Heterocyclic terpenes: linear furano- and pyrroloterpenoids

Yonghong Liu,*[a] Si Zhang[a] and Pedro J. M. Abreu[b]

Covering: January 1970 to December 2005

The emphasis of this review is on linear furano- and pyrroloterpenoids, together with their relevant biological activities, source organisms and country of origin. First total syntheses that lead to the revision of structures or stereochemistries have been included, and 206 references are cited.

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Pedro Abreu graduated in chemistry at the Free University of Brussels (Belgium) in 1975, and returned to Portugal that year to work in the chemical industry. In 1978 he joined the Chemistry Department of the Faculty of Science and Technology (FCT), New University of Lisbon, where he received his PhD in Organic Chemistry in 1987. After a post-doctoral appointment with Professor Takao Yokota at the Faculty of Agriculture, University of Tokyo (1987), he returned to FCT to pursue his teaching and research activities as Professor of Natural Products Chemistry. In the last decade the research interests have been focused on the isolation, characterization, and biological evaluation of natural products from African and Portuguese medicinal plants, and algae of the Portuguese coast.

Yonghong Liu   **Si Zhang**   **Pedro Abreu**

1 Introduction

This review covers the literature from 1970 to 2005 and describes 326 compounds from 206 articles. We show the structures of novel compounds, and previously reported compounds where there has been a structural revision or a newly established stereochemistry. Previously reported compounds for which first syntheses or new bioactivities are described have been referenced, but separate structures have not generally been shown.

2 Reviews

A number of reviews have dealt with natural sesquiterpenoids,[1] diterpenoids,[2] sesterterpenoids[3] and triterpenoids.[4] General reviews include those of marine natural products.[5,6] Where appropriate, references to other reviews have been included in the following sections.

3 Furanoterpenoids

3.1 Furanosesquiterpenoids

3.1.1 Monofuranosesquiterpenoids.

3.1.1.1 Dendrolasin-type furanosesquiterpenoids. Dendrolasin **1** is a very well-known compound, and four syntheses have been reported.[7–10] An investigation of the sponge *Dysidea herbacea*, collected on the Great Barrier Reef, has led to the identification of sesquiterpenoid **2**.[11] A furanosesquiterpene **3** has been isolated from the marine sponge *Dysidea fragilis* (Mont.) from Brittany.[12] An isomer of dehydrodendrolasin **4** has been isolated from the Australian nudibranch *Ceratosoma brevicaudatum*, collected around the jetty at Rapid Bay, South Australia.[13] The absolute configuration of (+)-myoporone **5**, a furanosesquiterpenoid from *Myoporum montanum*,[14] was determined by enantioselective synthesis.[15] Dictyodendrillins A–C **6–8** were isolated from a South Australian *Dictyodendrilla* species.[16] Dictyodendrillin B **7** was prepared by a concise route in 43% overall yield.[17]
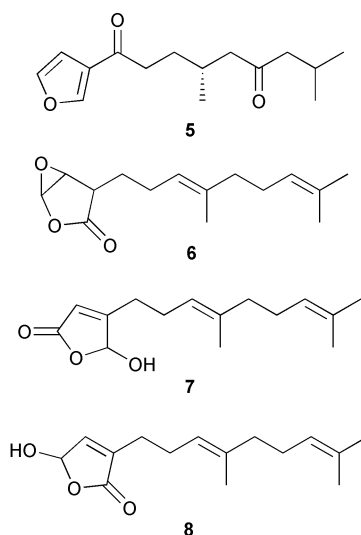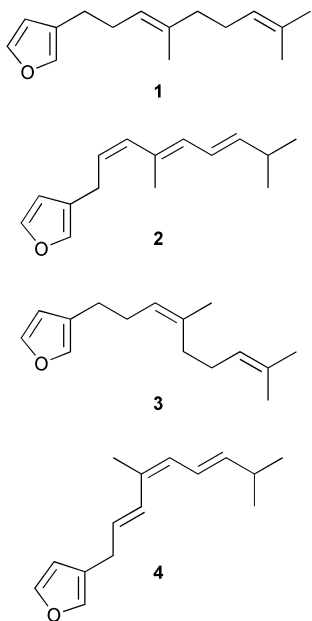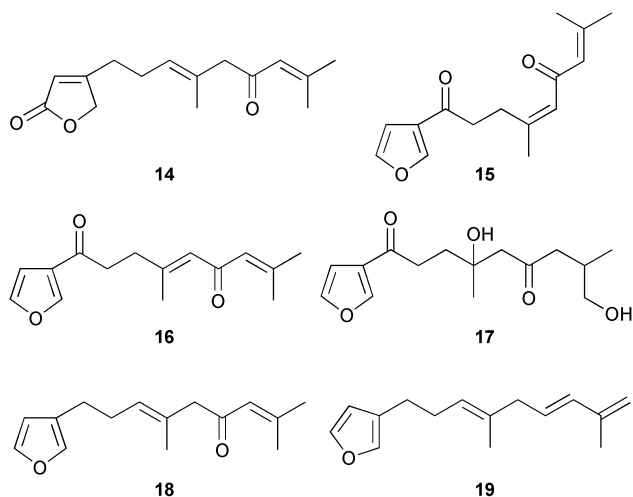

The *R* configuration of the hydroxyl group in 4-hydroxy-myoporone (athanagrandione) **9**[18] has been established by an interrelationship with (+)-eremoacetal.[19] The first total synthesis of the stress factor (+)-hydroxymyoporone **9** has been established and its absolute configuration reassigned.[20] The furanoterpene isodehydrodendrolasin **10** has been obtained from a tropical marine sponge *Euryspongia deliculata*, collected at Heron Island on the Great Barrier Reef, Australia.[21] Two homofarnesane lactones, **11** and **12**, and farnesane lactone **13** have been found in the aerial parts of *Gochnatia glutinosa*. This is the first time that homofarnesanes have been isolated from plants, although several compounds of this type have been obtained from insects.[22]
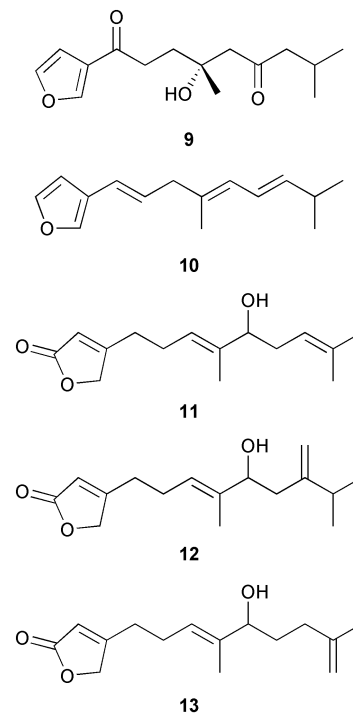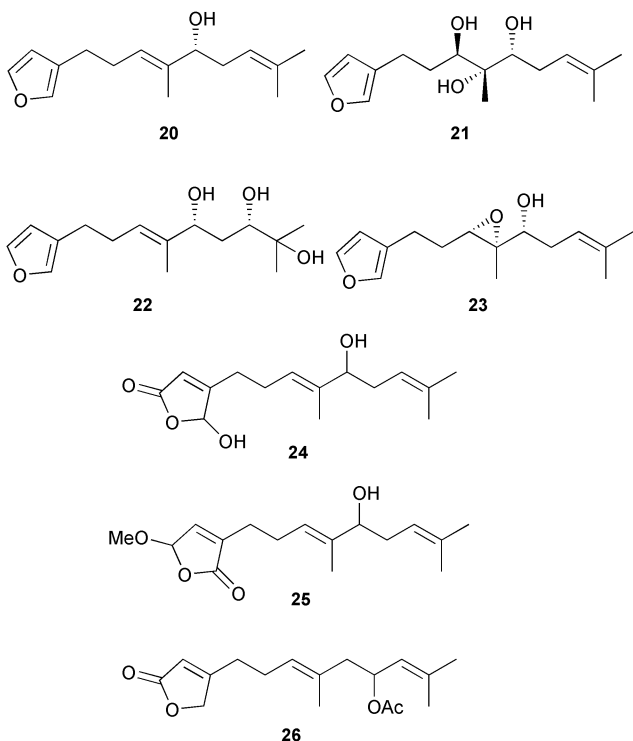

Four sesquiterpenoids **14–17** that are related biosynthetically to ipomeamarone, the well-known sweet potato phytoalexin, have been isolated from the root tissue of sweet potato (*Ipomoea batatas*) infected with the fungus *Cerutocystis fimbriata*.[23] Japanese workers have obtained another phytoalexin, **18**,[14] from this system

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in the same way. An isodehydrodendrolasin derivative **19** has been obtained from nudibranchs of the Cantabrian Sea belonging to the *Hypselodoris* genus, which use this compound as a deterrent against predators.[24]
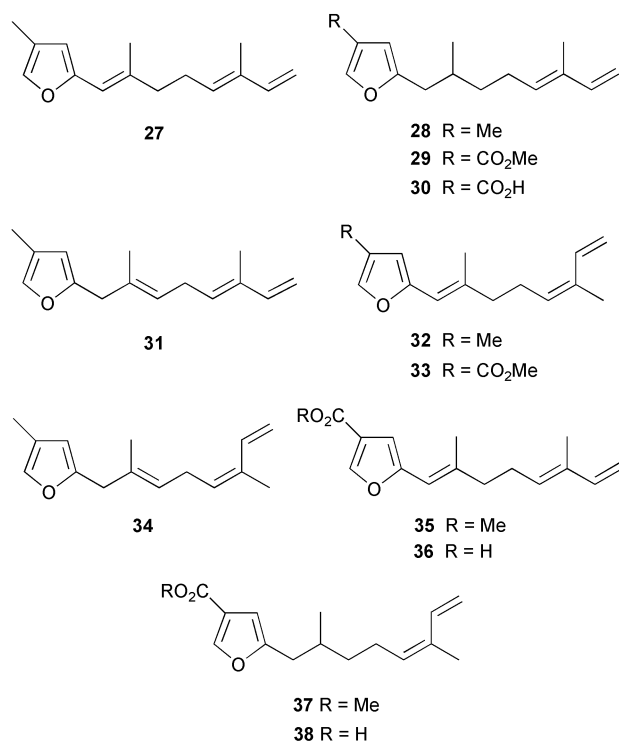
The sesquiterpene **26** has been isolated from *Eremophila forrestii*, a medicinal plant in the arid regions of Western Australia.[27]

sensitive and decomposed on storage. The product **28** was also isolated from *Sinularia firma*.[28] The dehydrovernopolyanthofuran **39** has been obtained from *Vernonia polyanthes*.[29] Practical syntheses of the anti-inflammatory furanosesquiterpene **36**, a metabolite of *Sinularia* sp.,[28] employ a strategy based on the Claisen rearrangement.[30]

Six furanosesquiterpenes of the dendrolasin type, **20–25**, have been isolated from a cytotoxic extract of the deep ocean tunicate *Ritterella rete*,[25] whilst known members of this sesquiterpene group have been found in the Patagonian nudibranch *Tyrinna nobilis*.[26] The sesquiterpene **26** has been isolated from *Eremophila forrestii*, a medicinal plant in the arid regions of Western Australia.[27]

The furanosesquiterpenoid **40** was isolated from the Mediterranean alcyonacean *Alcyonium pulmatum*.[31] A furanosesquiterpene **41** has been obtained from the soft coral *Lobophytum catalai*, which was collected from the Andaman and Nicobar Islands.[32] Actinolide A **42** is a sesquiterpenic lactone, found in an extract of the stems of *Actinodphne lancifolia*.[33]
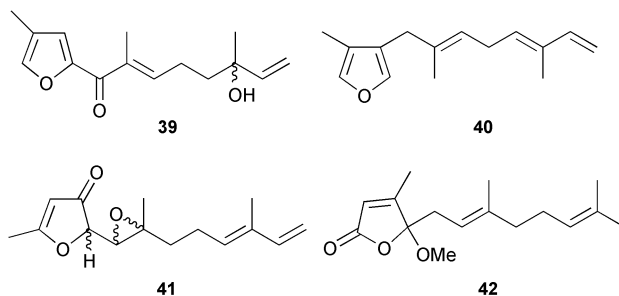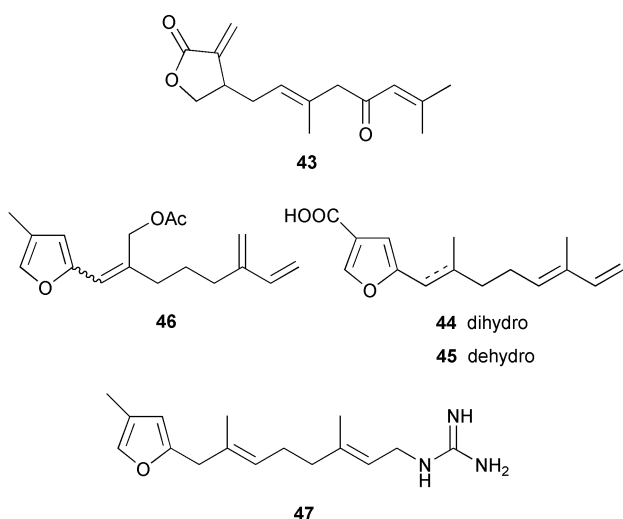
3.1.1.2 Other types of furanosesquiterpenoids. Continuing their studies of Australian soft corals, Bowden *et al.* have isolated twelve structurally related furanosesquiterpenes, **27–38**, from *Sinularia capillosa*.[28] Compounds **27**, **28**, and **31** were extremely acid-

Anthecotulide **43** has been isolated from *Anthemis cotula*.[34] The isolation and structure determination of two furanosesquiterpenes, **44** and **45**, from the soft coral *Sinularia lochmodes* have been described.[35] Another *Sinularia* sp. contains the furanosesquiterpene **44**.[36] A sesquiterpene named algoafuran **46** has been found in an extract of the nudibranch *Leminda millecra*, collected in Algoa Bay, South Africa.[37] Siphonodictidine **47** has been synthesized for the first time in a concise and regiocontrolled manner in an overall yield of 25.7%.[38] Siphonodictidine **47** is the secondary metabolite of an Indo-Pacific sponge *Siphonodictyon* sp.,[39] which burrows

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44 dihydro
45 dehydro

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57.[47] A peroxynerolidol derivative, fercoperol **58**, has been found in *Ferula communis* ssp. *communis*.[48] A cyclic sesquiterpene peroxysemiketal, **59**, has been isolated from *Artemisia maritima*.[49]

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into living coral. Among the members of this class discovered so far,[40,41] siphonodictidine is remarkable for its biological action,[39] as it inhibits growth of the coral and appears to be deployed by the sponge to kill coral polyps in its immediate vicinity. Apart from this specific function, which is essential for the survival of the sponge, siphonodictidine exhibits significant antifungal and antimicrobial activity against Gram-positive and Gram-negative bacteria.

