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REVIEW

Marine natural products†

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Covering: 2009. Previous review: *Nat. Prod. Rep.*, 2010, **27**, 165

This review covers the literature published in 2009 for marine natural products, with 857 citations (588 for the period January to December 2009) referring to compounds isolated from marine microorganisms and phytoplankton, green, brown and red algae, sponges, cnidarians, bryozoans, molluscs, tunicates, echinoderms, mangroves and other intertidal plants and microorganisms. The emphasis is on new compounds (1011 for 2009), together with the relevant biological activities, source organisms and country of origin. Biosynthetic studies, first syntheses, and syntheses that lead to the revision of structures or stereochemistries, have been included.

1 Introduction

This review is of the literature for 2009 and describes 1011 new compounds from 352 articles, a small decrease from the number (1065) of compounds reported for 2008.[1] As in previous reviews, the structures are shown only for new compounds, or for 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 are referenced, but separate structures are generally not shown. Where the absolute configuration has been determined for all stereocentres in a compound, the identifying diagram number is distinguished by addition of the † symbol. In the previous review,[1] a new section describing compounds from mangroves and other intertidal species was introduced. That section included compounds from microorganisms isolated from mangroves and other sources in the intertidal zone. For consistency, all reports for microorganisms from that region will now appear in the 'Marine microorganism and phytoplankton' section of this review. In compiling this review, large differences were noted in the detail with which the geographic location and taxonomy of the field samples were recorded. As regards location, these ranged from highly specific with GPS coordinates to "*source not given*" or just a wide geographical area such as "*South Pacific*". For taxonomy there were variations ranging from full genus/species description to "*unidentified species*". In one classic example, which has reluctantly been included in this review, it was "*unidentified marine fungus, source not given*". The requirements of the leading journals in the field of natural products are quite specific and unless full descriptors are provided, the paper will not be considered for publication. In this electronic age there is no reason not to have an exact description of the location, and with the molecular biology tools now readily available, assignment at the genus level is usually attainable. To ensure that the reporting of marine natural products research is carried out with the highest possible accuracy, it would be very desirable to get away completely from the "*unidentified marine fungus, source not given*" descriptor. There are guidelines available: as a reader of this review you may also be a reviewer of manuscripts – if not now, perhaps in the future. It would be helpful to the marine

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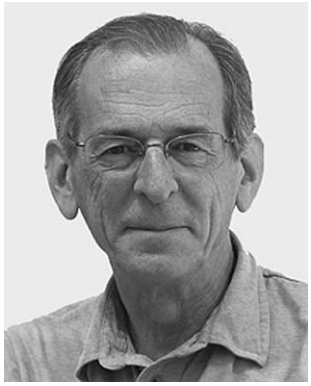
† This paper is part of an *NPR* themed issue on Marine Natural Products.

natural products community and to the Editors if such glaring discrepancies were pointed out in any papers you might referee.

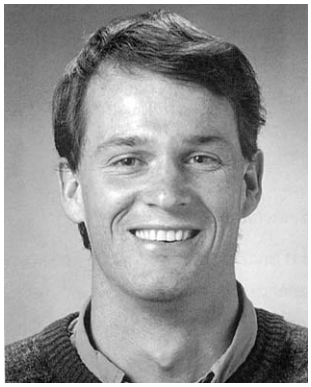
2 Reviews

A comprehensive review of marine natural products reported in 2007 has appeared,[2] as well as the highlights of compounds reported in 2008.[3] A focus on drug development and pharmacology of marine natural products has been described in several reviews.[4–8] Reviews on more specific types of biological activities include antimalarials,[9–12] antitumour compounds[13–19] and antifoulants.[20,21] Specific compounds that were reviewed include the halichondrins,[22] variolins,[23] aplysinopsins,[24] and aplyronine A,[25] while more general classes of compounds such as sterols from soft corals,[26] aziridine alkaloids,[27] benzothiazole alkaloids,[28] muscarine, imidazole, oxazole and thiazole alkaloids,[29] ribosomal peptides,[30] phospholipids,[31] terpenyl-purines,[32] non-methylene-interrupted fatty acids,[33] molluscan antimicrobial peptides,[34] indole alkaloids with a non-rearranged monoterpenoid unit,[35] diterpenes from gorgonians,[36] sesquiterpenoids,[37] diterpenoids,[38] verticillane derivatives,[39] 2,11-cyclised cembranoids from the Caribbean[40] and siderophores were reported.[41,42] Conotoxins and



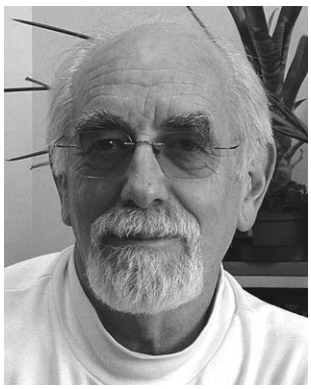
John Blunt

John Blunt obtained his BSc (Hons) and PhD degrees from the University of Canterbury, followed by postdoctoral appointments in Biochemistry at the University of Wisconsin–Madison, and with Sir Ewart Jones at Oxford University. He took up a lectureship at the University of Canterbury in 1970, from where he retired as an Emeritus Professor in 2008. His research interests are with natural products, and the application of NMR techniques to structural problems.



