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Heterocyclic terpenes: linear furano- and pyrroloterpenoids

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Covering: 2006 to 2013

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Abstract: This review of furano- and pyrroloterpenoids covers the literature, 180 articles in all, published from January 2006 to December 2013. The relevant biological activities, source organisms, country of origin, and first total syntheses that lead to the revision of structures or stereochemistries of the compounds are described.

Keywords: Heterocyclic terpenes · Linear furanoterpenoids · Linear pyrroloterpenoids · Bioactivity

1. Introduction

This review of the literature from 2006 to 2013 covers the new occurrence of furano- and pyrroloterpenoids and describes 253 compounds in all from 180 articles.[1] A number of reviews have dealt with natural sesquiterpenoids,[2-7] diterpenoids,[8-11] sesterterpenoids,[12, 13] triterpenoids,[14-18], carotenoids and polyterpenoids.[19-23] Other general reviews are: "Marine natural products".[24-30] In this review, we show structures of linear furano- and pyrroloterpenoids, and previously reported linear furano- and pyrroloterpenoids where there has been a structural revision or a newly established stereochemistry, previously reported linear furano- and pyrroloterpenoids for which first syntheses, new bioactivities, or new sources are described are referenced, and this review also added the furanotetrotepenoids and furanocarotenoids.

Linear furano- and pyrroloterpenoids constitute small subgroups in which a terpenoid backbone are connected to differently substituted furan or pyrrole rings.[31] Functional groups furan and its derivatives were widespread in natural products from terrestrial to marine organisms and irrespective of an isoprenic or polyketide origin, has been purported to possess enzyme-inhibiting functions.[32] Molecules with antifouling activity represent a number of types including alkaloids, terpenoids, lactones, and pyrroles.[33] Butenolide (furan-2(5H)-one) inhibited marine fouling.[34,35] The butenolides were most likely to inhibit QS systems, since various butenolides are known to antagonize QS systems.[36] It has been demonstrated that the furanone scaffolds inhibit formation of bacterial films by inhibiting quorum sensing through accelerated LuxR turnover.[37] In structure-activity studies of limonin, it has been determined that the furan ring in the citrus limonoid structure are critical for the antifeedant activity of the limonoids against Colorado potato beetle larvae.[38] Plants appear to use lactones to prevent being eaten and to avoid biofouling by bacteria while some animals use lactones to regulate their biochemical processes.[32] Pyrolle skeleton looks like an enhancer of the deterrent activity exerted by the pyrrole counterpart.[39]

2. Furanoterpenoids

2.1. Furanosesquiterpenoids

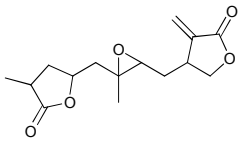
Five sesquiterpene lactones **1–5**, and the known antheindurolide B, have been found in an extract from the aerial part of *Anthemis arvensis* (Kladovo, Serbia).[40] The structure originally proposed of antheindurolide B has been revised to **6**. Four sesquiterpene peroxides **7–10** have been obtained from a soft coral of the *Sinularia* genus (Northeastern coast of Taiwan).[41] Whilst vignoside **11**, a glucoside that inhibits the growth of human stomach cancer, has been obtained from Japanese adzuki bean *Vigna angularis*.[42] The bisabolane derivatives boivinianins A **12** and B **13** have been identified as components of the stem bark of *Cipadessa boiviniana* (Northwest area of Madagascar).[43] Whilst bisabolangelone **14**, isolated from *Angelica koreana* (Cheongju, Korea), inhibits the production of melanin in α-melanocyte stimulating hormone-activated B16 melanoma cells or mellan-a cells.[44] The acaricidal active principle of an extract from the roots of *Ostericum koreanum* (Seoul, Korea)[45] which affected adults of the *Dermatophagoides* genus, has been identified as the known sesquiterpene bisabolangelone **14**. The sesquiterpenoids **15** have been found in an extract from the sea hare *Aplysia dactylomela* (La Palma, Canary Islands).[46] Heliespirone C **16** was a sesquiterpene with two spiro heterocyclic skeleton, which have been isolated from *Helianthus annuus* (Junta de Andalucia, Jerez, Spain).[47] The levels of activity shown by heliespirone C (56% inhibition) at 10^{-3} M in the coleoptiles bioassay, relative to controls, suggest that they may be lead compounds for agrochemicals. The structures of heliannuols G and H also obtained from this species, have been revised to **17** and **18**, respectively, as a consequence of enantiocontrolled total syntheses.[48] Two sesquiterpenes, sinularioperoxide E **19** and the ethoxy ester **20** were reported from a collection of soft coral *Sinularia* sp (Northern east coast, Taiwan).[49] Stable-isotope precursor feeding studies using *Doriopsilla* sp (Arflor, Setubal, Portugal) established that a drimane ester mixture and 15-acetoxy-*ent*-pallescensin[50] were derived *de novo* via the classical mevalonate pathway, that serve as defensive compounds

to deter predation.[51] The acetyl pelseneeriol-1 **21** and acetyl pelseneeriol-2 **22** have been obtained from the marine nudibranch *Doriopsilla pelseneeri*.[51] The study also led to the characterisation of the **21** and **22**. A study of the aerial parts and the roots of *Dorema kopetdaghense* (Khor Valley, Khorasan Razavi Province, Iran)[52] afforded the sesquiterpene derivatives kopetdaghins C–E **23**–**25**. A farnesyl phenol, grifolinone B **26**, with inhibitory activity against nitric oxide production, has been found in a methanolic extract of the inedible mushroom *Albatrellus caeruleoporus* (Okutama, Tokyo, Japan).[53] A further species of this genus, *A. flettii* (Bamfield, Vancouver Island, Canada),[54] contains another dimeric merosesquiterpenoid, albatrinellin **27**, together with the 16-alcohol corresponding to the ketone grifolinone B **26**. Studies of an extract from the roots of *Ligularia dentate* (Sendai City, Miyagi Prefecture, Japan)[55,56] afforded bisabolane sesquiterpenes **28** and **29**. The carabrane derivative **30**, has been obtained from *Carpesium lipskyi* (Mahan Mountain, Gansu Province, China).[57] The furanosesquiterpene **31** has been identified as a component of *Ximenia Americana*.[58] Flowers of *Anthemis auriculata* (Kresna, Bulgaria)[59] contain seven linear sesquiterpene lactones **32**–**38**. The furanosesquiterpene **39** has been found in the soft coral *Sinularia asterolobata* (Bali, Indonesia).[60] A furanosesquiterpene isomicrocionin-3 **40** has been isolated from a marine sponge of the *Fasciospongia genus* (Berlengas Islands, Portugal),[61] whilst lingshuiolides A **41** and B **42**, and lingshuiperoxide **43** have been found in an extract of the sponge *Dysidea septosa* (Lingshui Bay, Hainan Province, China).[62] A *seco*-lactarane sesquiterpene, strobiluric acid **44**, has been obtained from liquid cultures of the fungus *Strobilurus stephanocystis* (Chiba, Japan).[63] A farnesane derivative **45** has been isolated from the aerial parts of *Senecio cannabifolius* (Changbai Mountain, Jilin Province, China).[64] The nerolidane sesquiterpene **46** has been isolated from the seeds of *Amomum xanthioides* (Seoul, Korea). Compound **46** exhibited cytotoxicity against SK-OV-3 and SK-MEL-2 cells at IC_{50} values 16.7 and 8.6 μM, respectively, using a SRB bioassay.[65] Another nerolidane derivative **47** and its glucoside **48** have been found in an extract from the leaves of *Crataegus pinnatifida*

(Liaoning Province, China).[66] Dalberpene **49** was a sesquiterpene, which has been obtained from the stems of *Dalbergia parviflora* (Bangkok, Thailand).[67] The Indian soft coral *Sinularia kavarattiensis* (Gulf of Mannar, Tamil Nadu, India) contained the sesquiterpene **50**, which showed antifouling activity agaist *Balanus amphitrite* at EC_{50} value 11.21μg/mL.[68] 3,4-dehydrotheaspirone **51** has been obtained from the leaves of *Juniperus brevifolia* (Pedreira, Nordeste, São Miguel, Azores, Portugal).[69] Xylacarpins D **52** and E **53** were two bisabolane derivatives, which have been obtained from cultures of the fungus *Xylaria carpophila* (Gaoligong Mountain, Yunnan Province, China).[70] Chromatography of an extract from the fermentation of *Trichoderma* sp PR-35 led to the isolation of the bisabolane derivative **54**. This endophytic fungus have been obtained from *Paeonia delavayi* (Songming County, Yunnan Province, China).[71] The sesquiterpenoid aspergillusene B **55** has been found in cultures of a sea fan *Annella* sp (Coastal area in Suratthani Province, Thailand) derived strain of the fungus *Aspergillus sydowii*.[72] Whilst two *ar*-bisabol derivatives **56** and **57** have been obtained from the stem bark of *Fraxinus sielboldiana* (Lu Mountain, Jiangxi Province, China).[73] The stem bark of *Illicium difengpi* (Beijing, China)[74] contained the sesquiterpene lactone **58**. The sesquiterpene glycoside **59** has been found in extract of *Breynia fruticosa* (Nanning, Guangxi Province, China).[75] A lactone (6*R*)-dehydroxysipandinolide (**60**), probably derived from a germacrane sesquiterpene, has been isolated from the rhizomes of *Curcuma wenyujin* (Wenzhou, Zhejiang Province, China).[76] Neroplofurol **61** was a nerolidol derivative, which has been found in the inner stem bark of *Oplopanax horridus* (Alaska, USA).[77] The roots of *Ferula ferulaeoides* (Shawan, Xinjiang Province, China) contained two sesquiterpenes, ferulactones A **62** and B **63**.[78] A chemical study of the soft coral *Sinularia capillosa* (Dongsha Atoll, Taiwan)[79] afforded three sesquiterpenoids, named capillobenzopyranol **64**, capillobenzofuranol **65**, and capillofuranocarboxylate **66**. **64** exhibited weak cytotoxicty against P-388 with ED_{50} values of 12.7 μM, **65** exhibited antiviral activity with IC_{50} 13.5 μM, **64** significantly inhibited iNOS