The sesquiterpenes **48–50** have been isolated from *Arctotis arctotoides*.[42] The sesquiterpenoid **51** has been isolated from the root tissue of sweet potato (*Ipomoea batatas*) infected with the fungus *Cerutocystis fimbriata*.[23] Compound **52**, which possesses a sesquiterpenoid skeleton of the caleprunane type, has been isolated from *Calea prunifolia*.[43] The structures of cyclonerodiol oxide and epicyclonerodiol oxide, which were isolated from the fungus *Trichoderma polysporum*, have been shown to be **53** and **54**, respectively.[44]
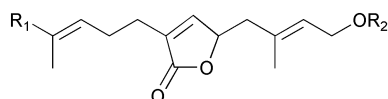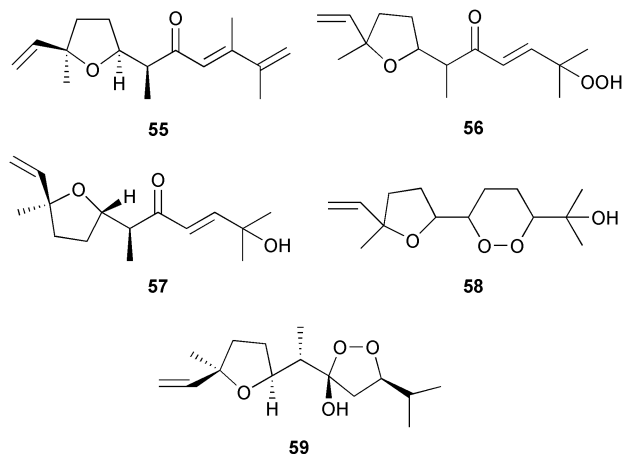
48 R₁ = CHO, R₂ = H
49 R₁ = CHO, R₂ = Ac
50 R₁ = CH₂OAc, R₂ = Ac

51

52

53 R₁ = H, R₂ = CMe₂OH
54 R₁ = CMe₂OH, R₂ = H
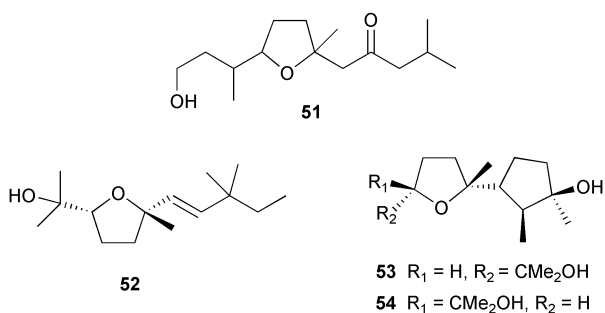
The sesquiterpene **55**, related to davanone, has been isolated from *Artemisia reptans*.[45] The new nerolidol derivative arteincultone **56** has been isolated from *Artemisia inculta*.[46] The essential oil of *Artemisia pallens* (davana oil) contains more than 50 components, one of which was identified as the nerolidol derivative
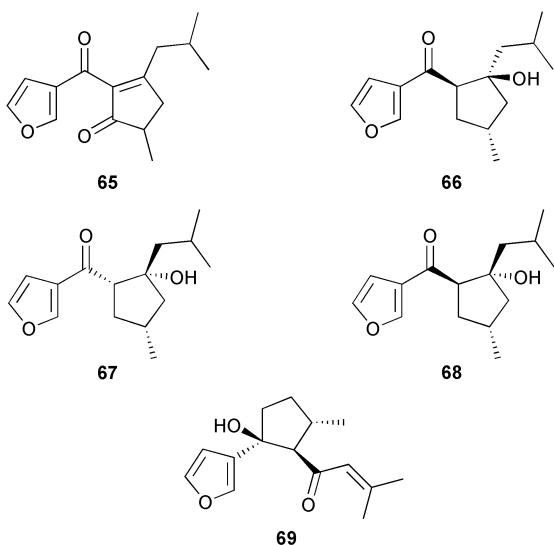
The davanone-type peroxides epiarteincultone **60** and spiro-arteincultone **61** have been extracted from *Artemisia abrotanum*. These two metabolites were also prepared synthetically by singlet and triplet oxygen oxidation respectively, and **61** showed schizoniticidal activity against *Plasmodium falciparum*.[50] The essential oil of *Santolina oblongifolia* contains the *cis*- and two *trans*-isomers of **62**.[51] The structures of (+)-myomontanone **63** and isomyomontanone **64**, which are furanosesquiterpenoids from *Myoporum montanum*, were shown to be the aldol condensation products of (+)-myoporone **5**, which is also present in this plant.[14]

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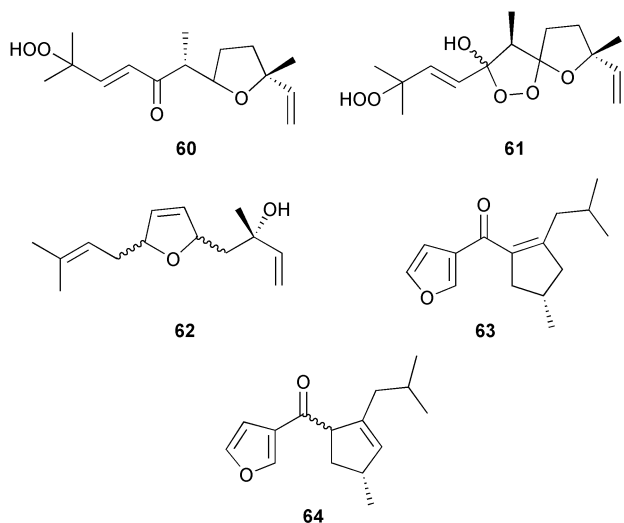
The furanosesquiterpene merrekentrone D **65** has been found in the roots and rootstocks of *Merremia kentrokaulus*.[52] Four furanosesquiterpene β-hydroxy ketones previously isolated from *Myoporum* sp.[53] have now been assigned complete stereostructures from NMR and X-ray data. The compounds are (5*R*,7*R*,9*S*)-9-hydroxy-5,9-dihydromyomontanone **66**, (5*S*,7*R*,9*R*)-9-hydroxy-5,9-dihydromyomontanone **67**, (5*R*,7*R*,9*R*)-9-hydroxy-5,9-dihydromyomontanone **68** and (4*S*,7*S*,8*R*)-4-hydroxy-10,11-didehydro-4,8-dihydromyodesmone **69**.

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Plakortone G **70** is a highly cytotoxic sesquiterpene, isolated from a Caribbean sponge of the *Plakortis* genus.[54] Two furanosesquiterpenoid ketones, dihydrocrassifolone **71** and crassifolone **72**, were isolated from the wood essential oil of *Myoporum crassifolium* from New Caledonia.[55] The furanosesquiterpene laevidiene **73** has been isolated from *Cadlina iaevis* from the Cantabrian Sea (Atlantic Ocean).[56] The structure **74** has been assigned to a furanosesquiterpenoid obtained from the extract of the aerial parts of *Ixiolaena leptolepis*.[57] Two new furanosesquiterpene alcohols, pelseneeriol 1 **75** and pelseneeriol 2 **76**, have been isolated from the porostome nudibranch *Doriopsilla pelseneeri*, collected off the Portuguese coast (Atlantic Ocean).[58] An approach known to give regiospecific and stereospecific reactions has been applied to the first enantioselective synthesis of the natural (−)-microcionin 2 **77**, an example of a molecule containing a *trans* relationship between the methyl groups.[59] Microcionin was first
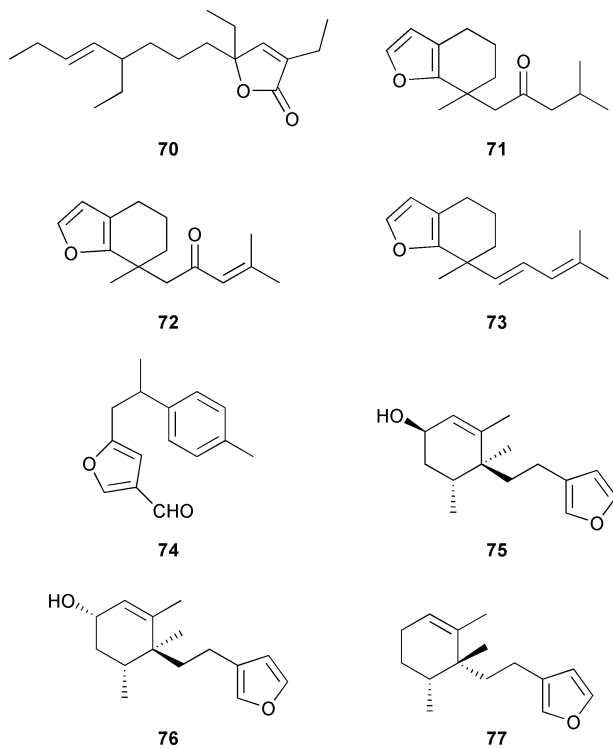
isolated from the sponge *Microciona toxystila*,[60] and later from the dorid nudibranch molluscs (*Dendrodoris grandiflora*) growing in contact with them.[61] A second group has also isolated this furanosesquiterpene from another species of dorid nudibranch molluscs, *Cadlina luteomarginata*.[62]

Tetraenol **78** has been isolated from the relict Chinese plant *Tetraena mongolica*.[63] The incubation of small colonies of *Sinularia capillosa*, freshly collected from Magnetic Island (Australia), with labeled mevalonolactone afforded the furanoquinol **79**, containing the label in the terpenoid portion of the sesquiterpene hydroquinone; this confirmed how mevalonate is incorporated into terpenoids *in vivo* in this soft coral.[64] The sesquiterpenoid derivative **80** has been obtained from the roots of *Ferula feruloides*.[65] The first total synthesis of cristatic acid **81** has been reported.[66] This bioactive sesquiterpene had previously been isolated from the fruiting bodies of the higher mushroom *Albatrellus cristatus*.[67] An asymmetric synthesis of (*R*)-sesquilavandulol has been achieved.[68] *Ferula ferulioides* also contains the farnesane derivatives **82** and **83**.[69,70]

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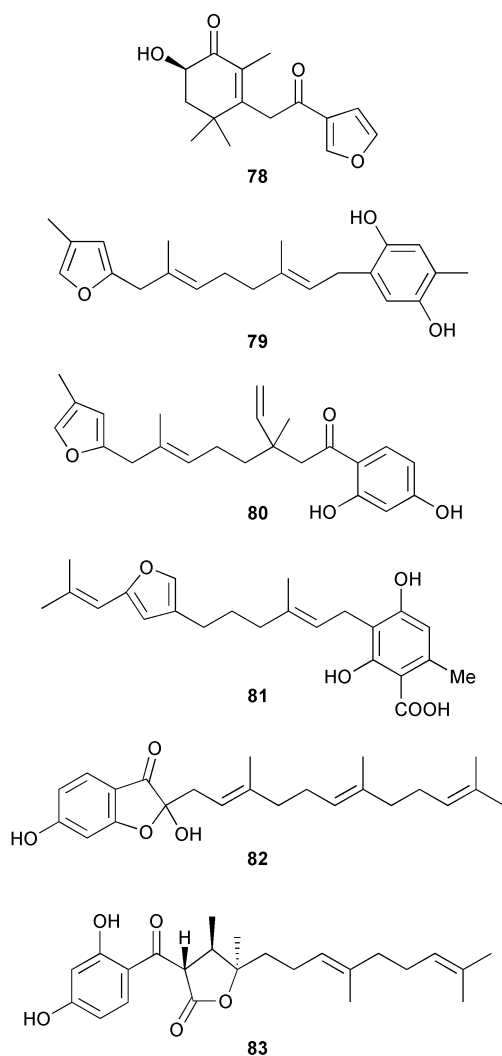
Four sesquiterpene coumarins **84–87**, showing nitric oxide production inhibitory effects, have been found in *Ferula fukanensis*.[71,72] The two dihydrofurochromone sesquiterpenes **88** and **89** have been obtained from the roots of *Ferula ferulaeoides*.[73]

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85 R = β-Me
86 R = α-Me

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88 R = β-Me
89 R = α-Me
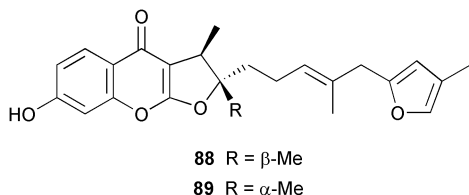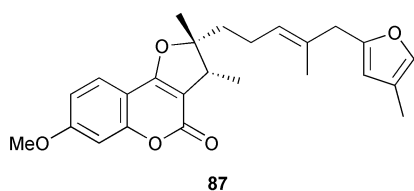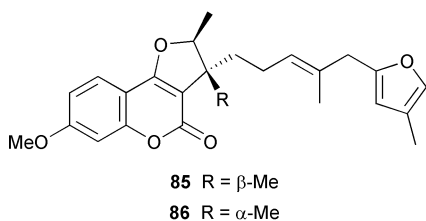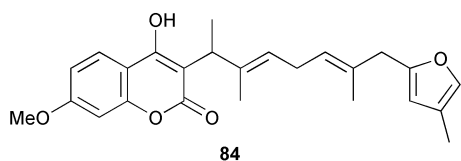
Five sesquiterpene phenylpropanoid derivatives, fukanedones A–E **90–94**, were isolated from the roots of *Ferula fukanensis*.