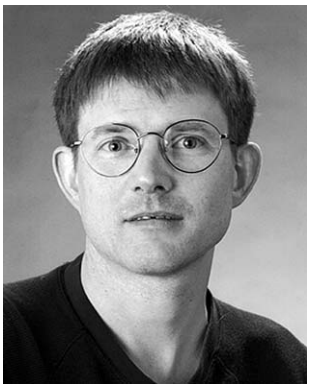
Brent Copp

Brent Copp received his BSc (Hons) and PhD degrees from the University of Canterbury, where he studied the isolation, structure elucidation and structure–activity relationships of biologically active marine natural products under the guidance of Professors Blunt and Munro. He undertook postdoctoral research with Jon Clardy at Cornell and Chris Ireland at the University of Utah. 1992–93 was spent working in industry as an isolation chemist with Xenova Plc, before returning to New Zealand to take a lectureship at the University of Auckland, where he is currently an Associate Professor.



Murray Munro

Murray Munro, now an Emeritus Professor at the University of Canterbury, Christchurch, New Zealand, worked on natural products, mainly of New Zealand origin, right through his career. This started with diterpenoids (PhD), followed by alkaloids during a postdoctoral spell with Alan Battersby at Liverpool. Following a sabbatical with Ken Rinehart at the University of Illinois in 1973, an interest in marine natural products developed with a particular focus on bioactive compounds. In recent years his research interests have widened to include terrestrial and marine fungi and actinomycetes as well as marine invertebrates.



Peter Northcote

Peter Northcote received his BSc and PhD degrees from the University of British Columbia, Canada, where he was a member of R. J. Andersen's marine natural products research group. He carried out postdoctoral research with Professors Blunt and Munro at the University of Canterbury before taking a position as a senior research scientist at Lederle Laboratories, American Cyanamid Co. He joined the faculty of the Victoria University of Wellington in 1994, where he is currently an Associate Professor in organic chemistry.

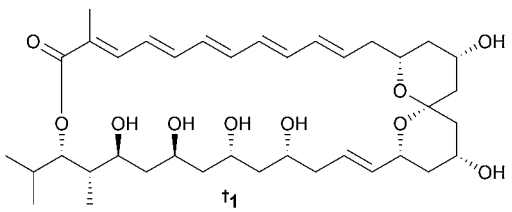
Michèle Prinsep

Michèle Prinsep received her BSc (Hons) and PhD degrees from the University of Canterbury, where she studied the isolation and structural elucidation of biologically active secondary metabolites from sponges and bryozoans under the supervision of Professors Blunt and Munro. She undertook postdoctoral research on cyanobacteria with Richard Moore at the University of Hawaii before returning to New Zealand to take up a lectureship at the University of Waikato, where she is currently a Senior Lecturer.

other peptide toxins continue to be reviewed extensively.[43–49] Compounds from particular types of organism were covered in reviews on *Sinularia* spp.[50] semi-mangroves,[51] bacteria[52–54] and sponges,[55,56] while the chemistry and biology of some Okinawan marine natural products have been described.[57] The methods for study, structural types and biological properties of the fucoidans have been summarised.[58] There has been a commentary on sponge–microbial symbioses.[59] Various aspects of the biosynthesis of marine natural products have been reviewed.[60–63] The fifth in a companion series providing an overview of synthetic aspects of marine natural products, covering publications in 2007, has appeared,[64] while more specific reviews that appeared in 2009 relating to the synthesis of marine natural products will be referenced in the seventh of that broad review series. Recent synthetic studies leading to structural revision of marine natural products have been collated.[65] The MarinLit database[66] has been updated and was used as the literature source for the preparation of this present review.

3 Marine microorganisms and phytoplankton

Microorganisms of marine origin continue to be a rich source of novel and/or biologically active metabolites, with 273 new compounds reported in 2009. Marinisporolides A **1** and B **2** are polyene macrolides isolated from culture of an actinomycete from the new genus *Marinispora* [sediment, (La Jolla, California)]. Under ambient light conditions marinisporolides A **1** and B **2** photoisomerised to the geometric isomers marinisporolide C–E, which were most likely artefacts. Marinisporolide A **1** had modest activity against *Candida albicans*.[67]



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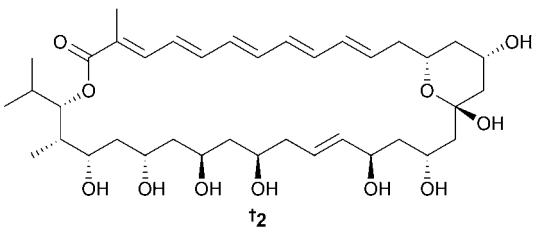