protein (36.7%) expression by LPS stimulation. Ashitabaol A **67** was an antioxidative sesquiterpene, which has been obtained from the seeds of *Angelica keiskei* (Nagahama, Japan).[80] Red alga *Laurencia catarinensis* (Ilha do Arvoredo, Santa Catarina, Brazil), contained halogenated metabolites **68** and **69**, which possessed cytotoxic properties.[81] The eudesmanolides **70**–**77**, which have been obtained from *Inula japonica* (Anhui Province, China).[82, 83] The *seco*-guaianolides **78**–**80**, isolated from *I. linearifolia* (Changfeng County, Anhui Province, China),[84] *Chloranthus anhuiensis* (Hexiang County, Anhui Province, China), *Artemisia anomala* (Hangzhou, Zhejiang Province, China),[85-87] exhibited very weak antifungal activity.[88] Schensianol A **81**, schensianolsides A **82** and B **83** were obtained from the aerial parts of *Euonymus schensianus* (Luanchuan County, Henan Province, China).[89] Another compound of this type **84** has been found in an extract from the roots of *Clerodendrum bungei* (Nanning, Guangxi Province, China) compounds were found to be moderately active to inhibit the proliferation of HeLa cells with the IC_{50} values 4.5 μM.[90] A megastigmane sulfonoglucoside, anisoposide B **85**, has been isolated from *Mallotus anisopodus*.[91] Extraction of a marine sponge of the *Spheciospongia* genus (Sanya, Hainan Province, China),[92] led to the isolation of spheciospongones A **86** and B **87**. Chromatography of an extract from the rhizomes of *Curcuma longa* (Chongzhou, Sichuan Province, China)[93] led to the isolation of the sesquiterpene **88**. Whilst a study of the roots of *Ginkgo biloba* (Nanjing, Jiangsu Province, China) afforded bilobanol **89**, a sesquiterpene trilactone.[94] Two halogenated sesquiterpenes **90** and **91** have been found in an extract from the marine red alga *Laurencia saltoi* (Rongcheng, Shandong Province, China).[95] From a *Tanacetum parthenium* extract afforded the epimeric *iso*-*seco*-tanapartholides **92** and **93**, whose structures were determined by chemical synthesis using (–)-α-santonin as starting material, these sesquiterpene lactones proved to be inhibitors of the NF-κB signaling pathway.[96] Three sesquiterpenes **94**–**96** have been isolated from *Laurencia luzonensis* (Sesoko Island, Okinawa).[97] Two studies on green alga *Bifucaria bifurcata* (Roscoff, France) defined the

metabolic makeup of this alga with the isolation of the sesquiterpenoids bibifuran **97** and eleganolone derivative **98**.[98, 99] The furanosesquiterpenoid negunfurol **99** has been obtained from the seed of *Vitex negundo* (Wanglang National Nature Reserve, Sichuan Province, China).[100] Hostasolide A **100** is a new lactone, which has been isolated from *Hosta ensata* (Linjiang City, Jilin Province, China).[101] Abiesesquine A **101** and abiesesquine B **102** are two bisabolane sesquiterpenoids, which have been isolated from *Abies holophylla* (Huairen village, Benxi city, Liaoning Province, China).[102] A bio-activity guided chromatography of an extract of *Angelica koreana* (Seoul, Korea)[103] roots afforded three bisabolane derivatives, osterivolones A **103**, B **104**, and D **105**. Okamurenes C **106** and D **107** have been obtained from the red alga *Laurencia okamurai* (Weihai coastline, Shandong Province, China).[104]



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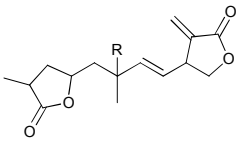

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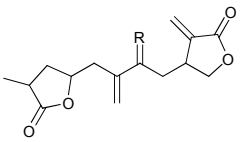
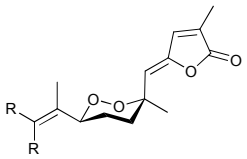
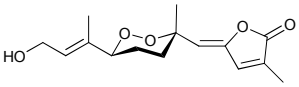
3 R = OH



4 R = OOH, H
5 R = OH, H
6 R = O



7 R_1 = CH_2OH, R_2 = H
8 R_1 = H, R_2 = CH_2OH



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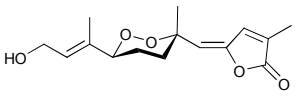

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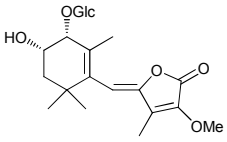

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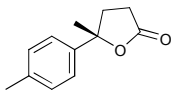

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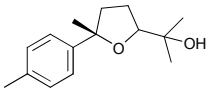

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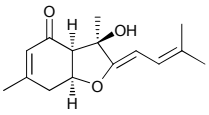

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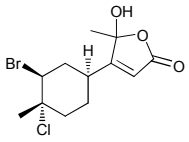

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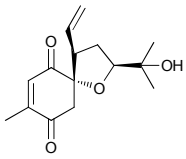

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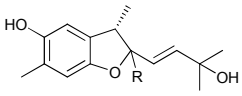

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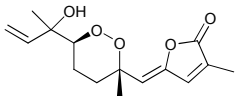
18 R = α–H



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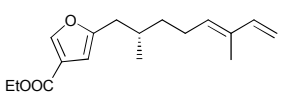

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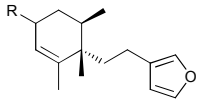

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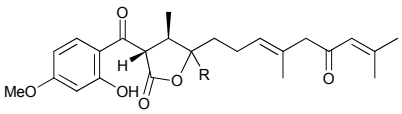
22 R = β- OAc



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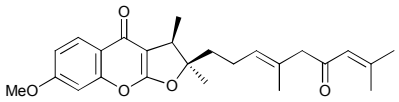
24 R = α–Me



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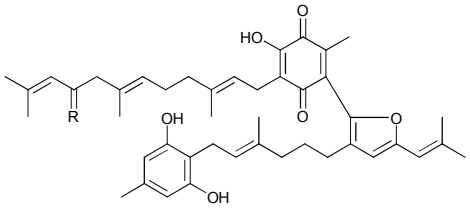

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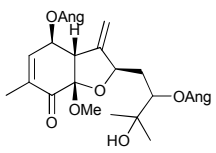

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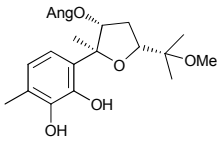

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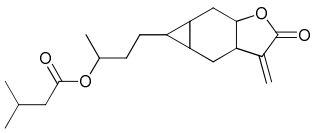

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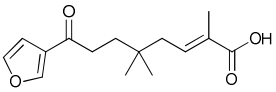

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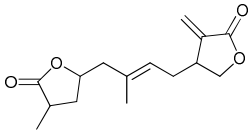

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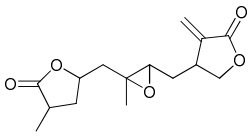

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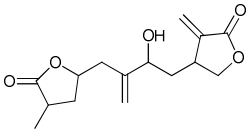

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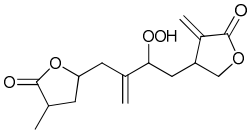

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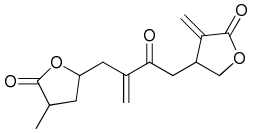

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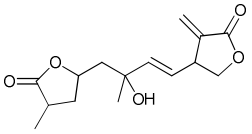

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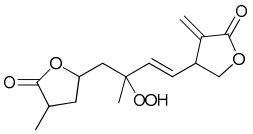

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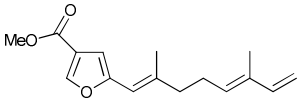

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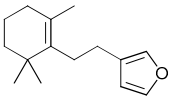

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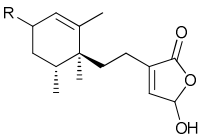
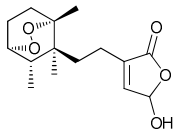