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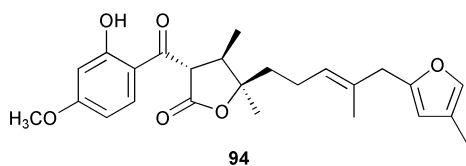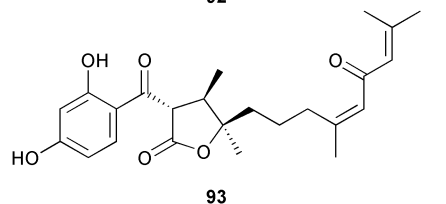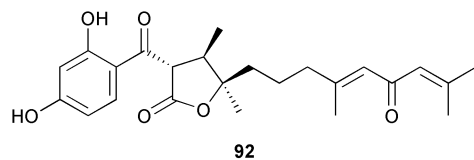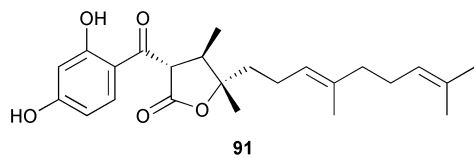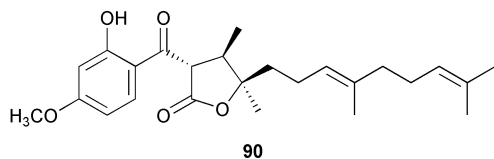
These compounds inhibited NO production and inducible NO synthase gene expression by a murine macrophage-like cell line activated by lipopolysaccharide and recombinant mouse interferon-γ.[74]
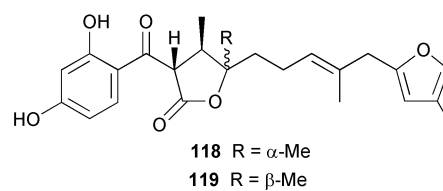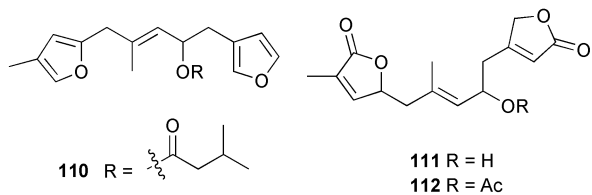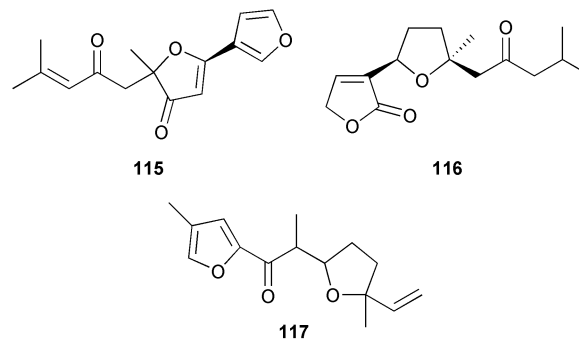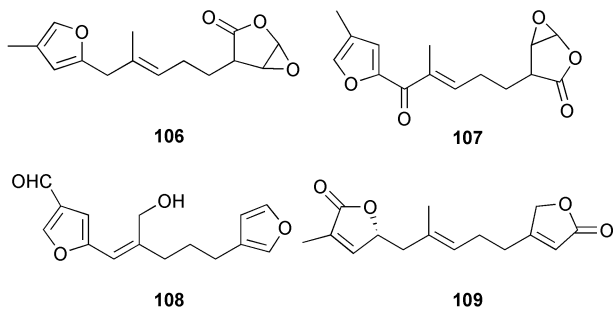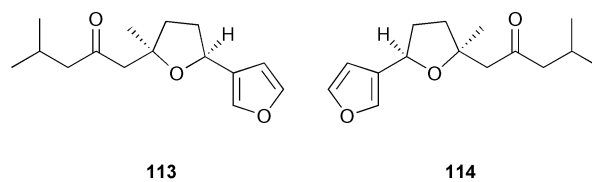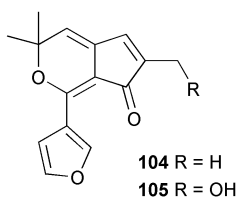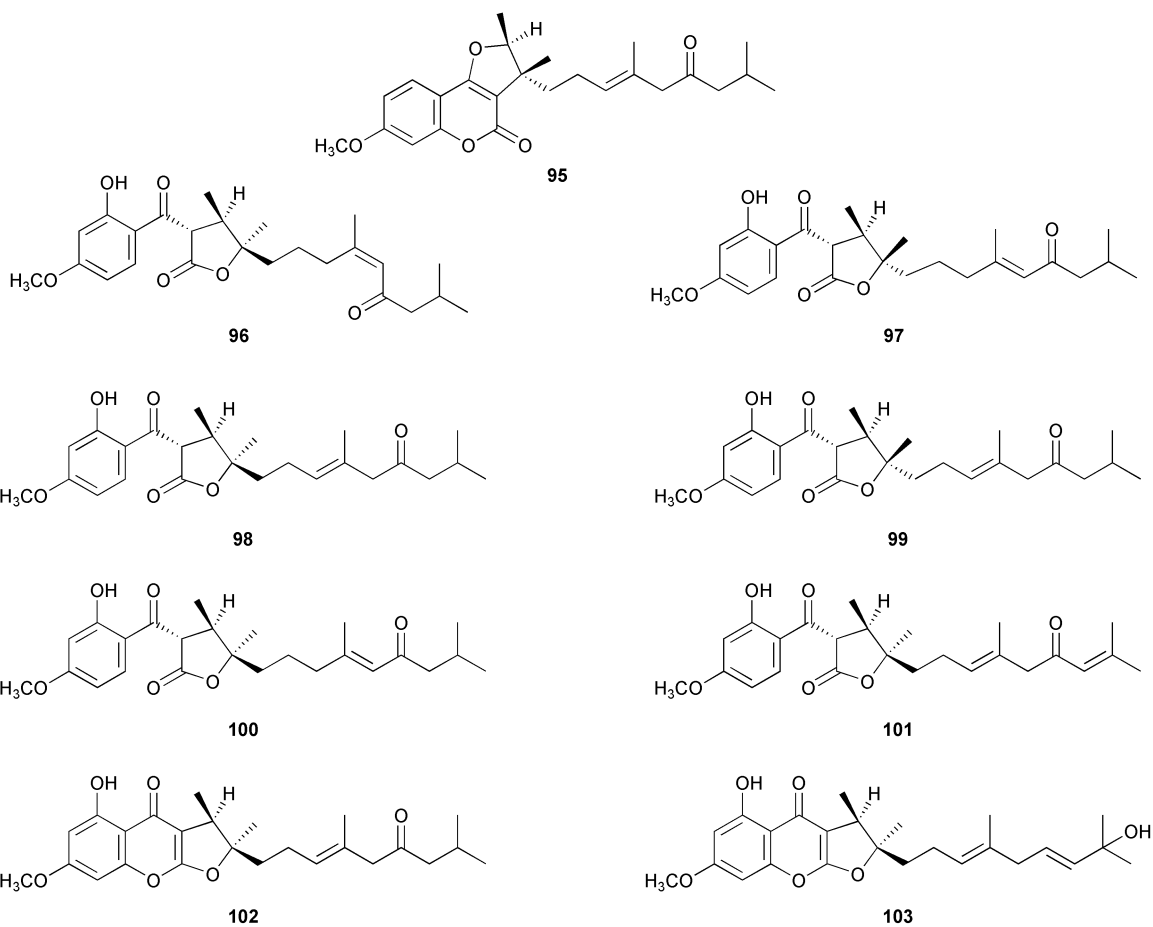
An efficient and stereodefined process is described for the first preparation of a prenyl-benzoylfuranone-type sesquiterpenoid, (±)-3-(2,4-dihydroxybenzoyl)-4,5-dimethyl-5-(4,8-dimethylnona-3(*E*),7(*E*)-dien-1-yl)tetrahydro-2-furanone **83**.[70] The synthetic strategy is based on the stereoselective construction of the key quaternary carbon center by nucleophilic addition of organometallic reagents to functionalized ketoamides derived from dihydroxyacetone dimer.[75] Pallidones B–J **95–103** have been isolated from the EtOAc extracts of the roots of *Ferula pallida* (Steud.) Korovin (Umbelliferae), which grows in Bulgan Somon of Hovd City, Mongolia.[76,77] Merrekentrones A **104** and B **105** have been found in the roots and rootstocks of *Merremia kentrokaulus*.[52]
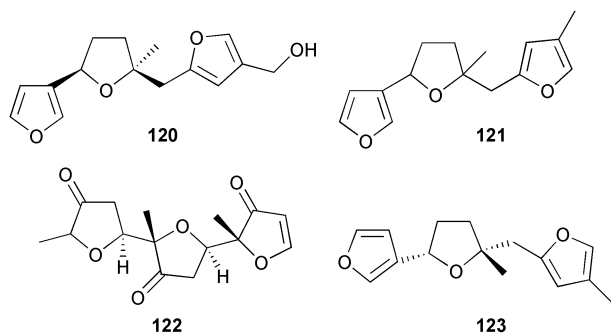
3.1.2 Bisfuranosesquiterpenoids. A variety of farnesyl/nerolidyl sesquiterpenoids from various plant sources have been identified. These include the lasiospermone derivative **106** from *Ursinia nana*,[78] and brachymerolide **107** and brachymeral **108** from *Brachymeris montana*,[79] one of the woody South African genera of the Anthemideae. The structure of a bisbutenolide, a likely precursor of the acetylenic sesquiterpene freelingyne, obtained from a species of the genus *Eremophila*, has been determined as **109**.[80] A nerolidol derivative, **110**, has been obtained from *Ursinia sericeae*.[81] The sesquiterpene bisbutenolides **111** and **112** have been isolated from *Eremophila homoplastica*.[27]

The work described in a detailed paper by Russell and Sutherland has confirmed the absolute configuration of (−)-ngaione **113**, and furthermore it has been conclusively demonstrated that ipomeamarone, a phytoalexin from the sweet potato, is in fact (+)-ngaione **114**.[82] On this basis, it is suggested that the use of the name ipomeamarone should be discontinued. Biosynthetic studies have shown that the three oxygen atoms in (+)-ngaione **114** (= ipomeamarone) are derived from molecular oxygen, not from water nor from the hydroxyl group of farnesol itself.[83] The absolute configuration of (+)-ipomeamarone **114** has also been independently determined.[84] A furanosesquiterpene, merrekentrone C **115**, has been found in the roots and rootstocks of *Merremia kentrokaulus*.[52] A sesquiterpenoids that are related biosynthetically to ipomeamarone which had been infected with the fungus *Cerutocystis fimbriata*, has the structure **116**.[23] A study of the roots of *Rehmannia glutinosa* led to the isolation of a sesquiterpene **117**.[85] Another species of this genus, *Ferula ferulioides*, contains farnesane derivatives **118** and **119**.[11]

3.1.3 Trisfuranosesquiterpenoids. A sesquiterpenoid **120** related biosynthetically to ipomeamarone **114**, the well-known sweet potato phytoalexin, has been isolated from root tissue of sweet potato (*Ipomoea batatas*) infected with the fungus *Cerutocystis fimbriata*.[23] Japanese workers have obtained[86] another phytoalexin **121**, from this system in the same way.
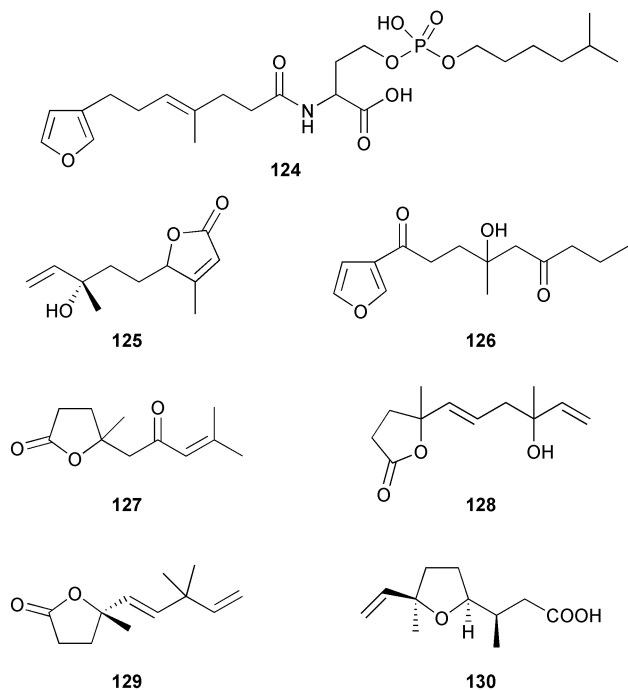
The sesquiterpene chilenone B **122**, a trimer of 2-methyl-3(2*H*)-furanone, has been obtained from the red alga *Laurencia chilensis*, and its structure determined by X-ray analysis.[87] The synthesis of the difuranosesquiterpene athanasin **123** has enabled its absolute configuration to be established.[88] Stereochemical studies

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104 R = H
105 R = OH

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114

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107

115

116

OHC

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109

117

110 R =

111 R = H
112 R = Ac

118 R = α-Me
119 R = β-Me

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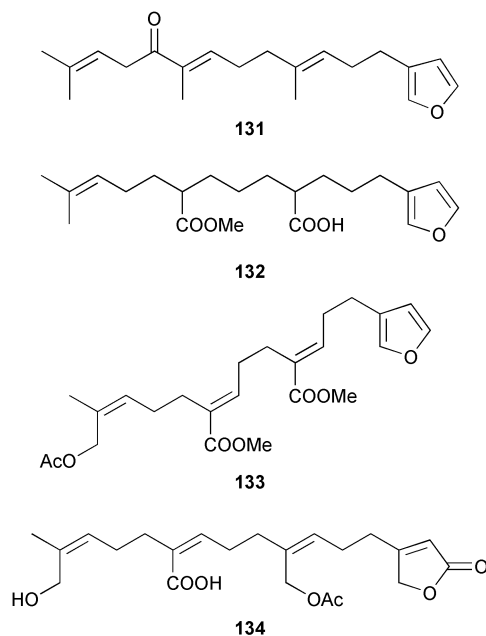
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131 132 133 134

on the biosynthesis of homoterpenes derived from nerolidol and geranyllinalool from higher plants, together with mechanistic, phylogenetic, and ecological aspects, have been reported.[89]