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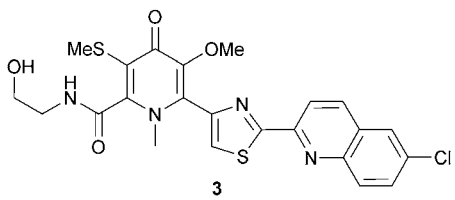

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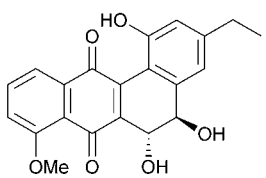
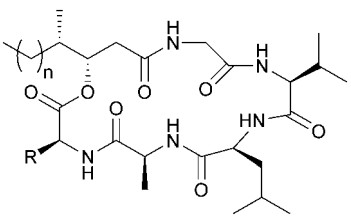


†**4**

Culture of *Saccharomonospora* sp. [sediment, (La Jolla, California)] yielded the alkaloid lodopyridone **3** with a unique carbon skeleton and modest cytotoxicity to HCT-116 cells.[68] An angucyclinone **4**, isolated from culture of *Saccharopolyspora taberi*, [sponge, (Tanzanian coast, Africa)], was active against a selection of human cancer cell lines.[69]

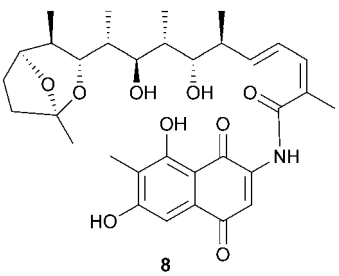
Of the arenamides A–C **5–7** from *Salinispora arenicola* [sediment, (Great Astrolabe Reef, Fiji)], **5** and **6** blocked tumour necrosis factor (TNF)-induced activation, inhibited nitric oxide and prostaglandin E_2 production and were moderately cytotoxic to HCT-116 cells.[70] Culture of *S. arenicola* [sediment, (Yap, Micronesia)] yielded the rifamycin antibiotic salinisporamycin **8**, which inhibited growth of A549 cells and displayed activity against *Bacillus subtilis* and *Staphylococcus aureus*.[71]



†**5** n = 5, R =

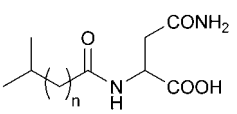
†**6** n = 3, R =

7 n = 5, R =



8

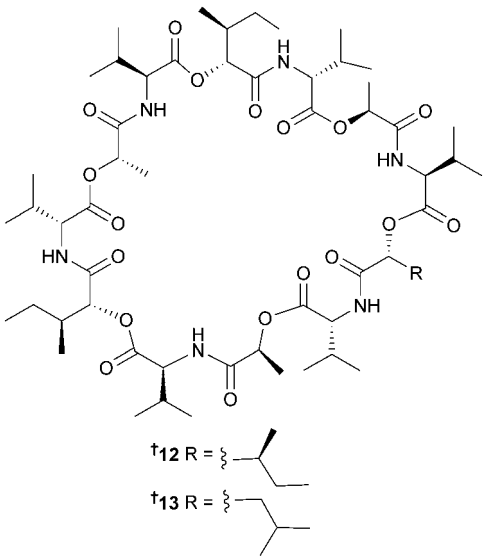
Antiprotealide, described previously as a synthetic compound,[72] was isolated as a natural product from a large-scale fermentation of *S. tropica*.[73] Culture of *Bacillus pumilus* [sediment, (Bahamas)] yielded lipoamides A–C **9–11**, in addition to known compounds, of which amicoumacin A[74] had activity against methicillin-resistant *Staphylococcus aureus* (MRSA).[75]



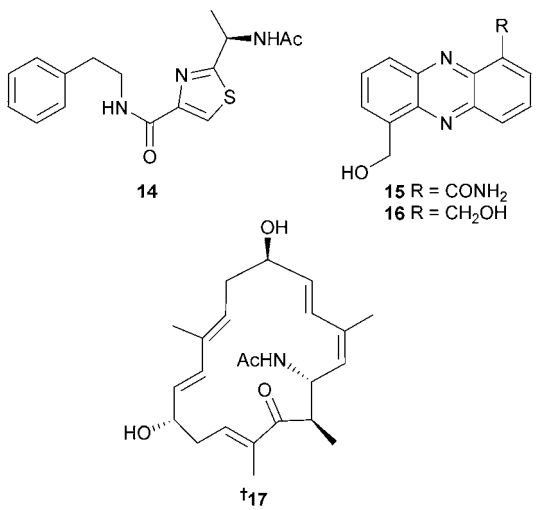
9 n = 7
10 n = 8
11 n = 9

Bacillistatins 1 **12** and 2 **13** are cyclodepsipeptides from *Bacillus silvestris* [Pacific Ocean crab, (Quellon, Chiloé Is., Chile)] and were strongly inhibitory against a number of human cancer cell lines and active against *Streptococcus pyrogenes* and

antibiotic-resistant *S. pneumoniae*.[76] Bacillistatin 2 **13** was synthesised *via* a 24-step convergent route utilising the Mitsunobu reaction.[77]