41 R = α- OH
42 R = β- OH



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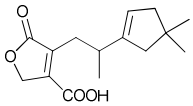

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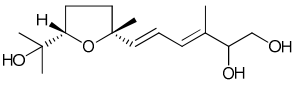

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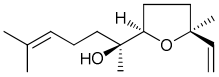

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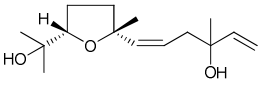
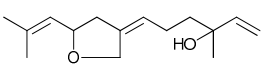


47 R = H
48 R = Glc



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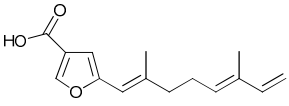

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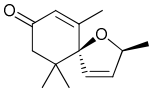

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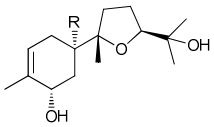
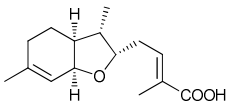


52 R = H
53 R = OH



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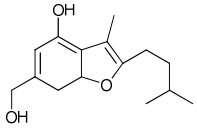

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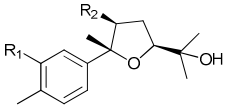
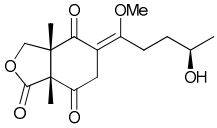


56 R_1 = OH, R_2 = H
57 R_1 = H, R_2 = OH



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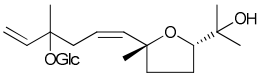

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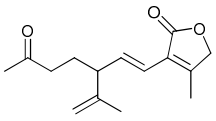

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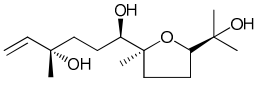

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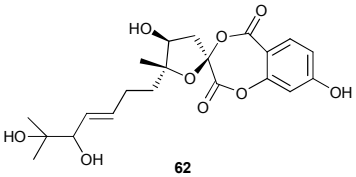

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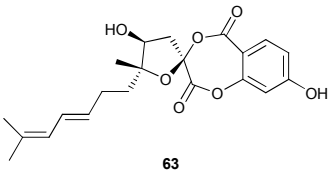

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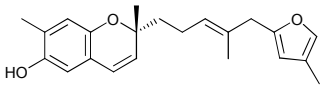

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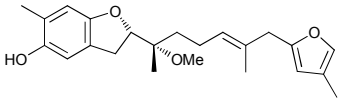

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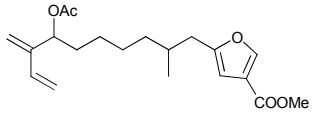

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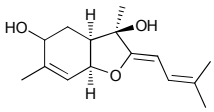

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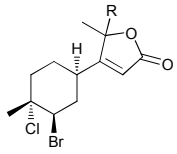
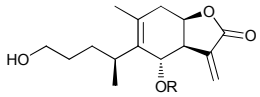
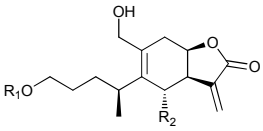


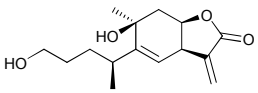
68 R = β–OMe
69 R = α–OMe



70 R = Ac
71 R = COPri
72 R = Mebu
73 R = Vali
74 R = Meval



75 $R_1 = R_2 = H$
76 R_1 = Ac, R_2 = OH



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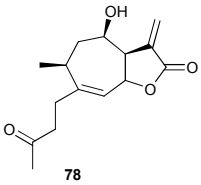

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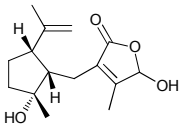

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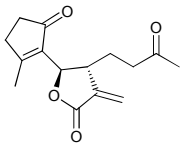

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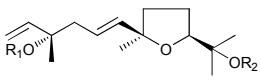
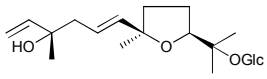


81 $R_1 = R_2 = H$
82 $R_1 = H$, R_2 = Glc
83 R_1 = Glc, $R_2 = H$



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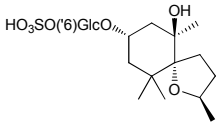

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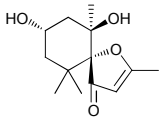

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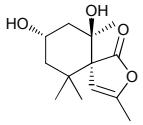

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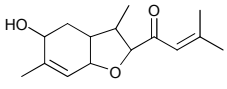

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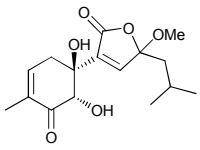

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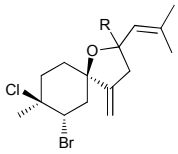
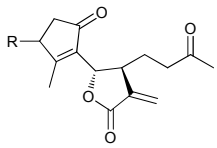
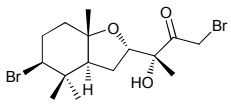


90 R = β-H
91 R = α-H



92 R = β-OH
93 R = α-OH



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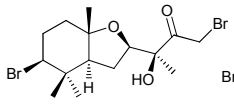

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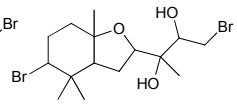

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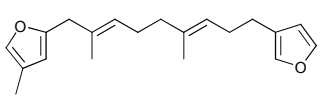

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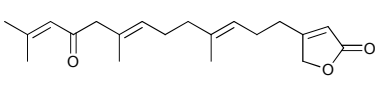

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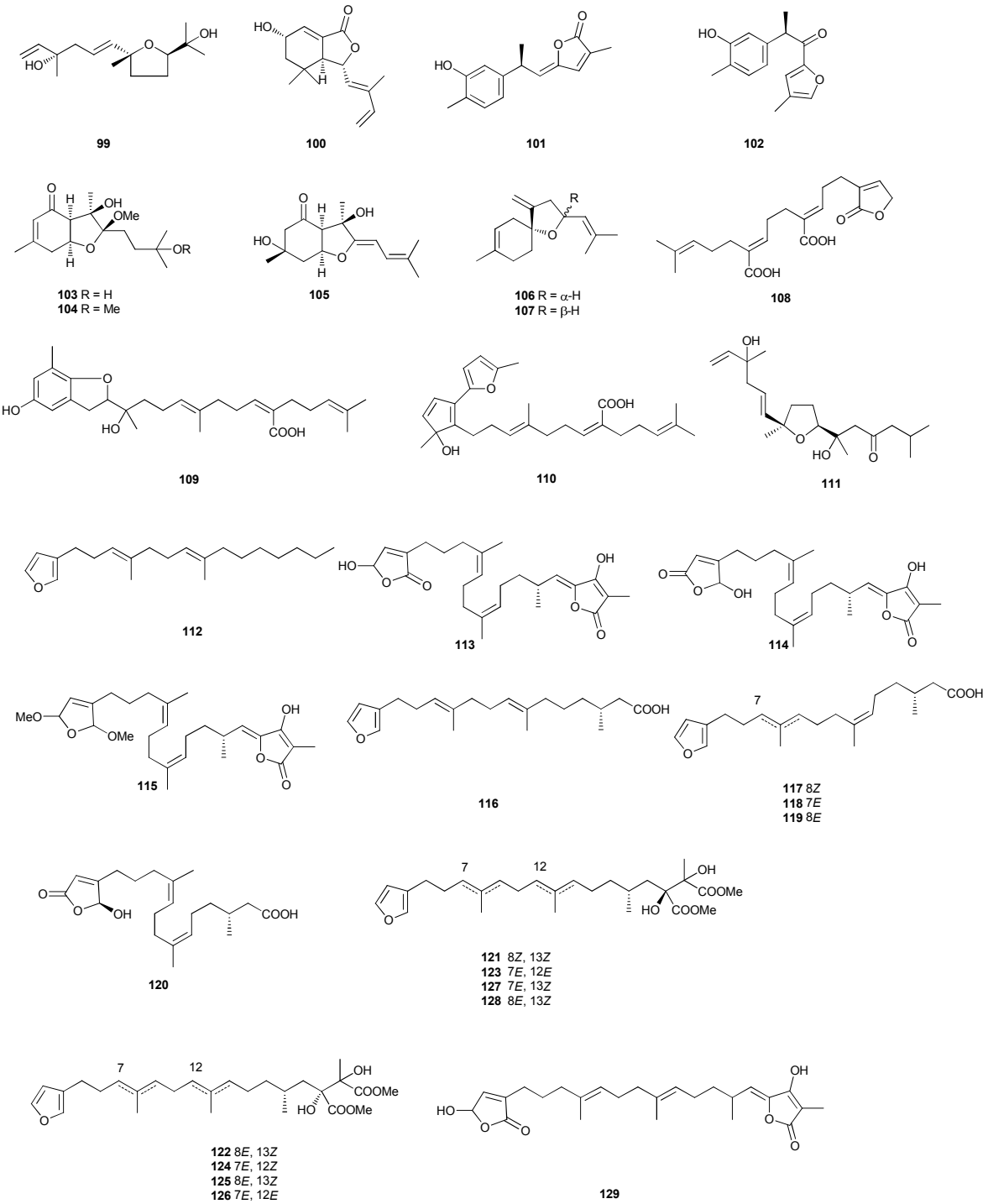


2.2 Furanoditerpenoids

The insect growth regulatory activity of linear diterpenoids such as **108** obtained from *Baccharis thymifolia* (Villavicencio, Mendoza Province, Argentina) has been investigated.[105] Thunbergol B **109** was isolated from *Sargassum thunbergii* (Busan, Korea) and was scavenger of the DPPH radical and of $ONOO^-$ from morpholinosydnonimine (SIN-1).[106] In another large survey, 342

species of marine alga were screened against the bacterium *Propionibacterium acnes*, and the bacteriostatic compound sargafuran **110** was isolated from Japanese marine alga *Sargassum macrocarpum*. Sargafuran **110** suggested to be of geranylgeraniol/shikimate origin, had low cytotoxicity and could be the basis of a new skin care treatment to prevent or improve acne.[107] Examination of a *Huea* species of antarctic lichen has led[108] to the isolation of hueafuranoid A **111** which has inhibitory action against protein tyrosine phosphatase 1B, a system which is part of the cellular signal transduction cascade.