3.1.4 Norfuranosesquiterpenoids. The Hawaiian sponge *Spongia oceania* contains pokepola ester **124**, a diester of phosphoric acid in which the alcohols are 5-methylhexan-1-ol and homoserine. The amine of homoserine forms an amide with a trinorfuranosesquiterpenic acid.[90] The norsesquiterpene **125** has been found in an extract of the aerial parts of *Artemisia inculta*, collected in three different locations in Egypt.[91] The sesquiterpenes **126** and **127** have been obtained from *Athanasia pinnata*.[92] The aerial part of *Calea crocinervosa* contains the trisnorsesquiterpene lactone crocinervolide **128**.[93] Compound **129**, which possesses the caleprunane skeleton, has been isolated from *Calea prunifolia*.[43] The norsesquiterpene **130** has been isolated from *Artemisia herba-alba*.[94]

a butenolide end-group may have taxonomic significance in the classification of the tribe Astereae (Compositae).[98]

The eleganolone diterpenoid **135** was amongst a series obtained from the alga *Bifurcaria bifurcata*.[99] Two diterpenes, **136** and **137**, isolated from a Western Australian species of *Spongia*, were obtained as 3 : 1 mixtures of enantiomers.[100] The brown alga *Bifurcaria bifurcata*, collected from Brittany on the Atlantic coast, contained two diterpenoids, bifurcane **138** (which inhibited the development of fertilized sea urchin eggs), and epoxyeleganolactone **139**.[101]

124

125 126

127 128

129 130

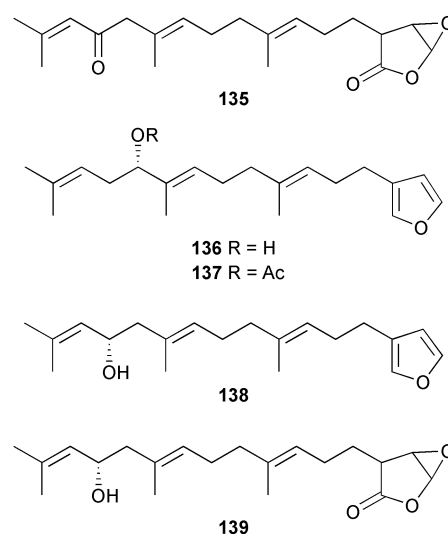135 136 R = H 137 R = Ac 138 139

3.2 Furanoditerpenoids

3.2.1 Monofuranoditerpenoids. The furan furosolidagonone **131** is among the constituents of *Solidago drummondii*.[95] Microglossic acid **132** (from *Microglossa zeylanica* collected in Sri Lanka)[96] and 17-(acetoxymethyl)thymifodioic acid **132** (from *Baccharis thymifolia*)[97] are further examples. It has been suggested that the occurrence of hydroxylated geranylgeraniol derivative **134** with
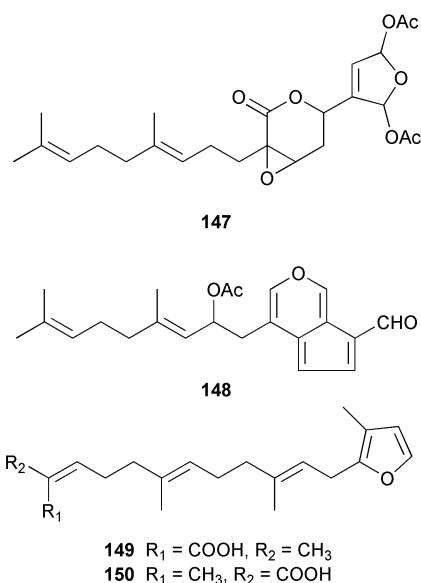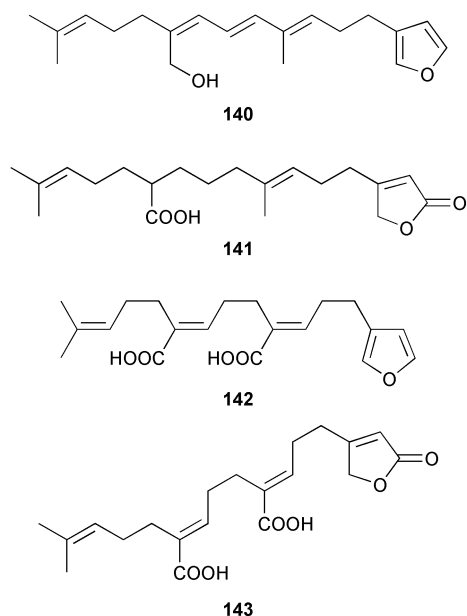
The furanoditerpene **140** was obtained from the Australian sponge *Thorectandra choanoides*.[102] The geranylgeraniol derivative **141** has been isolated from a Brazilian medicinal plant, erva-santa, *Baccharis ochracea* (Asteraceae).[103] Incanic acid **142** from *Conyza incana* possesses an *E* alkene geometry.[104] Inconyzic acid **143** was obtained from *Conyza incana*.[105]

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140

141

142

143

Compound **144** was obtained from specimens of the brown alga *Bifurcaria bifurcata* from two locations in Brittany.[106] Cacospongionolide C **145** was obtained from the Adriatic sponge *Fasciospongia caverrzosa*.[107] A number of acyclic diterpenoids possess a terminal furan ring, exemplified by conyzaleucolide A **146** obtained from *Conyza hypoleuca* (Compositae).[108]

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145

146
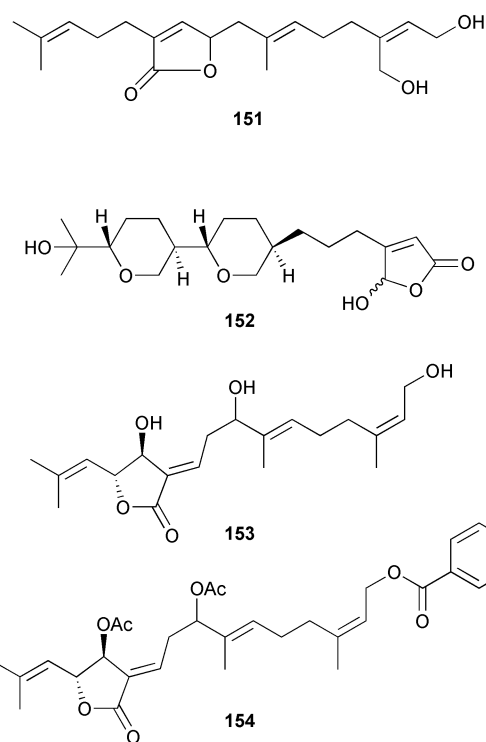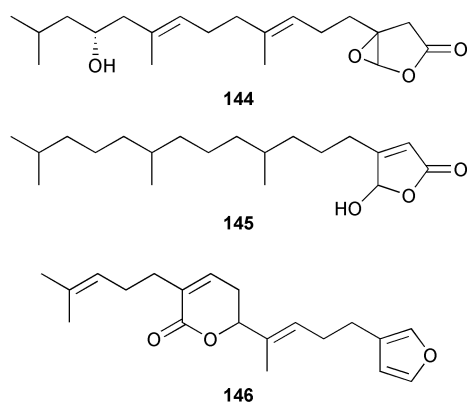
Marine organisms continue to yield oxygenated diterpenoids, of which thuridillin **147**, from the mollusc *Thuridilla hopei*, is an example.[109] Linear diterpenoids have been considered as chemotaxonomic markers in the genus *Cystoseira* (brown algae).[110] Halitunal **148** has been isolated from the marine alga *Halimeda tuna*,[111] and two acyclic furanoditerpene compounds, saurufuran A **149** and B **150**, have been obtained from the root of *Saururus chinensis*. Saurufuran A is a peroxisome proliferator-activated receptor γ (PPARγ) agonist, however, saurufuran B weakly activated PPARγ.[112] Thee geranyl-geraniol derivative **151** has been isolated from from *Diplostephium meyenii* (Asteraceae).[113]

Lingulatusin **152** and tuxpanolide **153** are geranyl-geraniol derivatives reported from from *Aster ligulatus*[114] and *Perymenium hintonii*,[115] respectively. An acyclic diterpene-γ-lactone, hanliuine I **154**, has been obtained from *Salix matsudan*.[116] The lactone naviculide **155** has been obtained from the liverwort *Porella navicularis*,[117] whilst some geranyl-linalool glycosides, the capsiansides,

147

148

149 R₁ = COOH, R₂ = CH₃
150 R₁ = CH₃, R₂ = COOH

151

152

153

154

have been reported from *Capsicum* plants.[118] The lactone **156** has been isolated from *Melampodium leucanthum*.[119]

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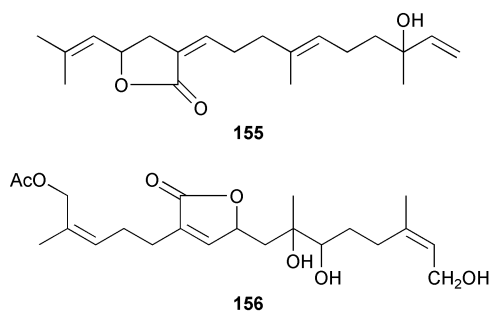
Hanliuin III **157** is a lactone obtained from *Salix matsudana*.[120] Cacospongin A **158** was isolated from a Philippine sponge, *Cacospongia* sp.[121] Examination of the resinous exudate of a *Madia* species has yielded madiaol **159**.[122] Examination of the sponge *Jaspis splendens* afforded (+)-subersin **160**, which is an inhibitor of 15-lipoxygenase.[123]


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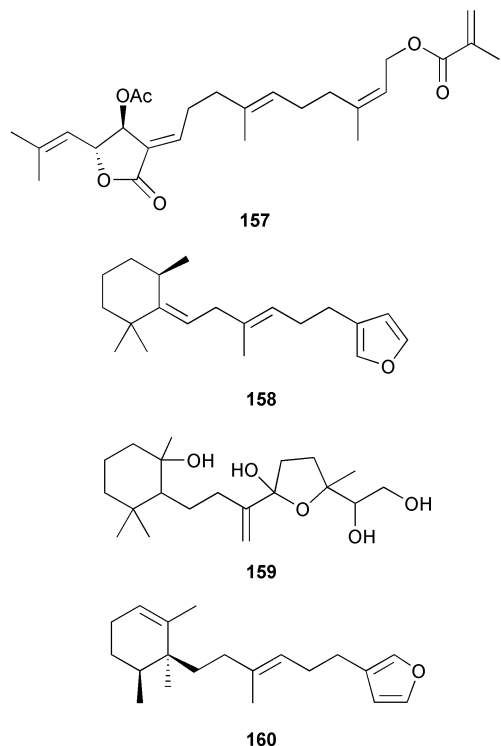
3.2.2 Bisfuranoditerpenoids. Caucanolides A–F **161–166** have been isolated from the gorgonian octocoral *Pseudopterogorgia bipinnata* collected in the south-western Caribbean Sea near Colombia. These compounds showed *in vitro* antiplasmodial activity against the malaria parasite *Plasmodium falciparum*.[124] A Korean collection of a sponge of the genus *Sarcotragus* was found to contain two bisfuranoditerpenoids, sarcotins K **167** and L **168**, which displayed weak cytotoxicity.[125]
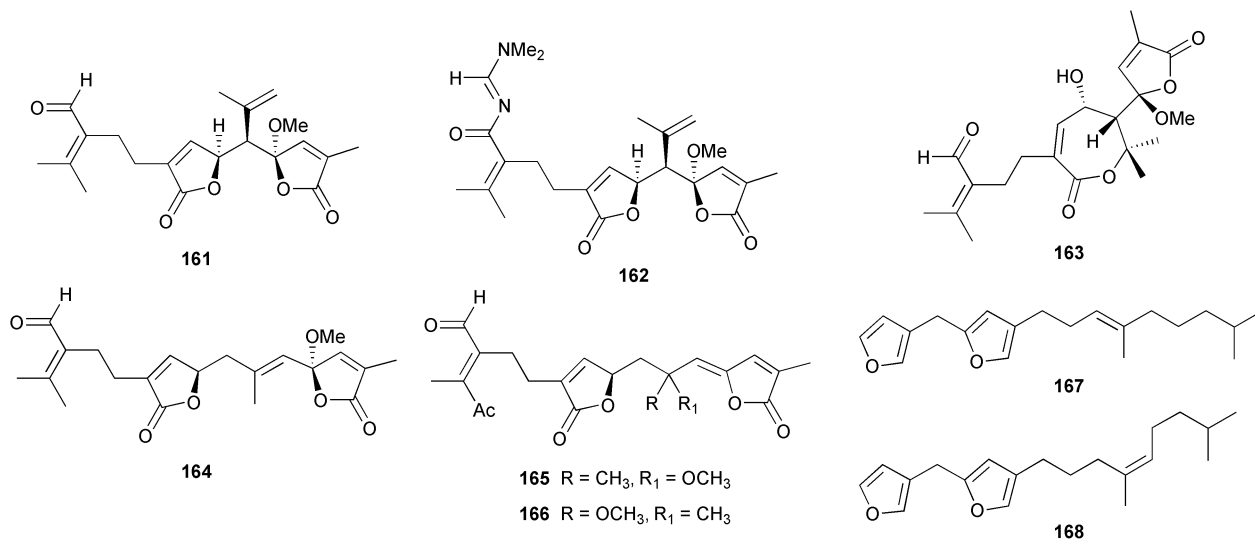
3.3 Furanosesterterpenoids

3.3.1 C$_{21}$ furanoterpenoids. Many C$_{21}$ furanosesterterpenes contain a furan ring at both ends of the molecule, such as nitenin **169** and dihydronitenin **170** from *Spongia nitens*,[126] and anhydrofurospongin-1 **171**[127] and furospongin-1 **172**[128] from *Spongia officinalis* and *Hippospongia communis*, respectively. The compounds **173** and **174** have been detected in a species of the genera *Spongia* and *Leiosella*, respectively,[129] whilst the γ-lactone furospongolide **175**[130] has been found in *Dysidea herbacea*.