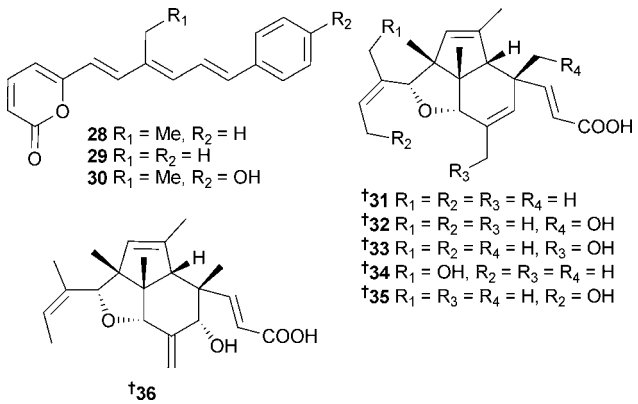


Culture of *B. vallismortis* [*Dysidea avara*, (Sanya Is., South China Sea)] yielded a thiazole alkaloid, neobacillamide A **14**.[78] 6-Hydroxymethyl-1-phenazine-carboxamide **15** and 1,6-phenazinedimethanol **16**, isolated from *Brevibacterium* sp. [purple vase sponge *Callyspongia* sp., (Kyung-po, S. Korea)], exhibited potent activity against *Enterococcus hirae* and *Micrococcus luteus*.[79] Scale-up of a culture of *Hahella chejuensis* [sediment, (Gejae Is., S. Korea)], source of chejuenolides A and B,[80] gave a 17-membered cyclic polyene, chejuenolide C **17**.[81]

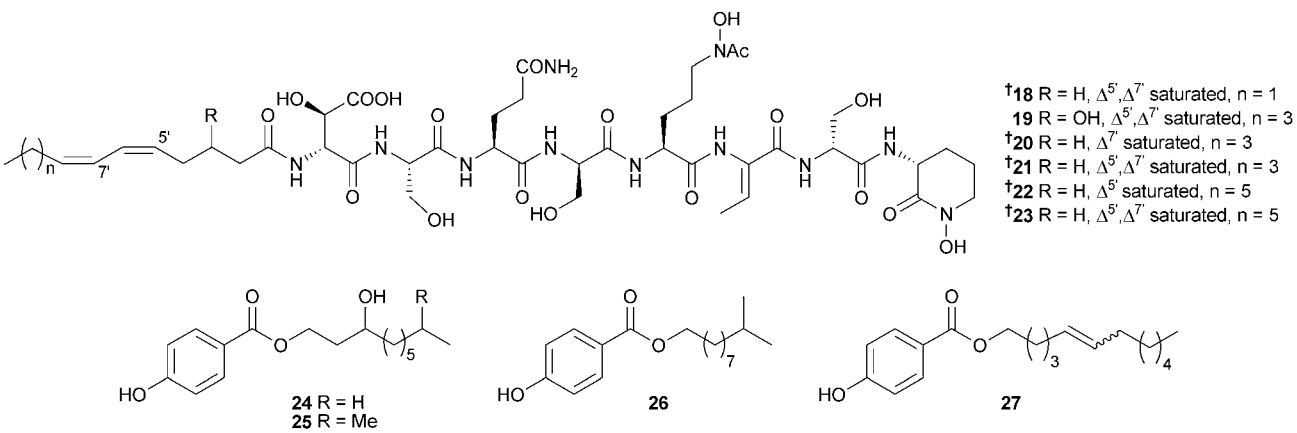


The amphiphilic siderophores loihichelins A–F, **18–23**, were isolated from *Halomonas* sp. (Loihi seamount, Hawai'i).[82] Culture of *Microbulbifer* sp. [calcareous sponge *Leuconia nivea*, (Concarneau, France)], yielded natural parabens. Of these, **24–27** were new with bacteriocidal or bacteriostatic properties, while the known octyl,[83] decyl[84] and dodecylparabens[85] were isolated for the first time as natural products.

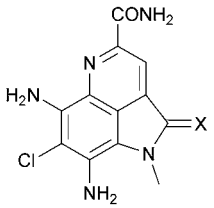
Culture of the myxobacterium *Nannocystis exedens* [sand, (Crete)] yielded phenylnannolones A–C **28–30**. Phenylnannolone A **28** inhibited P-glycoprotein and reversed daunorubicin resistance in A2780 ovarian cancer cells. Biosynthetic studies of **28** indicated a polyketide origin with a phenylalanine-derived starter unit of novel biosynthetic origins.[86] All of the indoxamycins A–F, **31–36**, unusual polyketides with six consecutive chiral centres isolated from *Streptomyces* sp. [sediment, (Kochi Harbour, Japan)], were moderately cytotoxic to HT-29 cells. Biosynthetic-feeding experiments indicated that indoxamycin A **31** was assembled from propionate units which initially formed a pentamethylindenofuran.[87]