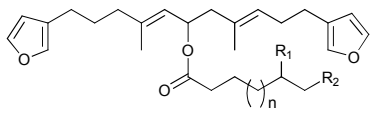
2.3. Furanosesterterpenoids

A C_{21} norfuranosesterterpenoid **112** was isolated from *Lendenfeldia* sp (Indonesia).[109] A series of furanosesterterpenoids **113**–**128** were isolated from a *Sarcotragus* sp (Soheuksan Island, Korea), **126** and **127** were antibacterial, **117** and **118** were cytotoxic, while **120** was inhibitory towards isocitrate lyase. The absolute configurations of **129**,[110] previously reported as a synthetic analogue, and **116** (*Sarcotragus* sp)[111] were also assigned.[112] The furanosesterterpenoid esters **130**–**132** were isolated from *Coscinoderma mathewsi* (Mooloolaba, Queensland, Australia).[113] The norsesterterpenoids irciformonins E–K **133**–**139** were isolated from *Ircinia formosana* (East of Taiwan), of which irciformonin I **137** was found to inhibit peripheral blood mononuclear cell proliferation. In the same study irciformonin A (*I. formosana*)[114] was re-isolated and the structure revised to **140**.[115] Palinurin (*I. variabilis*)[116] has been synthesized.[117] It was a non-ATP competitive glycogen synthase kinase 3β inhibitor. Antifouling activity has been reported [118] for the sesterterpenoid (7*E*,12*E*,20*Z*)-variabilin (*Sarcotragus* sp).[111] Two oxidized sesterterpenoids **141** and **142** were isolated from the Mediterranean *Spongia officinalis* (Sicily coast, Mazara del Vallo, Italy).[119] Six acyclic manoalide-related sesterterpenoids, hippolides C–H **143**–**148** were isolated from the South China Sea sponge *Hippospongia lachne* (Yongxing Island, Hainan Province, China). **145** showed weak anti-inflammatory activity, with IC_{50} value of 40.35 μM for PKCγ and PKCR, respectively.[120] One C_{21} norsesterterpenoidal natural product, ircinolin A **149**,

two C_{22} furanosesterterpenoids, 15-acetylirciformonin B **150**, and 10-acetylirciformonin B **151** were isolated from the sponge *Ircinia* sp (Orchid Island, Taiwan). **150** and **151** exhibited significant cytotoxic activity against K562, DLD-1, HepG2, and Hep3B cancer cell lines.[121] Bioactivity-guided fractionation of the ethyl acetate extract of a marine sponge *Xestospongia* sp (Sikao Sea, Trang Province, Thailand), led to the isolation of a thiophene-*S*-oxide acyclic sesterterpenoid **152**, which showed weak cytotoxicity against Vero cells.[122] Furospinosulin-1 **153**, a marine sponge-derived furanosesterterpenoid, exhibited selective antiproliferative activity against DU145 human prostate cancer cells under hypoxic conditions. **153** also demonstrated antitumour activity at 10–50 mg/kg in oral administration to a mouse model inoculated with sarcoma S_{180} cells. Mechanistic analysis revealed that **153** suppresses transcription of the insulin-like growth factor-2 gene, which was selectively induced under hypoxic conditions through prevention of the binding of nuclear proteins to the Sp1 consensus sequence in the IGF-2 promoter region.[123] A concise synthesis of **153** has been developed, and some structurally modified analogues were prepared. Biological evaluation of them revealed that the whole chemical structure was important for the hypoxia-selective growth inhibitory activity of **153**.[124] The norsesterterpenoid sarcotin P **154** has been isolated from the sponge *Sarcotragus* sp (Cheju Island, Korea).[125] Three acetylated sesterterpenoids, 25-acetoxyluffariellins A **155** and B **156**, and 25-acetoxyseco-manoalide **157**, were isolated from *Luffariella variabilis* (Orpheus Island, Australia). It was noted that the deacetylated versions were quickly formed if the sponge tissue was allowed to thaw before extraction, but only the acetylated compounds were isolated from the frozen sponge.[126] The cytotoxic aplysinoplides A–C **158**–**160** were isolated from *Aplysinopsis digitata* (Oshima-shinsone, Kagoshima Prefeture, Japan).[127] Manoalide (*Luffariella variabilis*),[128] manoalide-25-acetate (*Thorectandra excavatus*),[129] and secomanoalide (*L. variabilis*),[130] inhibited quorum sensing in bacteria.[131] 24-Ethylmanoalide **161** was obtained from *L.* cf. *variabilis* (Mayotte Island, Indian Ocean). Since no ethanol was used in the isolation, **161** was

presumed to be a natural product.[132] The Great Barrier Reef sponge *L. variabilis* contained a range of secondary metabolites, including manoalide and manoalide monoacetate. As manoalide monoacetate has previously been shown to have antibacterial and quorum sensing inhibition activity, and was readily converted to manoalide, which also exhibited similar activity, the monoacetate may provide a chemical defence against predation and microbial attack.[133] X-ray analysis of the crystalline product confirmed the structure and the reassignment of the absolute configuration of the structurally-related sponge metabolite alotaketal A **162**.[134] A sesterterpenoid, deoxymanoalide **163** was isolated from the nudibranch *Chromodoris willani* (Cape Zampa, Okinawa). The mollusk fed on a sponge containing manoalide and secomanoalide and was likely to biotransform them into **163**. **163** showed moderate antimicrobial activity against *Escherichia coli* and *Bacillus subtilis* and inhibited snake venom phospholipase A_2 at 0.2 to 0.5 μM.[135] *Rhabdastrella globostellata* (Amami-Oshima, Kagoshima, Japan), yielded a monocyclic sesterterpenoid glycoside rhabdastoside A **164**.[136] The extract of marine sponge *Hyrtios communis* (The northern reefs region, Palau) was found to inhibit activation of the transcription factor hypoxia-inducible factor-1 (HIF-in T47D human breast tumor cells. Bioassay-guided isolation led to the identification of six (**165**−**170**) sesterterpenes. Two sesterterpenes, thorectidaeolide A **165** and 4-acetoxythorectidaeolide A **166** were among the most potent inhibitors of hypoxia (1% O_2)-induced HIF-1 activation (IC_{50} values of 3.2 and 3.5 μM, respectively).[137] The chemical investigation of the recently described Mediterranean Homoscleromorpha sponge *Oscarella balibaloi* (Marseilles, Maire Island and Frioul Island, France) revealed an original family of five closely related glucosylated sesterterpenes **171**–**174**, named balibalosides. Balibalosides differ by the pattern of acetyl substitutions on the three sugar residues linked to the same aglycone sesterterpenoid core. From a biosynthetic perspective, these compounds may represent intermediates in the pathways leading to more complex sesterterpenes frequently found in Dictyoceratida, a sponge Order belonging to Demospongiae, a clade which is

phylogenetically distinct from the Homoscleromorpha. While steroid and triterpenoid saponins were already well known from marine sponges, balibalosides are the first examples of glycosilated sesterterpenes.[138]



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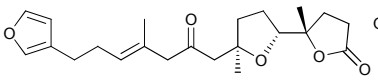

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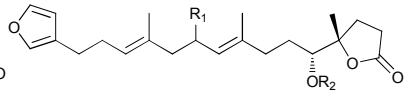

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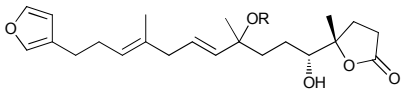

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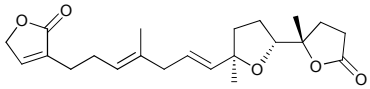

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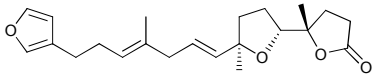

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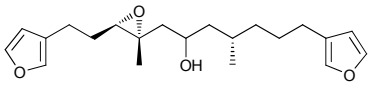