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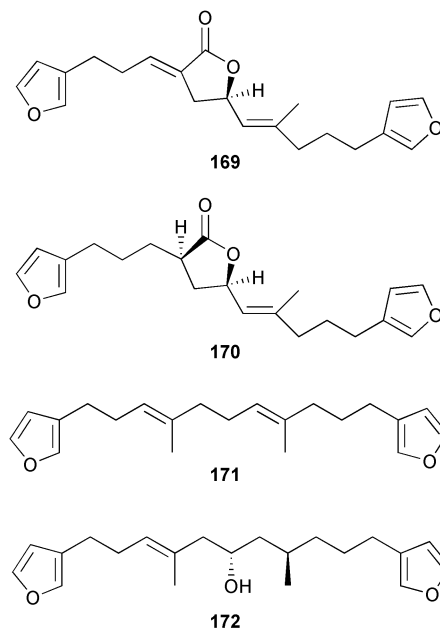
The sponge *Cacospongia scalaris* has provided a number of linear C$_{21}$ difurans, exemplified by cacospongione A **176**, cacospongienone A **177**, and cacospongienone B **178**.[131] The unsaturated lactone **179**, kurospongin, having ichthyotoxic and feeding-deterrent properties, has been isolated from a marine sponge *Spongia* sp.[132] Its absolute stereochemistry was established by applying Horeau's method to an alcohol derived from a Grignard reaction on the unsaturated lactone. The untenospongins A **180** and B **181**, obtained from a *Hippospongia* species,[133] possess

161

162

163

164

165 R = CH$_3$, R$_1$ = OCH$_3$
166 R = OCH$_3$, R$_1$ = CH$_3$

167

168

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coronary vasodilating properties. The sponge *Carteriospongia flabellifera*, collected from the Great Barrier Reef, contains 12,13-dehydrofurospongin 1 **182**.[134]

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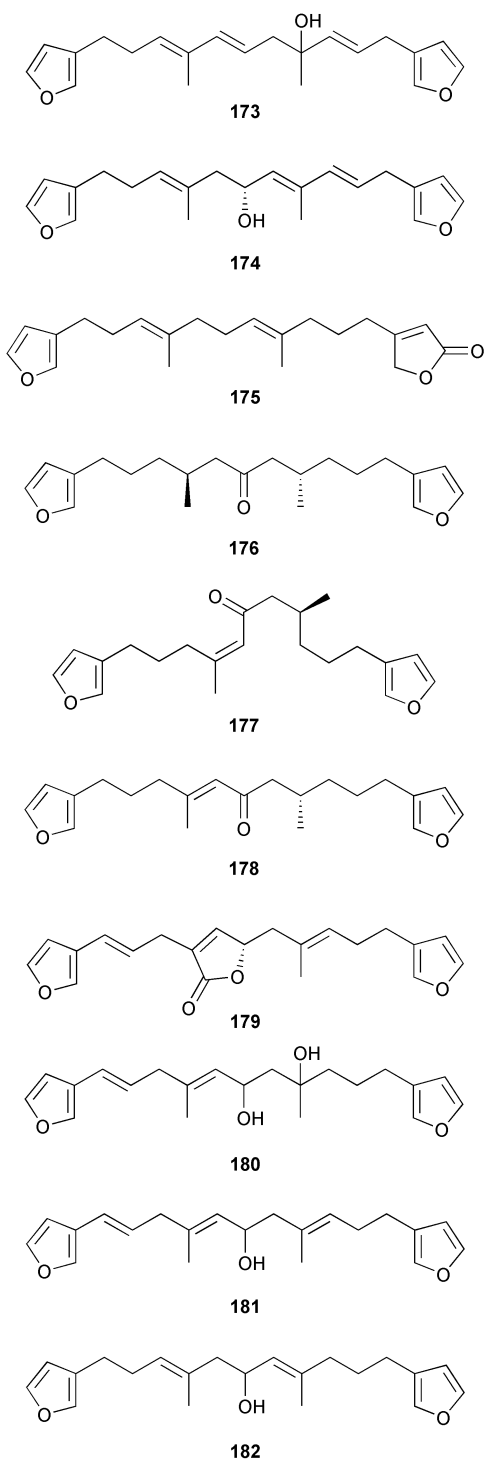
Degraded linear sesterterpenes have been isolated from sponges of the genera *Spongia*, *Carteriospongia* and *Hippospongia*. For example, untenospongin C **183** has been obtained from an Okinawan *Hippospongia* sp.[135] Isonitenin **184** is an additional C_{21} difuranoterpene from a Spanish collection of *Spongia officinalis*.[136] The degradation of tetronic acids with alkaline hydrogen peroxide, to mimic the formation of these compounds, has been reported.[137]

Ent-kurospongin **185** was isolated from a Korean *Sarcotragus* species.[138] A *Hippospongia* sp. from Goa, India, contained *ent*-untenospongin A **186**.[139]

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185

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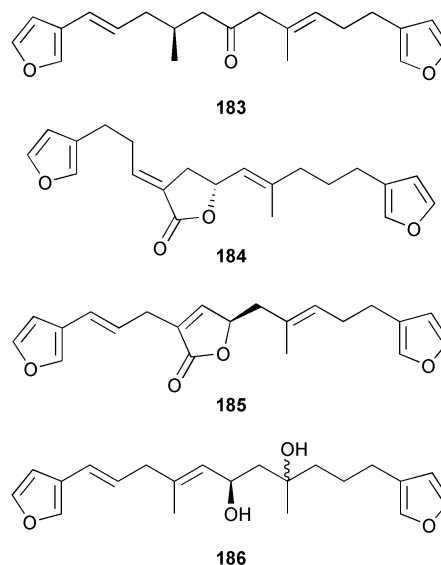
A C_{21} difuranoterpene, **187**, from a Mediterranean specimen of *Spongia virgultosa*, was found to be the enantiomer of (−)-untenospongin B from a Japanese *Hippospongia* sp.[133,140] Comparison of spectral data suggested that the structure of tetradehydrofurospongin-1 from an Australian *Spongia* sp.[129] should be revised from **188** to **187**.[140] The absolute configuration of the C_{21} difuranoterpene **189**, isolated from *Fasciospongia cavernosa* from the Arabian Sea,[141] has been determined by synthesis of its enantiomer.[142]
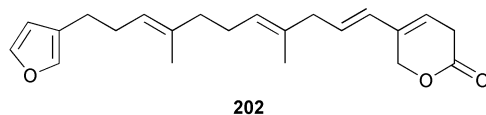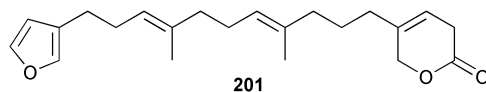

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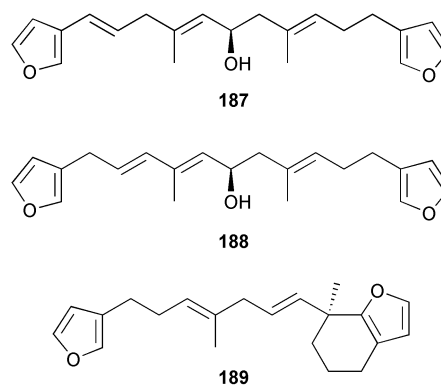
A specimen of *Spongia officinalis* from La Caleta, Cádiz, Spain, contained two additional minor C_{21} furanoterpenes, the weakly cytotoxic furospongin-5 **190** and cyclofurospongin 2 **191**.[143] A C_{21} norsesterterpenoid originally reported to have two conjugated double bonds, **192**,[129] has been revised to **193** on the basis of more complete spectroscopic data obtained from a sample isolated from an Australian specimen of *Spirastrella papilosa*.[144] The absolute stereochemistry was determined by degradation, and the name (−)-isotetrahydrofurospongin-1 proposed for this bisfuranoterpene.

Hippospongins E **203** and F **204**, from *Hippospongia* sp. of southern Australian waters, are truncated furanosesterterpenes incorporating diaminoethane.[150] A Korean collection of a sponge of the genus *Sarcotragus* was found to contain sarcotins I **205** and J **206**. These compounds have a unique C_{22} trinorsesterterpene skeleton, and might be degradation products of the corresponding sesterterpenes.[125]

203 R = H
204 R = Ac

205 R = Na
206 R = CH₃
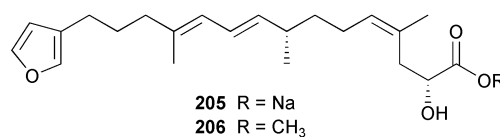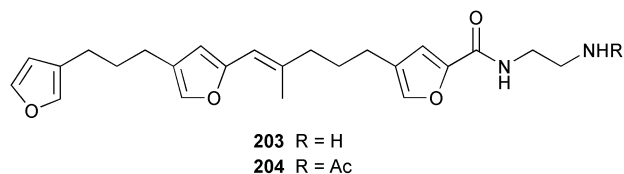
A moderately cytotoxic norsesterterpenoid, sarcotin N **207**, has been isolated from a Korean *Sarcotragus* species, and, in the same study, the previously reported sarcotin I **205** was found to have the 21*R* configuration.[138] Two trinorsesterterpenoid lactams, the sarcotragins A **208** and B **209**, have been isolated from a *Sarcotragus* species from Jaeju Island (Korea).[151]

The suggestion that ircinin 3 **194** and ircinin 4 **195** may arise by cleavage of the open forms of the tetronic acids[145] has been confirmed by the occurrence of the corresponding C_{21} carboxylic acids **196–200** in *Ircinia dendroides*.[146] A synthesis of ircinin 4 **195**, a metabolite of *Ircinia oros*,[145] employed a palladium-catalyzed reaction as the key step.[147]
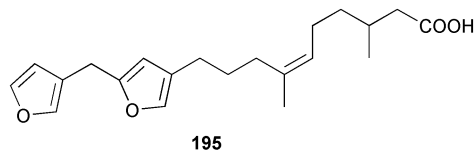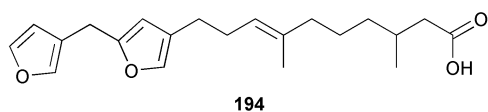
3.3.2 C_{22} norsesterterpenoids. A C_{22} γ-lactone, furodendin **201**, has been reported in the sponge *Phyllospongia dendyi*.[148] A furanoterpene, designated dehydrofurodendin **202**, was isolated from two different species of Madagascan sponges of the genus *Lendenfeldia*, both of which seem to be as yet undescribed.[149] Dehydrofurodendin **202** has been found to be a potent inhibitor of HIV-1 RT-associated DNA polymerase activity. It should be noted that **202** differs from **201** only in the additional double bond at C-16–C-17, which probably results from oxidation occurring at a late stage in its biosynthesis.
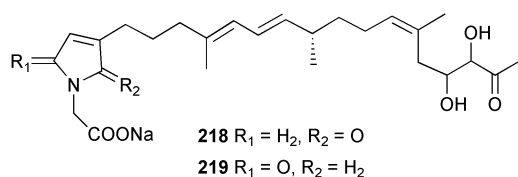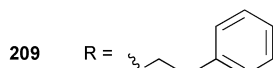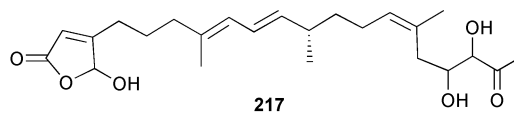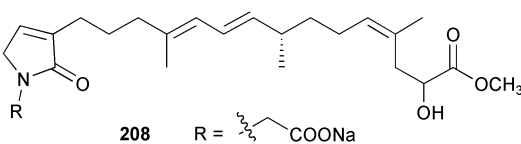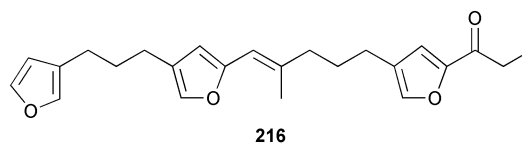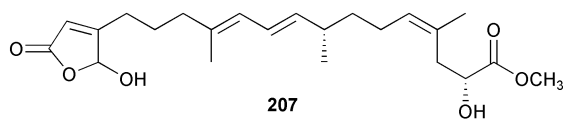

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3.3.3 C$_{24}$ norsesterterpenoids. Konakhin **210**, from a Senegalese sponge, represents a degradation product of the corresponding tetronic acid, and is possibly derived from fasciculatin.[152] The open form of the tetronic acid is a β-keto acid, and on decarboxylation it generates the enol as the substrate for chloroperoxidase. It is worth noticing that the rate-determining step in many electrophilic halogenations is the formation of the enol, and it is therefore possible that the decarboxylation and halogenation steps are biosynthetically linked. Two similar bisfurans, **211** and **212**, have been obtained from a North Adriatic collection of *Ircinia oros*,[153] and were found to be toxic to *Artemia salina* shrimp. Three norsesterterpenoids, **213–215**, isolated from an Okinawa *Ircinia* species, were found to be moderately cytotoxic against the KB cell line.[154]

A new C$_{24}$ furanoterpene, hippospongin D **216**, was isolated from a southern Australian collection of the marine sponge *Hippospongia* sp.[150] A moderately cytotoxic norsesterterpenoid, sarcotin O **217**, along with two pyrrolonorsesterterpenoids, sarcotrine F **218** and isosarcotrine F **219**, were isolated from a Korean *Sarcotragus* species.[138]