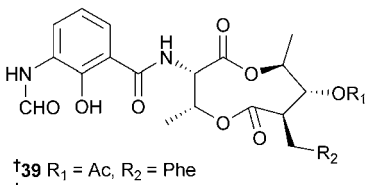
Ammosamides A **37** and B **38** are chlorinated tricyclic pyrroloquinoline alkaloids from *Streptomyces* sp. [sediment, (Bahamas)]. Ammosamide A **37** contains an unusual thio-γ-lactam ring and gradually converted to ammosamide B **38** on exposure



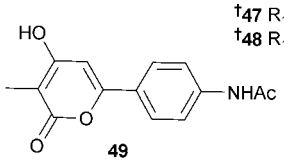
to air. Both **37** and **38** displayed potent cytotoxicity against a number of cancer cell lines. The target was identified as the motor protein, myosin.[88,89] Splenocins A–J **39–48** are nine-membered bis-lactones isolated from *Streptomyces* sp. [sediment, (La Jolla, California)] with potential for development for asthma treatment, due to suppression of cytokine production with minimal mammalian cell cytotoxicity.[90] Culture of *Streptomyces* sp. [sediment, (Atlantic Ocean)] resulted in isolation of albidopyrone **49**, a moderate inhibitor of protein-tyrosine phosphatase B.[91]



37 X = S
38 X = O

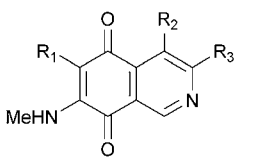


†**39** R_1 = Ac, R_2 = Phe
†**40** R_1 = *i*-propanoyl, R_2 = Phe
†**41** R_1 = *s*-butanoyl, R_2 = Phe
†**42** R_1 = benzoyl, R_2 = Me
†**43** R_1 = benzoyl, R_2 = $(CH_2)_2Me$
†**44** R_1 = benzoyl, R_2 = $(CH_2)_3Me$
†**45** R_1 = benzoyl, R_2 = $(CH_2)_4Me$
†**46** R_1 = benzoyl, R_2 = $CH(Me)(CH_2)_3Me$
†**47** R_1 = benzoyl, R_2 = Phe
†**48** R_1 = H, R_2 = Phe

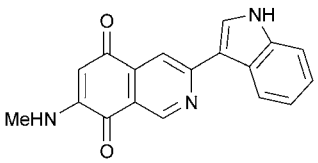


49

Mansouramycins A–D **50–53** are isoquinolinequinones obtained from culture of *Streptomyces* sp. [mud, (Jade Bay, German North Sea Coast)]. A related compound, 3-methyl-7-(methylamino)-5,8-isoquinolinedione of synthetic origin,[92] was isolated for the first time. Mansouramycin A **50** was moderately active against *S. aureus*, *B. subtilis* and *E. coli* and a strong inhibitor of the microalgae *Chlorella vulgaris*, *C. sorokiniana* and *Scenedesmus subspicatus.* All isolated compounds exhibited high cytotoxicity when tested in a panel of 36 tumour cell lines, with several showing high selectivity.[93]



50 R_1 = H, R_2 = R_3 = Me
51 R_1 =Cl, R_2 = H, R_3 = Me
52 R_1 = R_2 = H, R_3 = COOMe

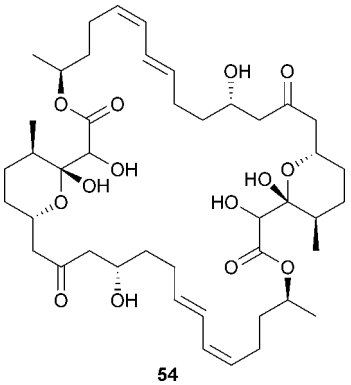


53

Fermentation of *Streptomyces* sp. [sediment, (Madagascar)] gave tartrolon D **54** which was strongly cytotoxic to A549, HT-29 and MDA-MB-231 cells,[94] while naseseazines A **55** and B **56**, diketopiperazines with a new dimeric framework, were isolated from culture of *Streptomyces* sp. [sediment, (Fiji)].[95]

Culture of another *Streptomyces* sp. [sediment, (Miyazaki Harbor, Japan)] gave two trialkyl-substituted aromatic acids, lorneic acids A **57** and B **58**. Both inhibited human platelet phosphodiesterase 5 (PDE5), but **57** was the stronger inhibitor.[96]

Tirandamycins C **59** and D **60** are dienoyl-tetramic acids isolated from fermentation of *Streptomyces* sp. [sediment, (Salt Cay,