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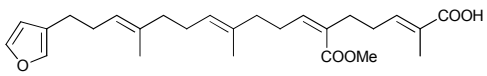

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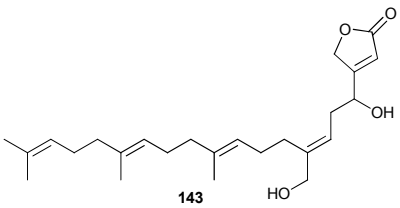

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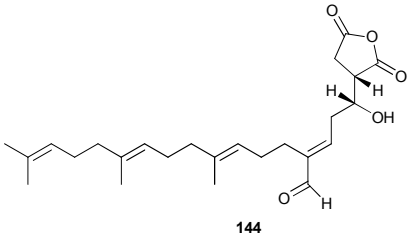

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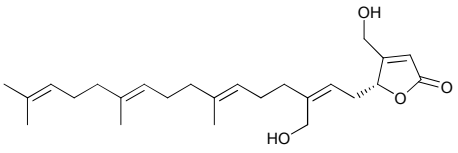

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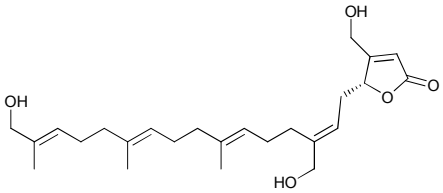

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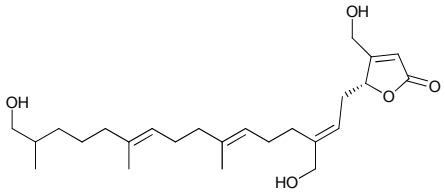

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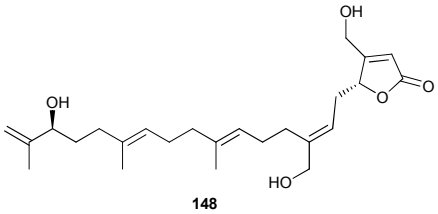

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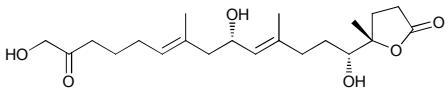

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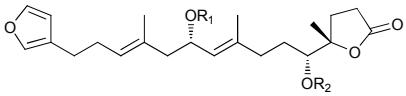

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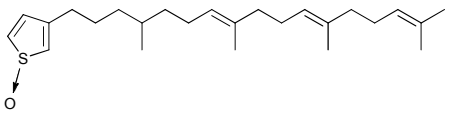

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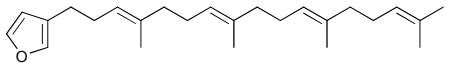

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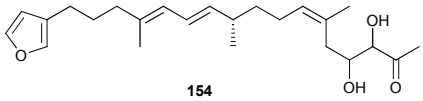

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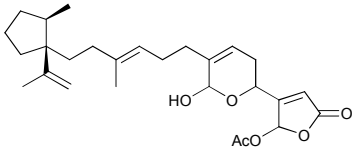

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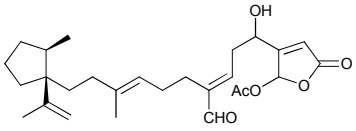

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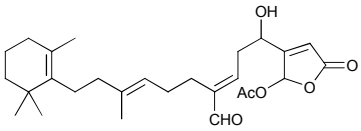

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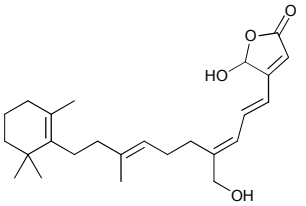

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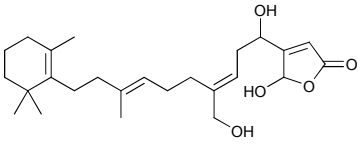

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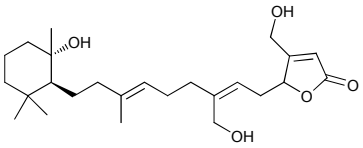

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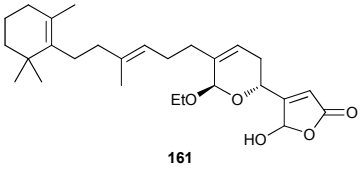

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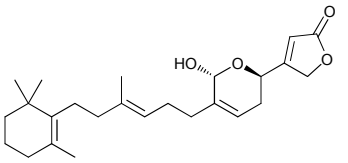

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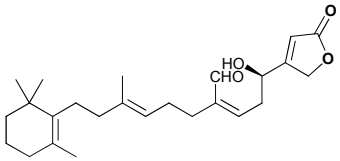

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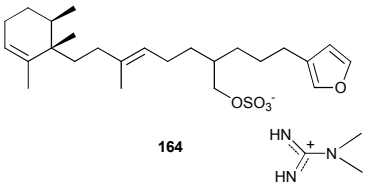

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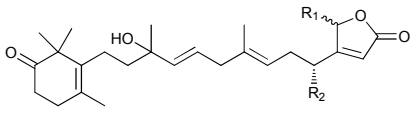

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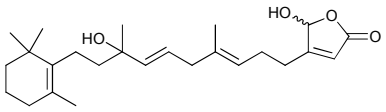

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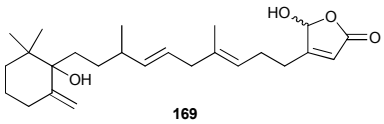

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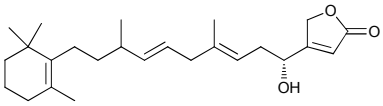

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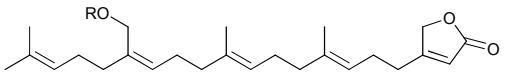

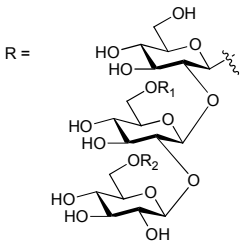

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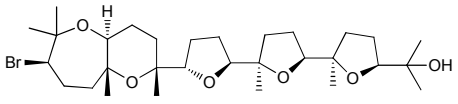

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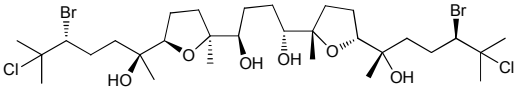

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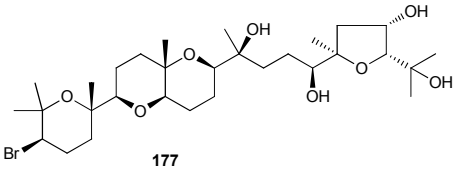

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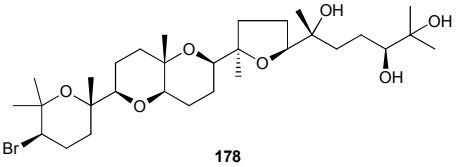

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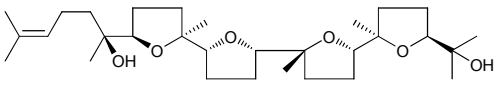

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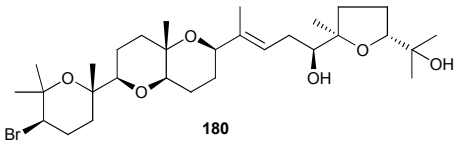

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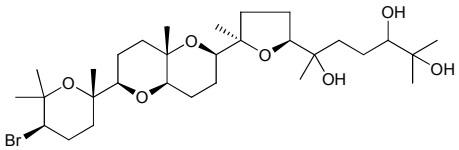

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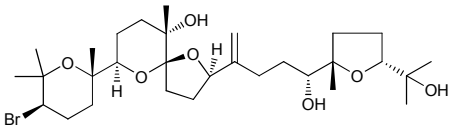

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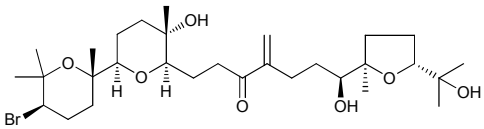

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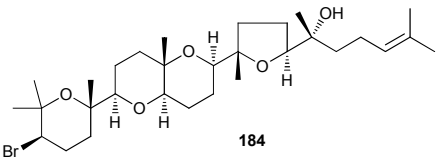

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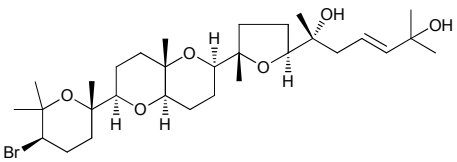

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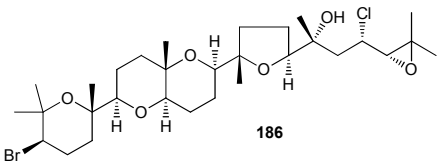

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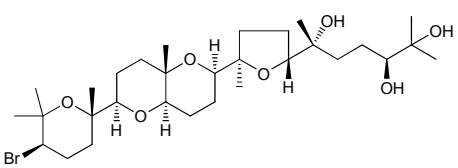