3.3.4 C$_{25}$ non-conjugated tetronic acid furanosesterterpenoids. Palinurin **220** is a linear furanosesterterpene previously reported from the Mediterranean sponge *Ircinia variabilis*.[155] Ircinic acid **221** was isolated from marine sponge *Ircinia* sp. collected from Fiji and also found from a Truck lagoon sponge.[156] Palominin **222** is another geometrical isomer obtained[157] from a Caribbean *Ircinia* species. Like many of these compounds from sponges, it possesses ichthyotoxic properties and thus may have a role in protecting the sponge against predators.
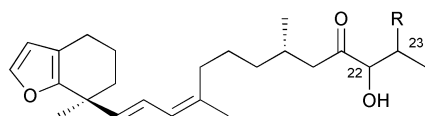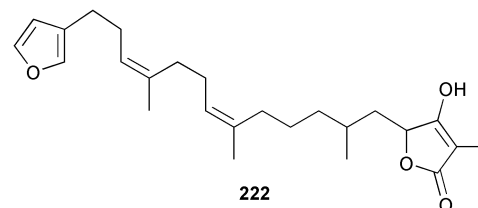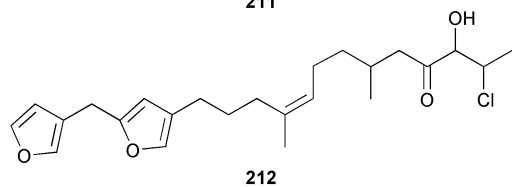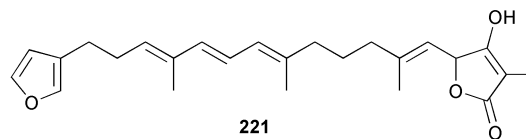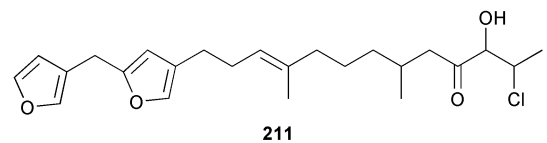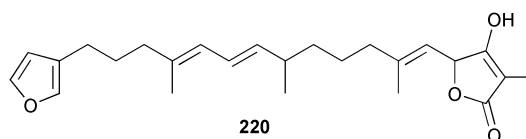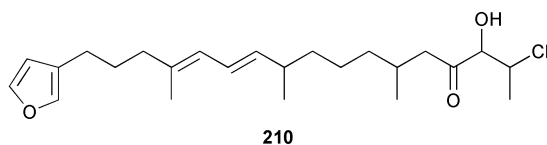
Compound **223** has been reported as a constituent of *Psarnrnocinia rugosa*.[158] The bisfurans spongionellin **224** and dehydrospongionellin have been described in extracts of a *Spongionella* species.[159] The okinonellins A **225** and B **226** are furanosesterterpenes from another *Spongionella* species, which inhibit cell-division in fertilized starfish eggs and again may play a role in marine chemical ecology.[160] Okinellin A **225**, isolated from the Okinawan marine sponge *Hippospongia* sp., is probably identical to hippospongin, and possesses antispasmodic activity.[161] Both the 8*S*,21*S*,22*S*,23*R*- and 8*R*,21*S*,22*S*,23*R*-isomers of okinonellin B **226**, which is a cytotoxic and antispasmodic agent from *Spongionella* sp., have been synthesized, but neither has the same optical rotation as the natural product.[162]

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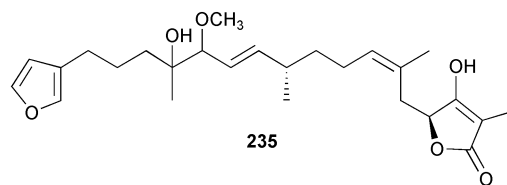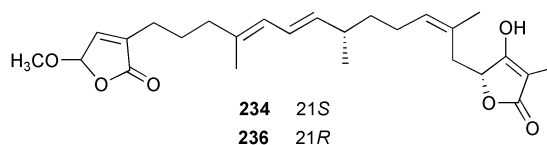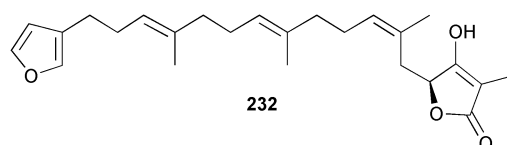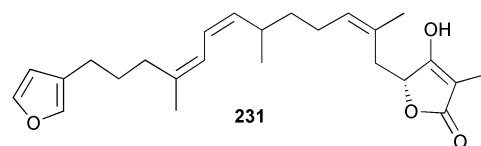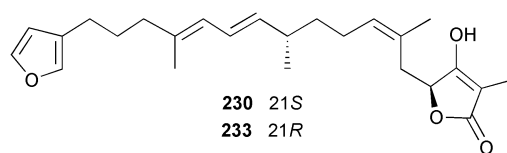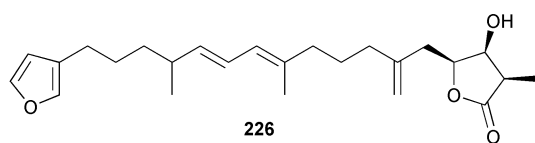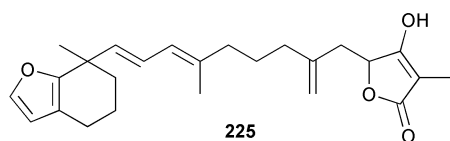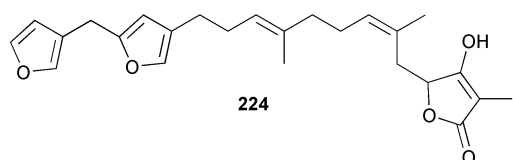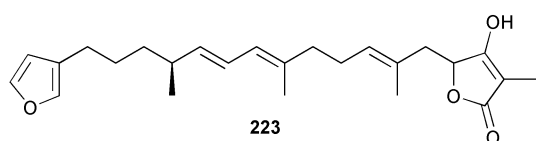
A tetronic acid with antimicrobial activity, **227**, has been isolated from an Australian sponge of the *Psammocinia* genus.[163] Isopalinurin **228**, which is a mild protein phosphatase inhibitor, was obtained from a South Australian *Dysidea* species.[164]

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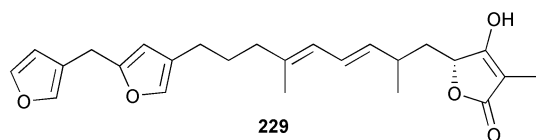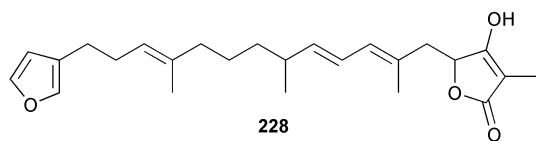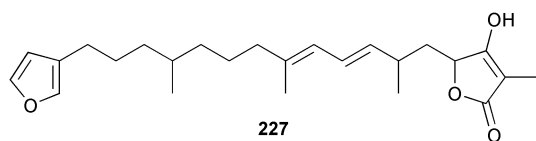
Cometin A **229** contains two furan rings and is another product obtained from Australian sponges.[165] Three cytotoxic furanosesterterpenoids, sacotins A–C **230–232**, were reported from a specimen of *Sarcotragus* sp. collected at Cheju Island, Korea.[166] The cytotoxic sesterterpenoids *epi*-sacotin A **233**, and sarcotins F **234** and M **235**, were isolated from same Korean *Sarcotragus* species.[125] *Epi*-sacotin F **236**[138] was found in two Korean *Sarcotragus* species.

Cytotoxic furanosesterterpenes palinurin **220** [155] and isopalinurin **228** [164] were re-isolated from a marine sponge *Psammocinia* sp. collected from Ulleung Island, Korea. The configuration at C-21 has not been previously investigated, and it has now been determined to be *R* on the basis of CD analysis.[167]

230 21*S*
233 21*R*

231

232

234 21*S*
236 21*R*

235

3.3.5 C$_{25}$ conjugated tetronic acid furanosesterterpenoids. Marine organisms, particularly sponges, have continued to provide a source of linear sesterterpenoids. The terminal units often comprise either a furan or a tetronic acid moiety. Two isomeric linear difuranosesterterpenes, ircinin 1 **237** and ircinin 2 **238**, were obtained from the sponge *Ircinia oros*, and contain a second furan ring.[168] Quite a number of these compounds contain a tetronic acid moiety and show strong antibiotic activity against *Staphylococcus aureus*. These are exemplified by variabilin **239** from *Ircinia variabilis*,[169] its double-bond isomer strobilinin **240** from *Ircinia strobilina*,[170] and fasciculatin **241** from *Ircinia fasciculata*.[171]

237

238
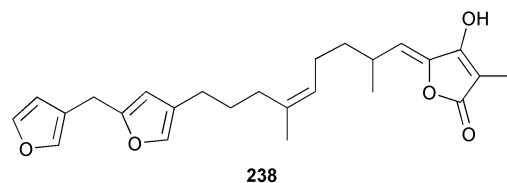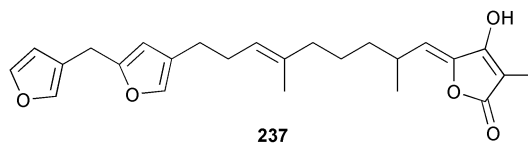
Compounds **242** and **243** occur in *Ircinia dendroides*.[146] Variabilin **239** and its double-bond isomers are quite widespread. As well as being obtained from sponges of the genus *Ircinia*, it has now been found in the New Zealand sponge *Sarcotragus*,[172] whilst 22-deoxyvariabilin **244** has been found in a *Thorecta* species collected

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off the Bay of Islands, New Zealand.[173] In an antimicrobial assay, 22-deoxyvariabilin inhibited the growth of *Staphylococcus aureus*, *Bacillus subtilis*, and *Candida albicans*. NMR studies of ircinins 1 **237** and 2 **238**, two difuranosesterterpenes isolated from a Fijian *Ircinia* sp., have been reported.[156] Two additional oxygenated furanosesterterpenes, **245** and **246**, have been described from an *Ircinia* species collected from Kaikoura, New Zealand.[174]

239

240

241

242

243

244 R₁ = H₂, R₂ = H
245 R₁ = O, R₂ = OH

246
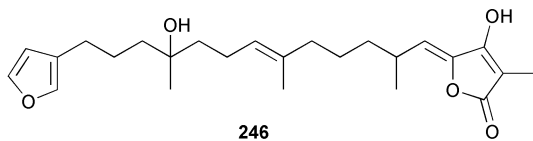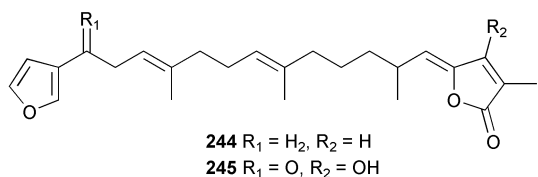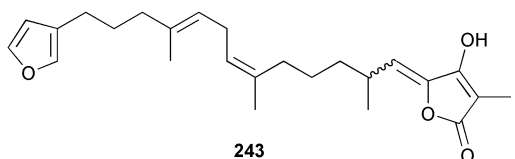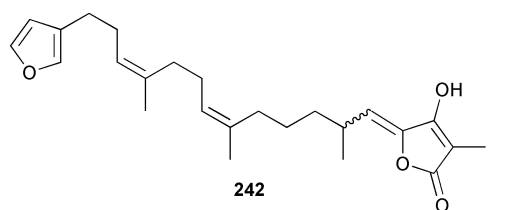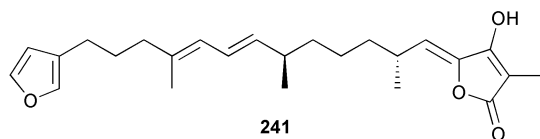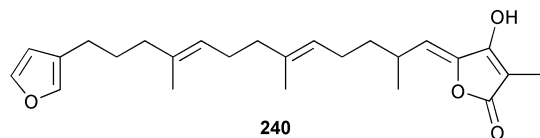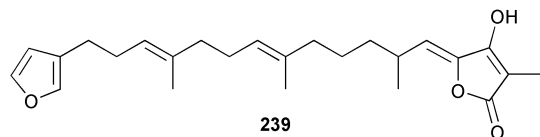
Variabilin is readily available from *Ircinia*, *Psammocinia*, and *Sarcotragus* species, and because it shows promising activity as an antiviral agent, its chemistry has been explored.[175] The tetronic acid moiety acts as a sensitizer for the production of singlet oxygen, which then reacts with the furan to give a range of products including hydroxybutenolides. The 22-O-methyl derivative is stable, and although it retains antiviral activity, it was not possible to dissociate the cytotoxicity from the antiviral activity. The decomposition of these furans has stimulated further

studies[176] on the regioselective oxidation of 3-alkylfurans with singlet oxygen. (18S)-Variabilin **247** is a widespread member of this series, and its absolute stereochemistry and that of some related tetronic acids have been established.[177,178] (18R)-Variabilin **248** has been isolated from the sponge *Ircinia fefix* from Colombia.[179] Two sesterterpenoids, **249** and **250**, isolated from an Okinawa *Ircinia* species, were found to be moderately cytotoxic.[154]

247

248

249 12Z
250 12E
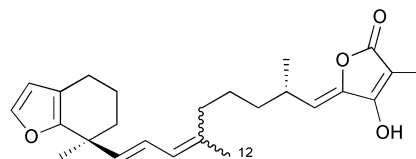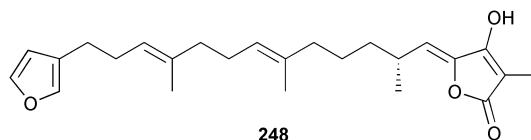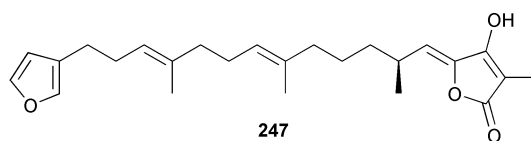
A re-investigation of the structure of strobilinin, originally isolated from *Ircinia strobilina*,[170] revealed that it consisted of two geometrical isomers, **251** and **252**.[180] The structures of (18S)-ircinin-l **237**,[168] (18S)-ircinin 2 **238**,[168] and strobilinins **251** and **252** have been tentatively assigned.[178] Two additional geometrical isomers, (8Z,13Z,20Z)-strobilinin **253** and (7Z,13Z,20Z)-felixinin **255**, were partially characterized after isolation as their 22-O-acetates from Columbian specimens of *I. felix*, *I. strobilina* and *I. campana*.[181] (8Z,13Z,18S,20Z)-Strobilinin **254** and (7E,12Z,18S,20Z)-variabilin **256** from a Maltese specimen of *I. oros* were characterized as their corresponding 22-O-methyl derivatives.[182] The first asymmetric synthesis of the marine furanosesterterpene tetronic acid 18S-variabilin **256**, from the sponge *Ircinia variabilis*, has been reported.[183] An efficient and stereodefined process is employed, featuring lipase-catalyzed asymmetric desymmetrization of two types of propanediol precursors incorporating the terpene skeleton.