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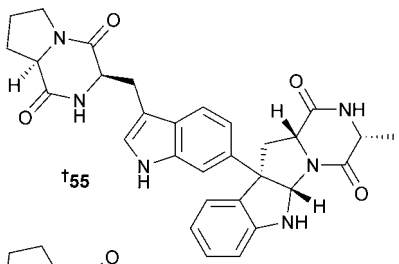
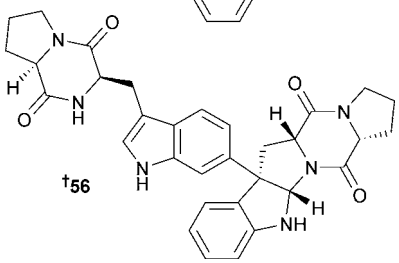
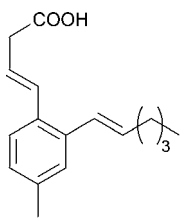


†**55**



†**56**



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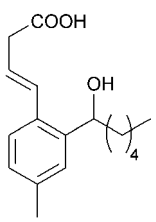
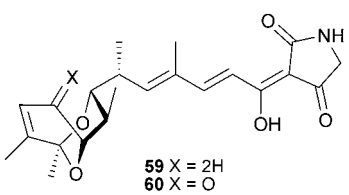


58

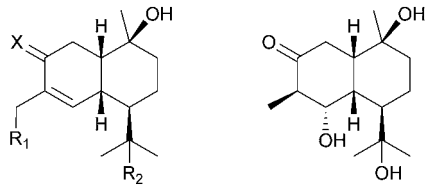
Virgin Islands)] along with the previously identified compounds tirandamycin A[97] and B.[98] This represented the first marine isolation of tirandamycins A and B. All metabolites displayed activity against vancomycin-resistant *Enterococcus faecalis* (VRE) with varying degrees of potency.[99]



59 X = 2H
60 X = O

Culture of *Streptomyces* sp. [sand, (Qingdao coast, China)] yielded two new sesquiterpenes, 15-hydroxy-T-muurolol **61** and 11,15-dihydroxy-T-muurolol **62**. The absolute configurations of

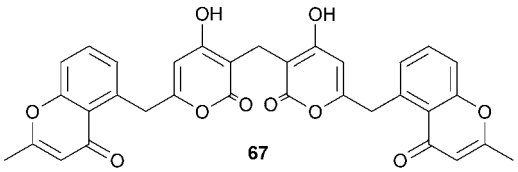
a number of sesquiterpenes isolated previously from the same strain and reported as amorphanes[100] have now been revised to those of the muurolane series, namely **63–66**. T-muurolol[101] and 3α-hydroxy-T-muurolol,[102] known cadinenes from plants, were isolated from a marine source for the first time.[103]



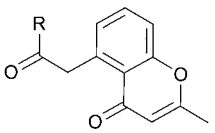
†**61** X = 2H, R_1 = OH, R_2 = H
†**62** X = 2H, R_1 = R_2 = OH
†**63** X = O, R_1 = R_2 = H
†**64** X = 2H, R_1 = H, R_2 = OH
†**65** X = O, R_1 = OH, R_2 = H

†**66**

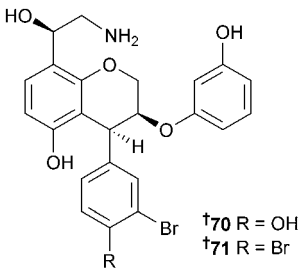
The polyketides phaeochromycins F–H, **67–69**, were obtained from *Streptomyces* sp. [sediment, (West Pacific Ocean)],[104] while ammonificins A **70** and B **71**, both hydroxyethylamine chroman derivatives, were isolated from *Thermovibrio ammonificans* [hydrothermal vent, (East Pacific Rise)].[105]



67

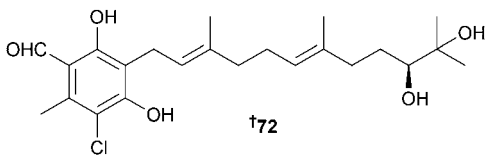


68 R = Me
69 R = $CH_2CH(OH)Me$



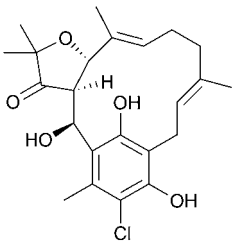
†**70** R = OH
†**71** R = Br

Fermentation of *Acremonium* sp. [sponge, *Stelletta* sp., (Jeju Is., S. Korea)], yielded four new sesquiterpenoids including the chlorinated merosesquiterpenoid chlorocylindrocarpol **72**, two cyclic merosesquiterpenoids, acremofuranones A **73** and B **74**, and dihydrobergamotene **75**.