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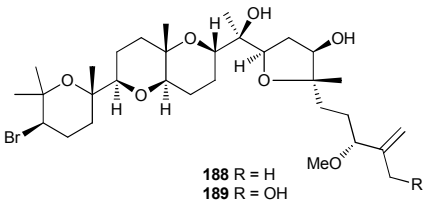


188 R = H
189 R = OH

2.4. Furanotriterpenoids

Total synthesis of the pentacyclic triterpene polyether (+)-enshuol, originally isolated from *Laurencia omaezakiana*,[139] established the absolute configuration as **175**.[140] The total synthesis of intricatetraol **176**, a triterpene polyether metabolite of *L. intricate*,[141] established the absolute configuration.[142] Two polyether triterpenes, aplysiols A **177** and B **178**, were isolated from the mantle of the sea hare *Aplysia dactylomela* (Hainan Island, China).[143] The absolute stereochemistry of the pentanyltetrahydrofuran fragment of **177** was established and the remaining centers assigned to be the same as the structurally related co-metabolite (+)-thyrsiferol.[144] A squalene-derived triterpene polyether, omaezakianol **179**, was isolated from *Laurencia omaezakiana* Masuda (Enoshima, Japan) along with **180**.[145] The squalenoid-derived triterpenoid laurenmariannol **181** was isolated from *L. mariannensis* (Hainan and Weizhou Islands, China). Laurenmariannol **181** showed modest cytotoxic activity against P388 tumour cells.[146] Spirodehydrovenustratriol **182** and 14-ketodehydrothyrsiferol **183** have been reported from the red alga *L. viridis* (Callao Salvaje, Paraiso Floral, Adeje, Tenerife, Canary Island).[147] Aplysiols C–E **184**–**186** have been isolated from the marine alga *Chondria armata* (Hazard Bay, Orpheus Island, Queensland, Australia) together with the known aplysiol B whose structure has been revised to **187**.[148] Aplysqualenols A **188** and B **189**, squalene-derived polyethers from the Caribbean sea slug *Aplysia dactylomela* (Bahia Salinas, Cabo Rojo, Puerto Rico), showed antiviral and antitumour activities.[149] Aplysqualenol A **188** exhibited inhibitory activity against SNB-19 CNS cancer and T-47D breast cancer, with IC_{50} values of 0.4 and 0.3 μg/mL, respectively. Aplysqualenol A **188** was very toxic against the Epstein-Barr virus in the VCA Elisa assay (EC_{90} = 0.08 μg/mL) with no accompanying toxicity seen in the host Daudi cells. Compounds **188** and **189** showed moderate antiplasmodial activity against *Plasmodium falciparum*, with IC_{50} values of 11 and 18 μg/mL, respectively. Ekeberins D_2–D_4 **190**–**192** were antiplasmodial squalene derivatives from the stem bark of *Ekebergia capensis* (Mount Kenya

Forest, Nanyuki area, Kenya).[150] Three cytotoxic oxasqualenoids, 15-dehydroxythyrsenol A **193**, prethyrsenol A **194**, and 13-hydroxyprethyrsenol A **195**, were isolated from *Laurencia viridis* (Paraiso Floral, Canary Islands).[151] Molecular docking studies in the avb3 integrin binding region were used to explain their biological properties. From an earlier collection of *L. viridis* (Callao Salvaje, Paraiso Floral, Adeje, Tenerife, Canary Islands), iubol **196** and the venustatriol and thyrsiferol derivatives **197**–**199** were isolated as moderately cytotoxic compounds.[152] The *in vitro* cytostatic activity of **196**–**199** was assessed by XTT assays, using several human cancer cell lines, including Jurkat (human T-cell acute leukemia), MM144 (human multiple myeloma), HeLa (human cervical carcinoma), and CADO-ES1 (human Ewing's sarcoma). Jurkat leukemic cells were the most sensitive cells to the tested polyether compounds. In particular, iubol **196**, 22-hydroxy-15(28)-dehydrovenustatriol **197**, and secodehydrothyrsiferol **199** showed the highest effectiveness against these cell lines (IC_{50}, 2.0–3.5 μM). It was also noteworthy that all the above compounds were active against the CADO-ES1 cell line in the range of 10–12 μM.

2.5. Furanotetraterpenoids

Two high molecular weight ether lipids, C_{151} and C_{153} lycopanerols H **200** and **201**, have been isolated from the lipid extract of a strain of the green microalga *Botryococcus braunii* (Yamoussoukro, Ivory Coast). **200** and **201** arise from the linkage via ether bridges of tetraterpenoid, *n*-alkylphenol and α-tocopherol units.[153] Lycopanerols H **200** and **201** could play a role in the prevention of oxidative damage to lipids in the L strains of *B. braunii*.

2.6. Furanocaroteoids

Peridinin, a nor-carotenoid, exhibits an exceptionally high energy transfer efficiency to chlorophyll A in photosynthesis in the sea. This efficiency would be related to the unique structure of peridinin.[154] Peridinin serves as photosynthesis accessory light harvesting pigment and extends the range of absorption for light-harvesting. It was associated with a protein and chlorophyll a and protects the light-harvesting pigments against photochemical damage caused by

singlet molecular oxygen. All-*trans*-peridinin **202** has been isolated from *Litophyton arboreum* (Red Sea, Hurghada, Egypt) as well as *Sarcophyton ehrenbergi* (Bali, Indonesia), **202** was the characteristic major carotenoid of dinoflagellates from symbionts (zooxanthellae) of corals with a C_{37} skeleton; it contains six stereogenic centers and several functional groups. The configurational assignment of **202** as 3*S*,5*R*,6*R*,3'*S*,5'*R*,6'*S* was established by CD investigations. **202** was tested for antiproliferative activity against the cell lines HUVEC and K-562 (IC_{50} 48.4, 53.8μM), and for cytotoxicity against the cell line HeLa (IC_{50} 51.9 μM), and showed moderate activities.[155] **202** presents a difficult challenge to the synthetic chemist. A method that involves a Wittig reaction between the appropriate conjugated phosphanylidenebutenolides and the C_{10} or C_{15} aldehyde provided an efficient route to the model compounds.[156] **202** from a dinoflagellate have been described.[157] The stereochemsitry of furanoid derivative sinensiachrome (3*S*,5*R*,8*S*)-5,8-epoxy-5,8-dihydro-10'-apo-*β*-carotene-3, 10'-diol **203** has been established.[158] Re-examination of persicaxanthin and persicachrome, from cling peaches, confirmed the structure of persicachrome as **204**.[159] Syntheses of the acetylenic and allenic C_{22}-apocarotenals and proof that were related to peridinin and pyrrhoxanthin (5',6'-epoxy-3,3'-dihydroxy-7,8-didehydro-5',6'-dihydro-10,11,20-trinor-β,β-caroten-11',19', olide 3-acetate) **205** were achieved by a C_{15}+C_7 reaction.[160] An apoviolaxanthinol structure has been derived for persicaxanthin, from the French plum, which also yielded the corresponding 5,8-furanoid oxide persicachrome **206**.[161] HPLC methods have been devised for separating diastereoisomeric and epimeric carotenoid furanoid oxides, and analysis of the purified products has allowed determination of the absolute configurations of and the diastereoisomeric mutatoxanthins 5,8-epoxy-5,8-dihydro-β,β-carotene-3,3'-diols **207**[162] and of the neochromes 5',8'-epoxy-6,7-dide hydro-5,6,5', 8'-te trahydro-β,β-carotene-3,5,3'-triols **208**.[163] Eugster and his co-workers have synthesized the diastereoisomeric (5*R*,8*R*,5'*R*,8'*R*)-, (5*R*,8*S*,5'*R*, 8'*S*)-, and (5*R*,8*R*,5'*R*,8'*S*)-aurochromes **209**–**211**, respectively, and the *meso*-forms (5*R*,8*R,*5'*S*,8'*S*)-and (5*R*,8*S*,5'*S*,8'*R*)-aurochrome **212** and **213** by condensation of

the C_{10} Wittig salt with the appropriate isomer of the C_{15} aldehyde.[164] Acid-catalyzed isomerization of (5*S*,6*R*)-5,6-epoxy-5,6-dhiydro-β,β-carotene similarly gave the 8-epimeric mutatochromes **214** and **215** (5*S*,8*S*)-and (5*S*,8*R*)-5,8-epoxy-5,8-dihydro-β,β-carotene, which were fully characterized by spectroscopic methods.[165] Carotenoid epoxides are being found in increasing variety. Although xanthophyll epoxides were among the most common naturally occurring carotenoids, and carotene 5,6-epoxides have frequently been reported as minor constituents of carotenoid extracts, the identification of luteochrome (5*R*,6*S*,5'*R*,8'*R*)-5,6; 5',8'-diepoxy-5,6,5',8'-tetrahydro-*β*-*β*-carotene **216** in Brazilian sweet potatoes was the first report of the isolation of a carotenoid with an unhydroxylated 5,6-epoxy-5,6-dihydro-*β*-ring optically active form.[166] One has the feature of a 4,5-epoxy-4,5-dihydro-*ε*-end-group and both have 7,8-dihydrostructures; this latter feature has previously only been reported in cyclic carotenoids isolated from animal sources. The compounds were characterized by spectroscopic methods, as (3*S*,3'*R*) 4',5'-epoxy-3,6,3'-trihydroxy-7,8,4',5',7',8'-hexahydro-*γ*,*ε*,-caroten-one **217** and (3*S*,3'*R*)-5,6-epoxy-3,3'-dihydroxy-5,6,7',8'-tetrahydro-β-β-caroten-11',19'-olide **218**. Detailed studies leading to the rigorous assignment of stereochemistry as (3*S*,6*R*,3'*R*,6'*R*) for prasinoxanthin itself have been presented.[167] C_{33}-, C_{35}-, and C_{39}-peridinins **219**–**221** were synthesized.[154,168] A C_{37} carotenoid, isolated as a mixture of esters **222**, were reported from the clam *Paphia amabillis* (Mimase, Japan).[169]