251

252

253 18*R*

255 18*S*

254

256

260

261

262

263

264
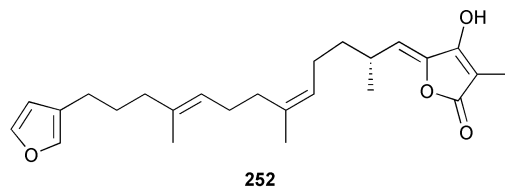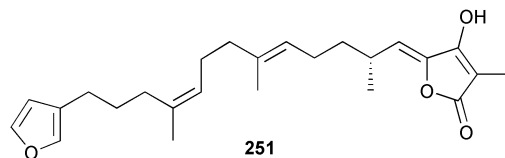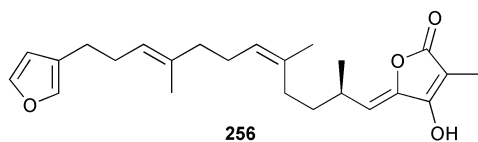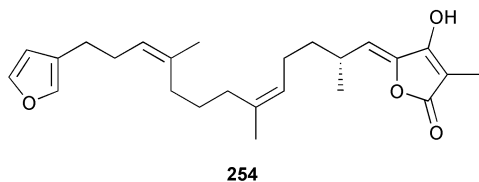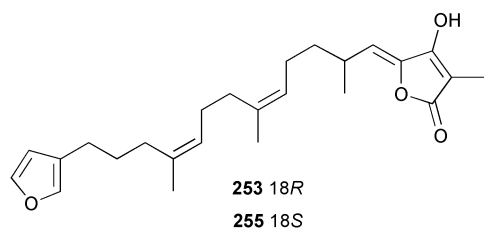
Three new furanosesterterpenes, **257–259**, and the known cytotoxic compounds (7*E*,12*E*,18*R*,20*Z*)-variabilin, (8*E*,13*Z*, 18*R*,20*Z*)-strobilinin, (7*E*,13*Z*,18*R*,20*Z*)-felixinin [also known as (7*E*,13*Z*,18*R*,20*Z*)-variabilin], and (7*Z*,13*Z*,18*R*,20*Z*)-felixinin, were isolated from a Korean marine sponge, *Psammocinia* sp. These compounds were evaluated for cytotoxicity against a panel of five human tumor cell lines, and most of the compounds showed toxicity to SK-MEL-2.[167] A mixture of (8*E*,13*Z*,20*Z*)-strobilinin and (7*E*,13*Z*,20*Z*)-felixinin displayed significant inhibition of DNA replication and a moderate antioxidant profile.[184]

257 12,13-dehydro

258 12,13-dihydro

259
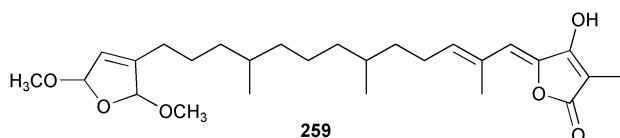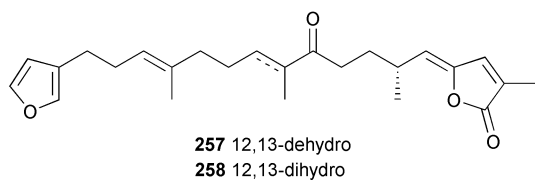
Eight cytotoxic furanosesterterpenoids, namely ircinins 1and 2, sacotins D **260** and E **261**,[166] sacotins G **262** and H **263**,[125] (7*E*,12*E*,18*R*,20*Z*)-variabilin, and (8*E*,13*Z*,18*R*,20*Z*)-strobilinin,[138] were reported from a specimen of *Sarcotragus* sp. collected off Cheju Island, Korea. 22-Deoxy-23-(hydroxymethyl)variabilin **264** was isolated from both the South African nudibranch *Hypselodoris capensis* and the sponge *Fasciospongia* sp. on which it was feeding.[185]

3.3.6 C₂₅ monofuranosesterterpenoids. Simple furans are exemplified by furospongin 3 **265** and furospongin 4 **266**, identified from *Spongia officinalis*.[145] The sponge *Spongia idia* (*Leiosella idia*) from Pt Loma, San Diego, contained idiadione **267**.[186] Idiadione was found to be toxic to the sea star *Pisaster giganteus*, a brine shrimp *Artemia* sp., and the ectoproct *Membranipora memoranacea*, and
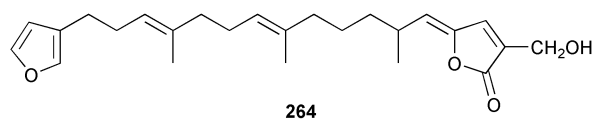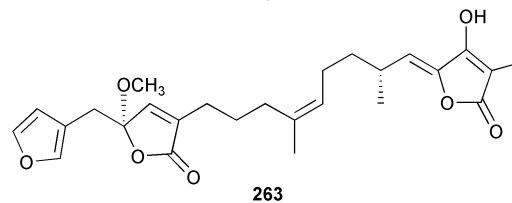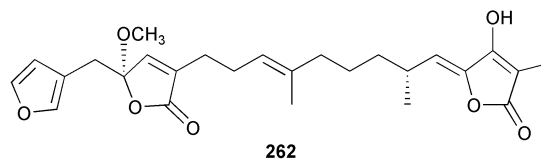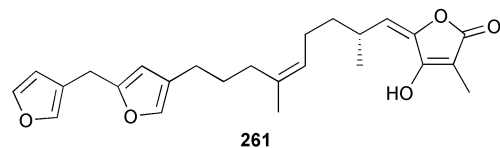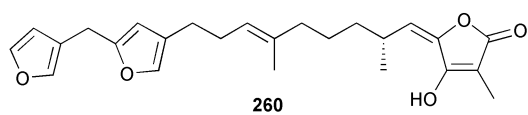
also immobilized the larvae of the red abalone *Haliotis rufescens* in sea-water. Idiadione **267** was synthesized from citronellal, establishing the stereogenic centre as *S*.[187]

265 R₁ = Me, R₂ = COOH

266 R₁ = COOH, R₂ = Me

267
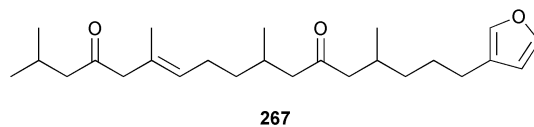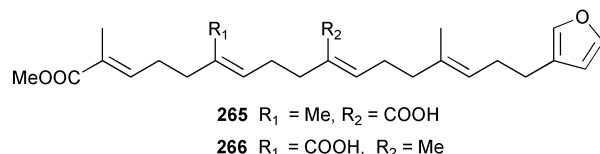
The sesterterpenoid **268**, obtained from the Caribbean sponge *Thorecta horridus*,[188] possessed a marked inflammatory activity, inducing the release of histamine and causing oedema in the paw of test animals. In contrast, thorectolide mono-acetate **269**, obtained from a New Caledonian marine sponge of the genus *Hyrtios*,[189] possessed anti-inflammatory properties. The epoxyfuran carboxylic acid **270** has been isolated from a Western Australian *Spongia* species.[100] A cytotoxic sesterterpenoid, cacospongionolide D **271**, was isolated from *Fasciospongia cavernosa* from the Bay of Naples.[190] A specimen of *Spongia officinalis* from La Caleta, Cádiz, Spain, contained demethylfurospongin 4 **272**, which was weakly cytotoxic against the P-388 cell line.[143] A linear C₂₅ furanoterpene, furospinosulin 1 **273**, has been isolated from *Ircinia spinosula*.[191] The bicyclic lactone astakolactin **274** was obtained from specimens of *Cacospongia scalaris* collected from the Gulf of Astakos, Greece.[192]

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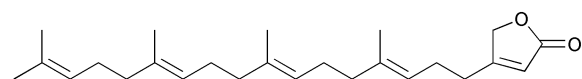
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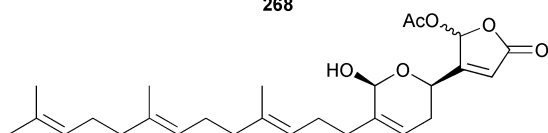
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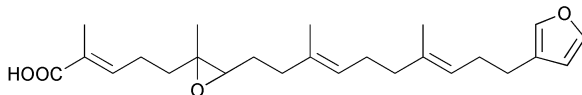
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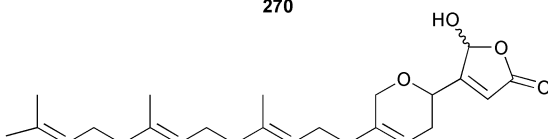
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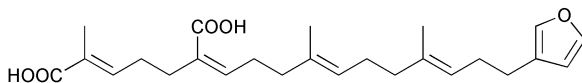
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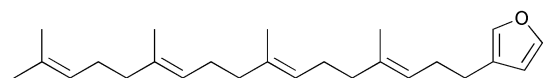
273

274

3.3.7 C₂₅ bisfuranosesterterpenoids.
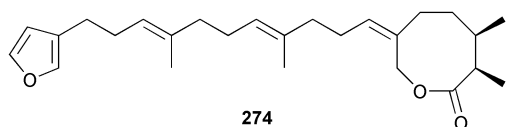
3.3.7 C$_{25}$ bisfuranosesterterpenoids. Luffarin R **275** has been isolated[193] from *Luffariella geometrica*. A cytotoxic sesterterpenoid, (6Z)-luffarin-V **276**, has been isolated from *Fasciospongia cavernosa* from the Bay of Naples.[190]
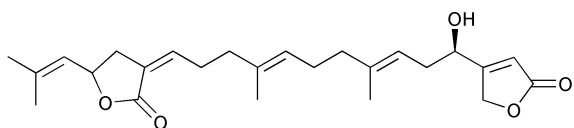
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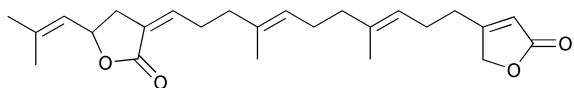
276

3.3.8 C$_{25}$ trisfuranosesterterpenoids. Three C$_{25}$ furanoterpenes, hippospongins A–C **277–279**, were isolated from a southern Australian collection of the marine sponge *Hippospongia* sp. Hippospongin A **279** was found to be a mild antibiotic, inhibiting the growth of *Staphylococcus aureus*.[150]
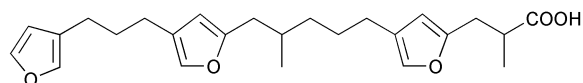
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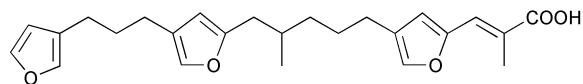
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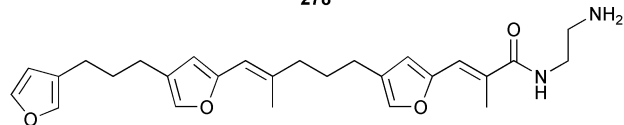
279

3.3.9 Salts of sesterterpenoids. Four unstable sulfate esters of furanosesterterpenes, **280–283**, were obtained from *Ircinia variabilis* and *I. oros* of the northern Adriatic Sea.[194] A Californian sponge of the family Halichondriidae contained sulfated sesterterpene halisulfate 3 **284**,[195] which possesses antimicrobial and anti-inflammatory properties. The 22-*O*-sulfates **285** and **286** of palinurin and fasciculatin, which were toxic to brine shrimp *Artemia salina*, were isolated from *Ircinia variabilis* and *I. fasciculata*, respectively.[196] A sodium salt of the pyrroloterpenoid sarcotragin A **208** was isolated from a *Sarcotragus* sp. collected from Jaeju Island in Korean waters.[151] A sodium salt of trinorsesterterpene acid sarcotin I **205**,[125] and the sodium salts of four pyrroloterpenoids, sarcotrines E **287** and F **288** and isosarcotrines E **218** and F **219**,[138] were isolated from the Korean sponge *Sarcotragus* sp.
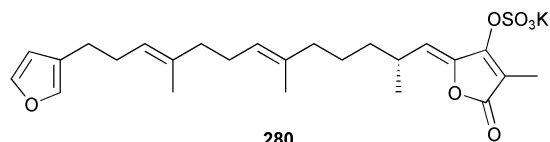
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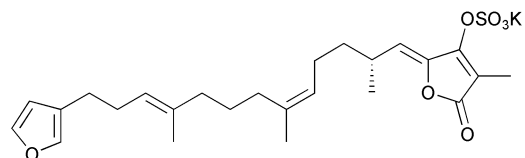
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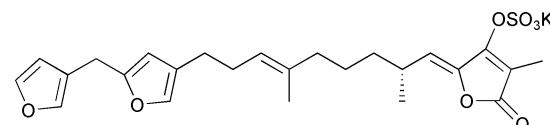
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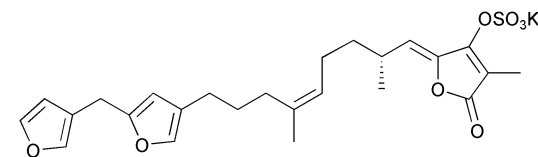
283

3.3.10 Esters of sesterterpenoids. (18*R*)-Variabilin-11-methyloctadecanoate ester **289** has been isolated from the sponge *Ircinia fefix* from Colombia.[197] The same sponge has yielded nine novel fatty acid esters, (7*E*,12*E*,18*R*,20*Z*)-variabilin