†**72**

A number of known sesquiterpenoids were also isolated including lignoren,[106] cylindrocarpol,[107] ascofuranone,[108] ascofuranol,[109] ascochlorin,[110] cylindrol B,[111] ilicicolin F,[111] dechloroilicicolin C,[111] ilicicolin C[111] and deacetylchloronectrin,[112] all of which were isolated from the marine environment for the first time.[113] Glycosyl benzenediols **76** and **77** were isolated from culture broth of *Acremonium* sp. [Demospongiae sponge, (Ishigaki Is., Okinawa)].[114] The aglycon of **76**



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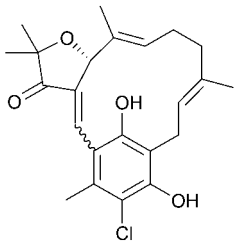

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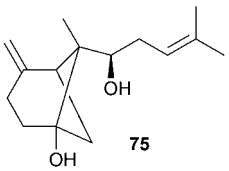
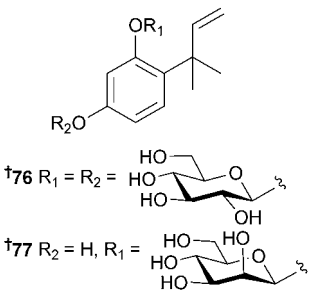


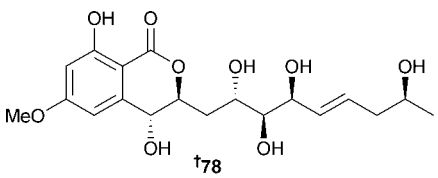
75

and **77**[115] and a glycoside very similar to **76**, but with a rearranged isoprene unit,[116] have been previously isolated as plant metabolites.

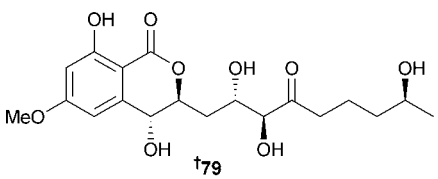


†**76** R_1 = R_2 =
†**77** R_2 = H, R_1 =

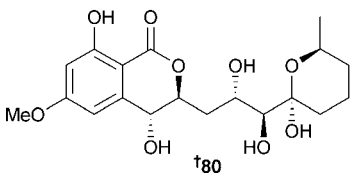
Fermentation of *Aigialus parvus* [mangrove wood (species and source not given)] resulted in the isolation of the nonaketide metabolites, aigialomycin F **78** and G **79**, **80**, 7′,8′-dihydroaigialospirol **81**, 4′-deoxy-7′,8′-dihydroaigialospirol **82** and rearranged macrolides **83** and **84**. Aigialospirol, previously described from the same species,[117] was reisolated and the previously suggested absolute configuration confirmed as **85**.



†**78**

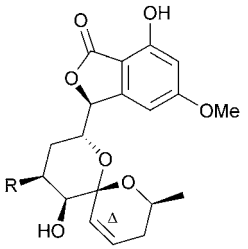


†**79**

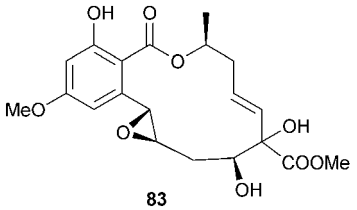


†**80**

The known terrestrial fungal metabolite 4-*O*-demethylhypothemycin[118] was isolated from the marine environment for the



†**81** R = OH, Δ saturated
†**82** R = H, Δ saturated
†**85** R = OH



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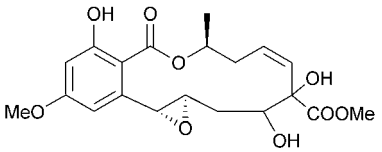

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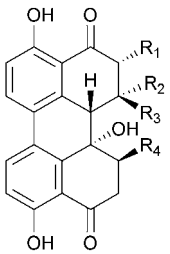
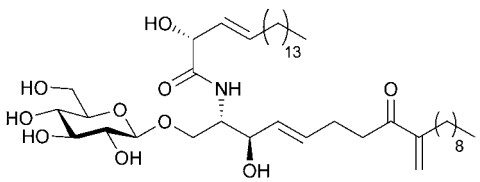
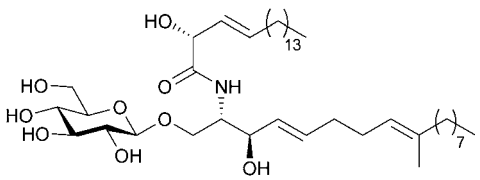


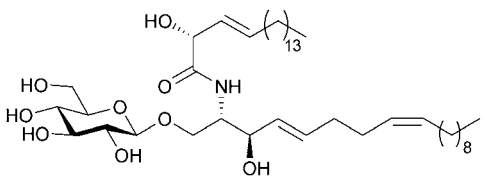
86 $R_1 = R_2 = OH$, $R_3 = R_4 = H$
87 $R_1 = R_2 = H$, $R_3 = R_4 = OH$