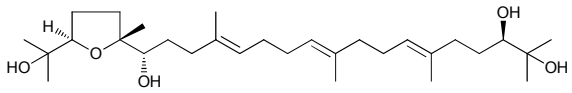
3. Pyrroloterpenoids

3.1. Pyrrolosesquiterpenoids

Total synthesis of glaciapyrrole A from an Alaskan *Streptomyces* strain[170] as well as of seven stereoisomers via a diastereoselective ruthenium-catalysed approach, from either geraniol or nerol, clarifed the relative configuration of natural glaciapyrrole A and a subsequent enantioselective synthesis of the unnatural enantiomer determined the configuration of the natural product as (11*R*,12*S*,15*S*)-(+)-glaciapyrrole A **223**.[171] An actinomycete of the ‘‘MAR4’’ group

(La Jolla, California, USA) was an excellent source of hybrid isoprenoid natural products,[172] yielding nitropyrrolins A–E **224**–**228**. Determination of the absolute configuration of nitropyrrolin B **225** via one-step acetonide formation from an epoxide, and application of the modified Mosher method afforded a general method for configurational assignment of trisubstituted epoxides. Nitropyrrolins A **224** and B **225** were moderately cytotoxic to HCT-116 cells, while nitropyrrolin D **227** was considerably more cytotoxic.[173] Heronapyrroles A–C[174] (**229**–**231**, respectively) were cytotoxic farnesyl nitropyrroles which were isolated from saline cultures of marine-derived bacteria of the actinomycete family Streptomycetaceae, Chemical analysis of a marine-derived *Streptomyces* sp CMB-M0423 (Beach sand off Heron Island, Queensland, Australia) yielded three members of the rare pyrroloterpene biosynthetic structure class. Heronapyrroles A–C **229**–**231** displayed promising biological activities with low to submicromolar IC_{50} activity against Gram-positive bacteria but no cytotoxicity toward mammalian cell lines. They did display very promising activity against the Gram-positive bacteria *Staphylococcus aureus* ATCC 9144 (IC_{50} 0.6–1.1 μM) and *Bacillus subtilis* ATCC 6633 (IC_{50} 1.1–6.5 μM).[174] The first synthesis of (–)-heronapyrrole C **231**, the enantiomer of a unique farnesylated 2-nitropyrrole natural product is described. With none of the chiral centers of heronapyrrole C **231** originally assigned, we proposed the most likely natural configuration on the basis of a putative biosynthetic pathway. The key step of the synthesis is a biomimetic polyepoxide cyclization cascade to establish the bis-THF moiety. Thus, (–)-heronapyrrole C **231** was synthesized in eight steps from commercially available starting materials.[31] While aspernidines A **232** and B **233** were two farnesyl isoindolinone-alkaloids, which have been found in an extract of the fungus *Aspergillus nidulans*.[175] Another fungus *Emericella* sp associated with *Aegiceras corniculatum* (Haikou, Hainan Province, China), contained the sesquiterpene-isoindolone ethers emeriphenolicins A–F **234**–**239**.[176] Chemical analysis of a specimen of the sponge *Ianthella cf. flabelliformis* (Lonsdale Wall, The Rip, Port Phillip Heads, Victoria,

Australia) returned two new sesquiterpene glycinyl lactams, ianthellalactams A **240** and B **241**.[177]



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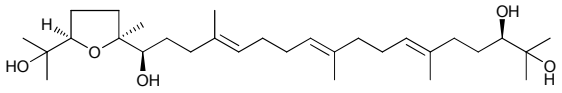

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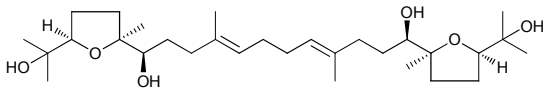

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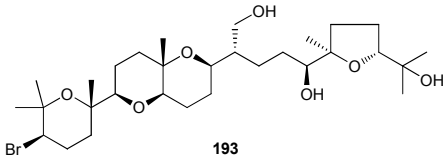

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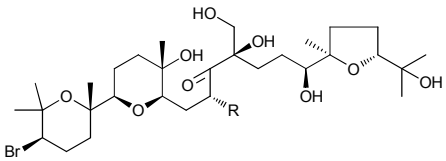

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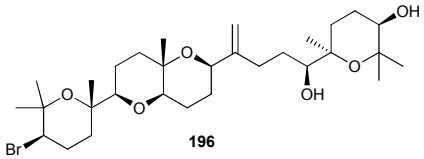
195 R = OH



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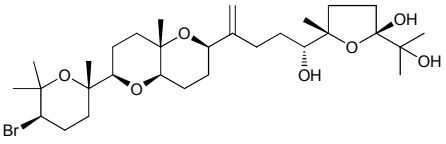

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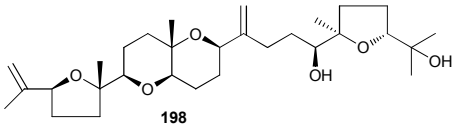

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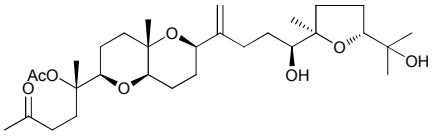

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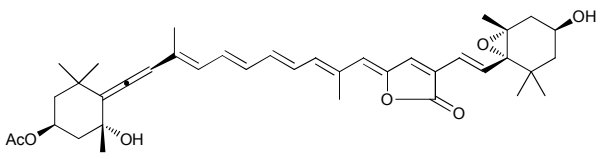
200 X = 9
201 X = 10



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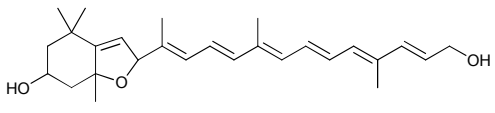

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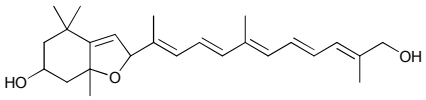

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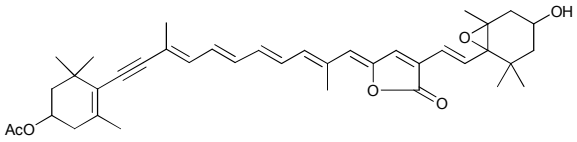

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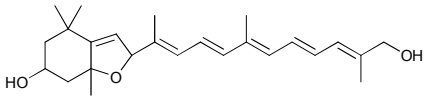

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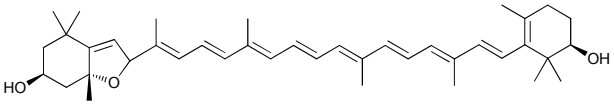

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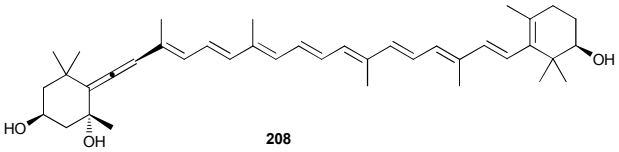

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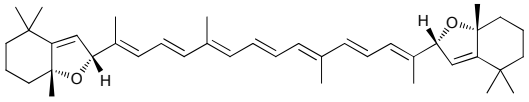

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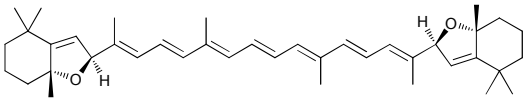

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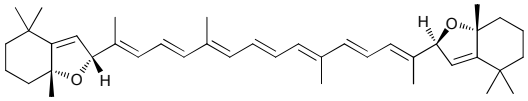

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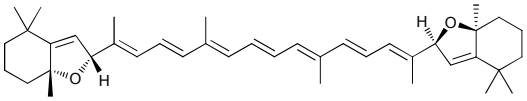

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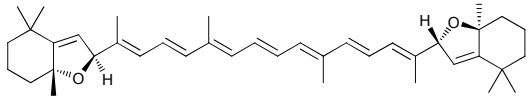

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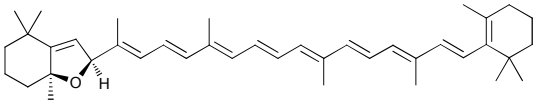