284

285

286

287 R₁ = H₂, R₂ = O
288 R₁ = O, R₂ = H₂
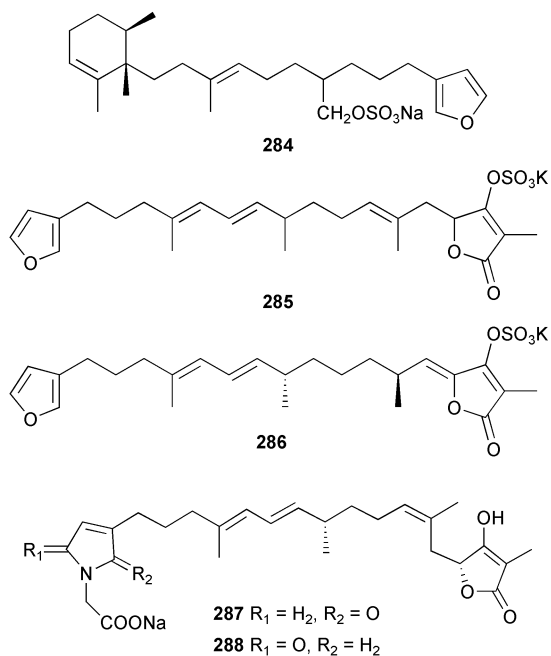
(5Z,9Z)-22-methyltricosadienoate, (7E,12E,18R,20Z)-variabilin (5Z,9Z)-tetracosadienoate, (7E,12E,18R,20Z)-variabilin hexadecanoate, (7E,12E,18R,20Z)-variabilin 10-methylhexadecanoate, (7E,12E,18R,20Z)-variabilin 15-methylhexadecanoate, (7E,12E, 18R,20Z)-variabilin 14-methylhexadecanoate, (7E,12E,18R,20Z)-variabilin 9-octadecenoate, (7E,12E,18R,20Z)-variabilin octadecanoate, and (7E,12E,18R,20Z)-variabilin 2,11-dimethyloctadecanoate (**290–298**).[198]

3.4 Furanotriterpenoids

3.4.1 C₃₀ terpenoids. A C₃₀ furanoterpene, furospinosulin 2 **299**, has been isolated from *Ircinia spinosula*.[191] Three triterpenoids, *viz.* hydroxymokupalide **300**, acetoxymokupalide **301**, and mokupalide **302**, have been obtained from a species of the genus *Megalopastas*.[199,200] The structure of mokupalide **302** was confirmed by total synthesis.[201]

299

300 R = OH
301 R = OAc
302 R = H
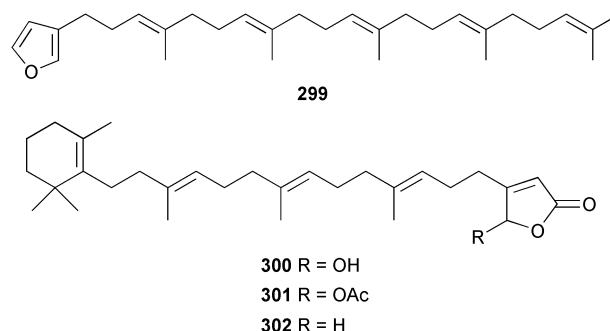
(Z,E,E)-Cupaniopsin A, (Z,E,Z)-cupaniopsin A, the 29-methyl ester of (Z,E,E)-cupaniopsin A, (Z,E,Z)-cupaniopsin C, 22-hydroxy-(Z,E,Z)-cupaniopsin C, 23-hydroxy-(Z,E,Z)-cupaniopsin C, (Z,E,Z)-cupaniopsin A methyl ester, and (Z,E,Z)-cupaniopsin E (**303–310**) were isolated from the bark of *Cupaniopsis trigonocarpa* Radlk. & Guillaumin, *C. azantha* Radlk. and *C. phallacrocarpa* F. Adema (Sapindaceae). Five of them exhibited potent binding activity on the peroxisome proliferator-activated receptor, the most potent being (Z,E,E)-cupaniopsin A **303**. This is the first report of linear furanotriterpenes isolated from the plant kingdom.[202]

R =

289

294

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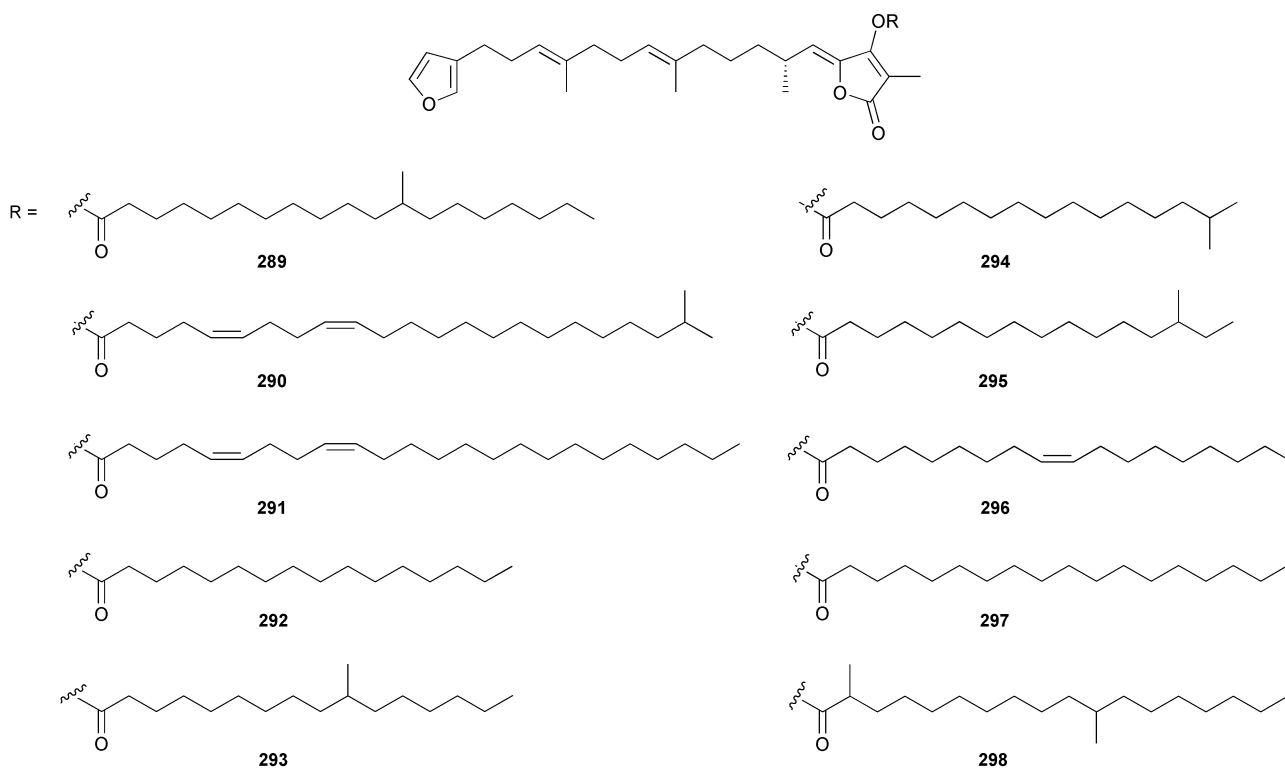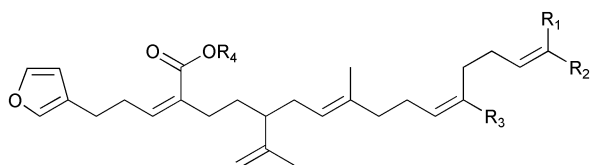
303 16*E* R$_1$ = CH$_3$, R$_2$ = CH$_3$, R$_3$ = COOH, R$_4$ = H
304 16*Z* R$_1$ = CH$_3$, R$_2$ = CH$_3$, R$_3$ = COOH, R$_4$ = H
305 16*E* R$_1$ = CH$_3$, R$_2$ = CH$_3$, R$_3$ = COOH, R$_4$ = CH$_3$
306 16*Z* R$_1$ = CH$_3$, R$_2$ = CH$_3$, R$_3$ = CH$_3$, R$_4$ = H
307 16*Z* R$_1$ = CH$_2$OH, R$_2$ = CH$_3$, R$_3$ = CH$_3$, R$_4$ = H
308 16*Z* R$_1$ = CH$_3$, R$_2$ = CH$_2$OH, R$_3$ = CH$_3$, R$_4$ = H
309 16*Z* R$_1$ = CH$_3$, R$_2$ = CH$_3$, R$_3$ = COOH, R$_4$ = CH$_3$

310
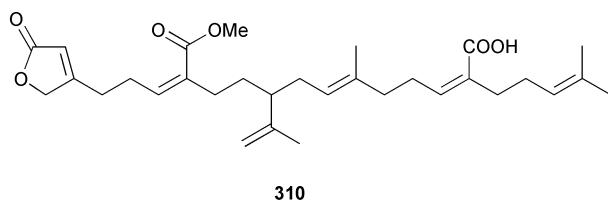
3.4.2 C$_{31}$ terpenoids. It has been suggested that a C$_{31}$ difuranoterpene, difurospinosulin **311** (isolated from *Ircinia spinosula*), could be derived from a C$_{35}$ linear furanoterpene by the loss of four carbon atoms.[191] A C$_{31}$ furanoterpene alcohol sulfate, named ircinol sulfate **312**, has been isolated from a marine sponge, *Ircinia* sp., collected off New Caledonia.[203] Ircinol sulfate is the second example of a C$_{31}$ furanoterpene encountered in marine sponges.

3.4.3 C$_{35}$ terpenoids. A linear C$_{35}$ furanoterpene, furospinosulin-3 **313**, has been isolated from *Ircinia spinosula*.[191]

4 Pyrroloterpenoids

4.1 Pyrrolosesquiterpenoids

Pyrrolostatin **314**, a lipid peroxidation inhibitor, was isolated from the culture of *Streptomyces chrestomyceticus* EC40.[204] Pyrrolostatin inhibited lipid peroxidation in rat brain homogenate. A *Streptomyces* sp. (NPS008187) isolated from a marine sediment collected in Alaska was found to produce three pyrrolosesquiterpenes, glyciapyrroles A **315**, B **316**, and C **317**. Glyciapyrrole A
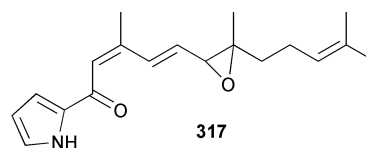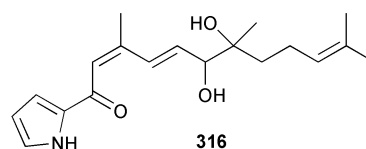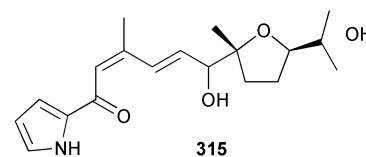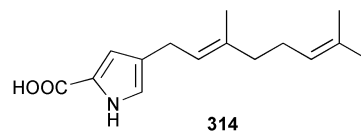
inhibited both colorectal adenocarcinoma HT-29 and melanoma B16-F10 tumor cell growth.[205]

4.2 Pyrrolosesterterpenoids and norsesterterpenoids

The pyrrolosesterterpenes sarcotrines A **318**, B **320**, C **322**, D **324**, E **287** and F **218**, *epi*-sarcotrines A **319**, B **321** and C **323**, and isosarcotrines E **288** and F **219**[125,138] have been isolated from a marine sponge of the genus *Sarcotragus*. Two trinorsesterterpenoid lactams, sarcotragins A **208** and B **209**, with structures similar to those of the sarcotrines, have been isolated from another *Sarcotragus* sponge collected from Jaeju Island in Korean waters.[151] It is quite feasible that sarcotrines and sarcotragins share the same biogenetic precursor, and that the latter are the degradation products of the former. Two microbial metabolites of palinurin **220**[155] (re-isolated from a Red Sea sponge, *Ircinia echinata*), palinurines A **325** and B **326**, are produced by the fungus *Cunninghamella* sp. NRRL 5695.[206] The possible transformation of furans to amides (*viz.* dehydro-3-enepyrrolidin-2-one and dehydro-3-enepyrrolidin-5-one) through a biomimetic reaction is certain to have applications in synthetic chemistry.

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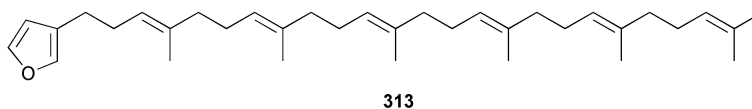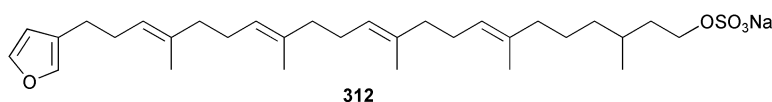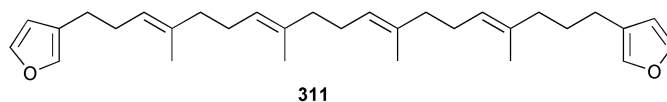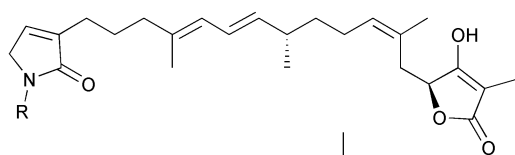
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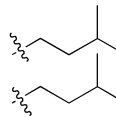
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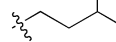
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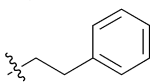
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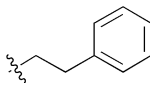
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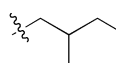
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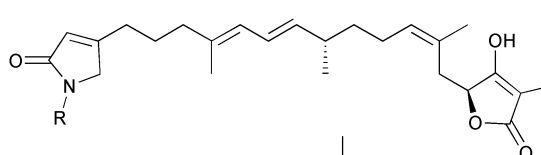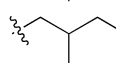
324 R =

325 R₁ = H₂, R₂ = O
326 R₁ = O, R₂ =H₂
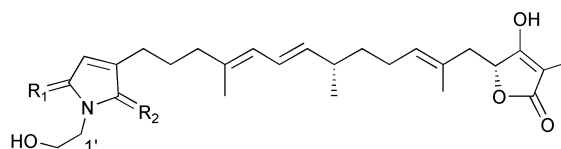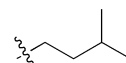
325 $R_1 = H_2, R_2 = O$
326 $R_1 = O, R_2 = H_2$

5 Acknowledgements

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