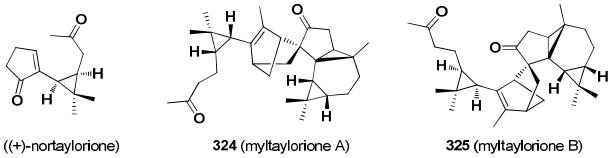
Eucalyptone (**307**) exhibited an inhibitory effect on adherent water-insoluble glucan synthesis.[104] Neomeranol (**311**) and (+)-vitrenal (**313**) have a potent inhibitory effect on the growth of plants[102,106-108] whereas nardoaristolone B (**314**) exhibited obvious protective effects on the injury of neonatal rat cardiomyocytes.[22] Compounds **315**-**318** were examined for their effects on enhancing the nerve growth factor (NGF). Compounds **316**-**318** showed enhancing activity.[109] Furthermore, compound **318** induced neurite outgrowth in PC 12D cells.[110] Finally, kunzeanone C (**319**) is an alkylated phloroglucinol metabolite from *Kunzea ambigua* that exhibited ichthyotoxic activity.[111]



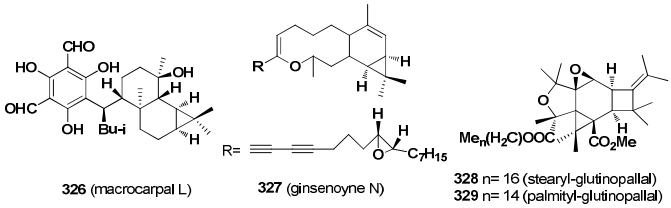
313 ((+)-vitrenal) **314** (nardoaristolone B)
315 R_1= H, R_2= Me (kissoone A)
316 R_1= H, R_2= CH_2OH (kissoone B)
317 R_1= H, R_2= CH_2OAc (kissoone C)
318 R_1= OAc, R_2= Me



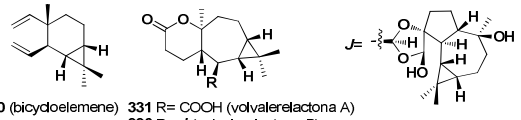
319 (kunzeanone C) **320** **321** (tridensene) **322**



323 ((+)-nortaylorione) **324** (myltaylorione A) **325** (myltaylorione B)



326 (macrocarpal L) **327** (ginsenoyne N)
328 n= 16 (stearyl-glutinopallal)
329 n= 14 (palmityl-glutinopallal)

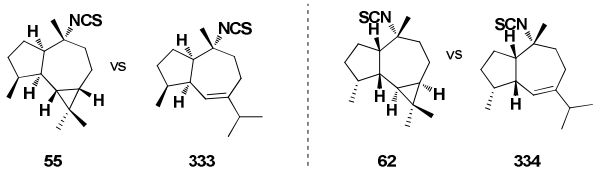


330 (bicycloelemene) **331** R= COOH (volvalerelactona A)
332 R= *J* (volvalerelactona B)

2.9 Biological role of the *gem*-dimethylcyclopropane unit in sesquiterpenes

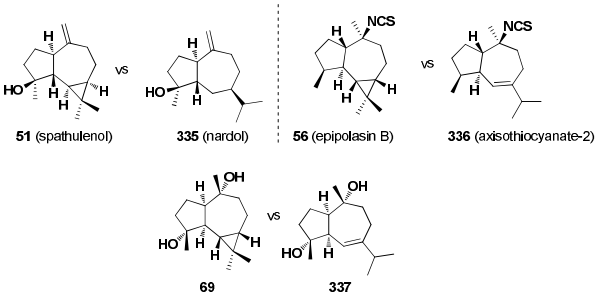
The presence of the *gem*-dimethylcyclopropyl group imposes a conformational rigidity on the part of the molecule to which it is attached. This in turn not only affects the chemistry of that part of the molecule but it can also affect the way in which the compound binds to specific receptors and hence it can influence the biological activity. Furthermore the presence of the two methyl groups can provide a lipophilic face to the molecule whereas with the free rotation of an isopropyl group the position of the methyl groups are much more flexible. In general these natural products which display biological activity have oxygen functions that are distant from the lipophilic dimethylcyclopropane ring. We have carried out a literature search of the biologically activities of the corresponding isopropyl derivates of the biologically-active sesquiterpenes containing a *gem*-dimethylcyclopropane unit in order to find a link between the presence of the *gem*-dimethylcyclopropyl unit and the biological activity. Some examples found are shown below.

Firstly, the presence of the *gem*-dimethylcyclopropyl unit instead of an isopropyl unit can change the biological activity of different compounds. Thus, aromadendrane **55** is an antimicrobial agent while compound **333** showed cytotoxic activity.[112] In the same way, aromadendrane **62** is an antimicrobial compound whereas its corresponding guaiane derivative **334** showed cytotoxic activity *in vitro* against L-1210 cells.[113]



55 **333** **62** **334**

On the other hand, sesquiterpenoids containing a *gem*-dimethylcyclopropane unit such as spathulenol (**51**), epipolasin B (**56**) and compound **69** have shown biological activity whereas their corresponding isopropyl derivatives nardol (**335**),[114,115] axysothiocyanate-2 (**336**)[116,117] and compound **337**[118,119] have not revealed any biological activity.



51 (spathulenol) **335** (nardol) **56** (epipolasin B) **336** (axisothiocyanate-2)

69 **337**

3 Conclusions

In summary, this review covered the isolation of sesquiterpenoids containing this *gem*-dimethylcarbocycle and whose biological activities are enhanced. The *gem*-dimethylcyclopropane ring remains intact in the biogenetic route leading to a large variety of secondary metabolites in many organisms. Nevertheless, many of these compounds have not been assessed in biological assays. This fact suggests that some of these compounds could show interesting unexplored biological activities. For this reason, new assays of inactive or untested compounds should be carried out with the aim of developing structure-activity relationship studies to find either new biologically-active compounds or new biological activities and obtain the common patterns responsible of the activity in these natural products.

Acknowledgements

This research was supported by a grant from the Junta de Andalucía (P07-FQM-02925) and in part from MINECO (AGL2012-39798-C02-01).

Notes and references

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Keywords Bioactivity, metabolites, sesquiterpenes, cyclopropanes, structure.

Abbreviations

A-2780	Human ovarian cancer cell line
A-549	Lung adenocarcinoma
A-735	Human malignant melanoma
B-16	Melanin carcinoma
BC-1	Lymphoma cell line
Bel-7402	Hepatoma cell line
BGC-823	Human gastric adenocarcinoma
CAKI 1	Kidney carcinoma
Cinn	Cinnamoyl
CNS	Central nervous system
CYP3A4	Cytochrome P450 3A4
Glc	Glucose
HCT-8	Colon cancer cell line
HeLa	Human cervical epitheloid
HIV-Rtase	Human immunodeficiency virus reverse transcriptase
HT-29	Colon adenocarcinoma
Huh-7	Cancer cell line
*i*Val	Isovaleroyl
Jurkat	Cancer cell line
KB	Tumor cell line
KE-97	Cancer cell line
MCF-7	Breast cancer cell line
MDA-MB-231	Breast adenocarcinoma
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NCI-H187	Lung cell line
SK-Hep1	Liver carcinoma
Tig	Tiglate
U-2 OS	Steosarcoma
WISH	HeLa derivative

† Electronic Supplementary Information (ESI) available: [tables listing the compounds, the species from which they were isolated, their biological activity and the bibliographical reference]. See DOI: 10.1039/b000000x/

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