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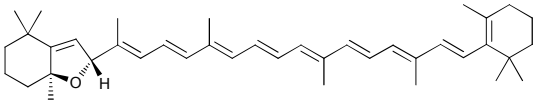

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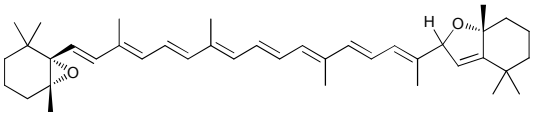

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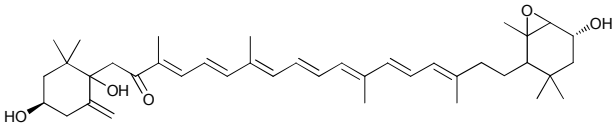

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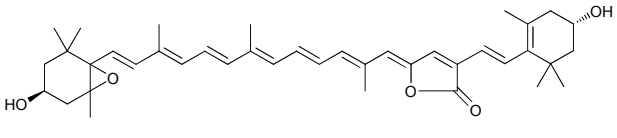

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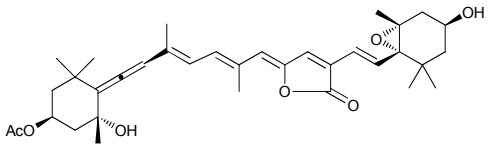

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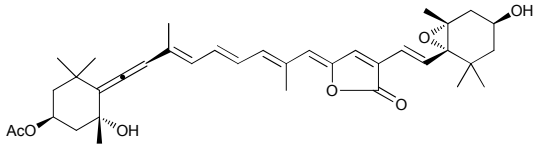

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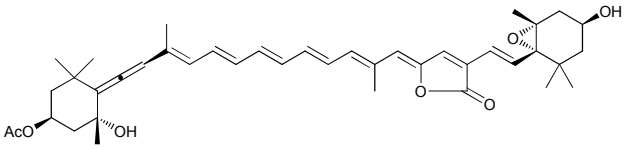

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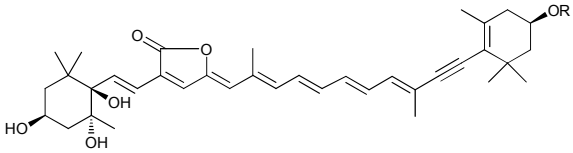
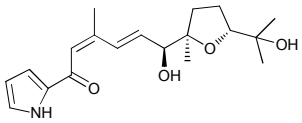


222 R = C22:6, C20:4, C20:1, etc



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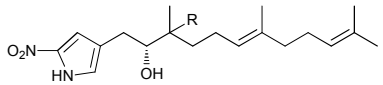
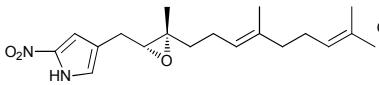
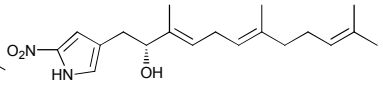


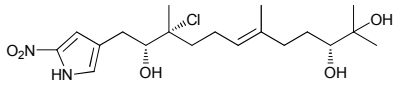
224 R = β-OH
226 R = α-Cl



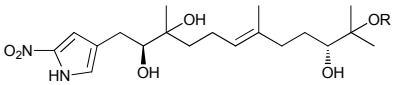
225



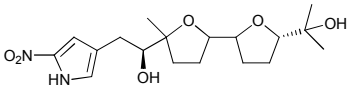
227



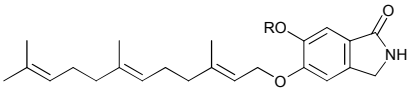
228



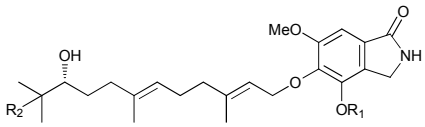
229 R = Me
230 R = H



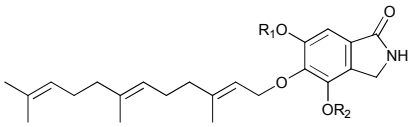
231



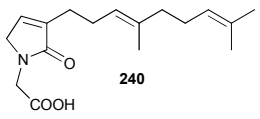
232 R = Me
233 R = H



234 R_1 = Me, R_2 = Cl
235 R_1 = H, R_2 = Cl
236 R_1 = Me, R_2 = OH



237 R_1 = H, R_2 = Me
238 R_1 = Me, R_2 = H
239 R_1 = R_2 = H



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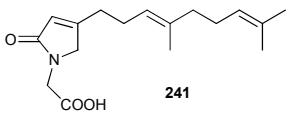
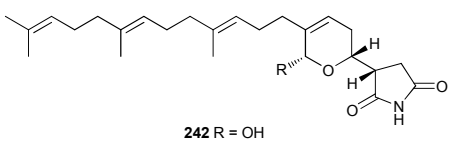
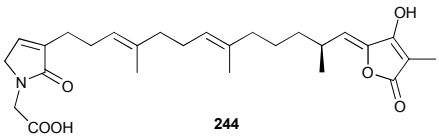


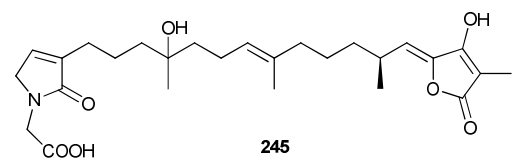
241



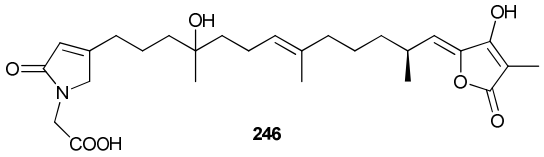
242 R = OH
243 R = OMe



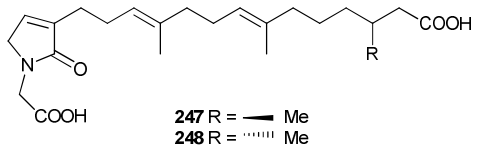
244



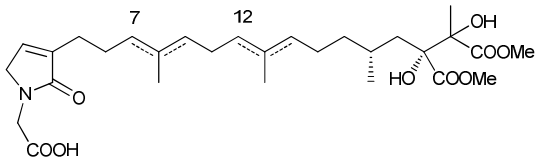
245

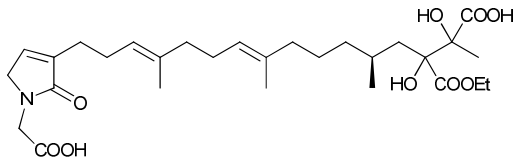


246



247 R = Me
248 R = Me





249

250 7*E*, 12*E*
251 7*E*, 13*Z*
252 8*E*, 13*Z*
253 8*Z*, 13*Z*

3.2 Pyrrolosesterterpenoids

Hippolides A **242** and B **243** were manoalide derivatives from *Hippospongia lachne* (Yongxing Island, Hainan Province, China). Compound **242** exhibited cytotoxicity against A549, HeLa, and HCT-116 cell lines with IC_{50} values of 5.22×10^{-2}, 4.80×10^{-2}, and 9.78 μM, respectively. It also showed moderate PTP1B inhibitory activitiy with an IC_{50} value of 23.81 μM, and compound **243** showed moderate cytotoxicity against the HCT-116 cell line and PTP1B inhibitory activity with IC_{50} values of 35.13 and 39.67 μM, respectively. In addition, **242** showed weak anti-inflammatory activity, with IC_{50} values of 61.97 μM for PKCγ and PKCR, respectively.[120] Six ircinialactam sesterterpenoids **244**–**249** have been reported from southern Australian and Antarctic collections of *Ircinia* sp and *Psammocinia* sp (Southern Australia and Antarctica) both from the family Irciniidae. All were isoform-selective glycine-gated chloride channel receptor modulators and have potential roles as neuronal pharmacological agents.[178] A series of sesterterpenoids **250**–**253** were isolated from a *Sarcotragus* sp (Soheuksan Island, Korea).[112]

4. Conclusions

Terpenoids are the most diverse class of natural products and were of interest since they are

found in almost all life forms where they carry out a myriad of functions ranging from primarily structural (cholesterol in cell membranes) to functional (carotenoids in photosynthesis, retinal in vision, quinones in electron transfer).[179] Terpenoids have a variety of roles in mediating antagonistic and beneficial interactions among organisms. They defend many species of plants, animals and microorganisms against predators, pathogens and competitors, and they are involved in conveying messages to conspecifics and mutualists regarding the presence of food, mates and enemies.[180]

Living organisms produce terpenoids for certain physiological and ecological functions. The idea that terpenoids have important biological functions has taken hold only recently, and there were considerable difficulties in testing these compounds in nature. Recent advances in analytical chemistry also help in functional studies by providing a much more comprehensive view of terpenoids present in and around individual organisms than was previously available. With the emerging discipline of chemical ecology, we will learn more about the roles of linear furano- and pyrroloterpenoids in the nature in the near future.

Acknowledgements

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