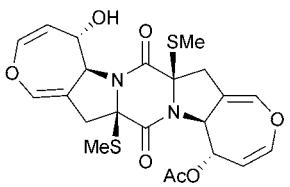
†**88**



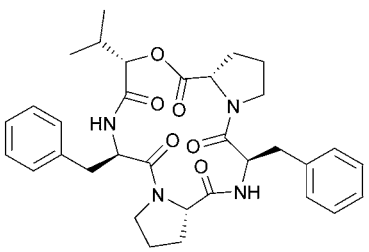
†**89**



†**90**



†**91**

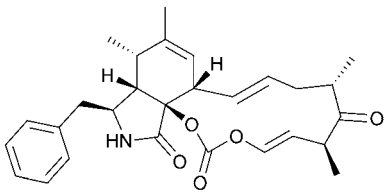


†**92**

first time.[119] Two new perylene derivatives, 7-*epi*-8-hydroxyaltertoxin I **86** and 6-*epi*-stemphytriol **87**, were isolated from culture of *Alternaria alternata*, [*Laurencia* sp., (Weizhou Is., South China Sea)].[120]

Alternaria raphani [sediment, sea salt field, (Qingdao, China)] yielded three cerebrosides, alternaroside A–C **88–90** and a diketopiperazine alkaloid, alternarosin A **91**,[121] while alternaramide **92**, a cyclic pentadepsipeptide, was isolated from culture of *Alternaria* sp. [sediment, (Masan Bay, S. Korea)].[122]

Five cytochalasins, Z_{16}–Z_{20} **93–97**, were isolated from *Aspergillus flavipes* [inner bark of the mangrove *Acanthus ilicifolius*, (Dongzhai Gang, China)]. The known fungal metabolite roselichalasin[123] was also isolated.[124]



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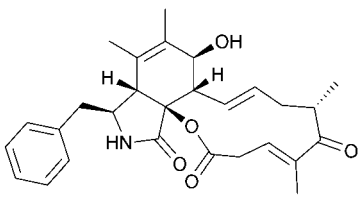

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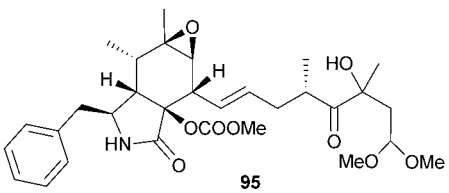

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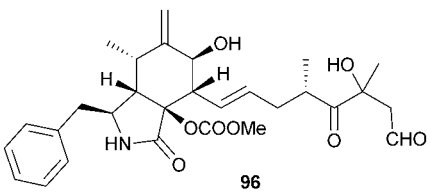

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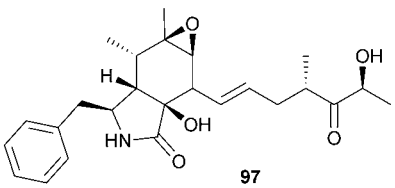
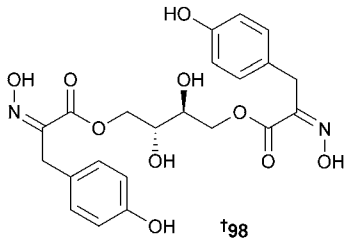
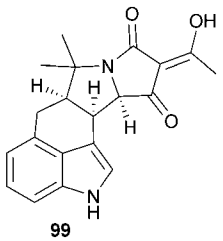


97

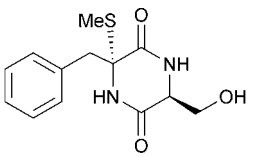
Fermentation of *Aspergillus aculeatus* [*Xestospongia testudinaria*, (Ton Sai Bay, Phi Phi Islands, Thailand)] resulted in the isolation of the tyrosine-derived aspergillusol A **98**, which selectively inhibited α-glucosidase from *Saccharomyces cerevisiae*. A methyl ester of 4-hydroxyphenylpyruvic acid oxime, a known synthetic compound,[125] was also isolated, but may be an artefact derived *via* methanolysis of **98** during isolation.[126]

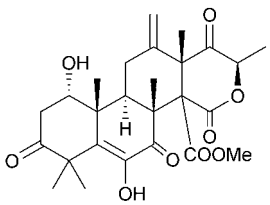
Iso-α-cyclopiazonic acid **99**, isolated from *Aspergillus flavus* [green alga *Enteromorpha tubulosa*, (Putian Pinghai, China)], was modestly cytotoxic to several human tumour cell lines.[127]


†98


99

A new gliotoxin analogue, **100**, was isolated from *Aspergillus fumigatus* [sediment, (Jiaozhou Bay, Qingdao, China)].[128] Fermentation of *Aspergillus insuetus* [*Petrosia ficiformis*, (Punta de Santa Ana, Blanes, Spain)] yielded the meroterpenoids terretonin E **101** and F **102**, and the known fungal metabolite aurantiamine,[129] isolated from a marine source for the first time. All were inhibitors of the mammalian mitochondrial respiratory chain.[130] A benzodiazepine analogue, 2-hydroxycircumdatin C **103**, was isolated from *Aspergillus ochraceus* [brown alga *Sargassum kjellmanianum*, (Dalian coastline, China)]. In addition, the known synthetic compound, (11a*S*)-2,3-dihydro-7-methoxy-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11(10*H*,11a*H*)-dione[131] was isolated from a natural source for the first time. 2-Hydroxycircumdatin C **103** exhibited significant 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical-scavenging activity.[132]


100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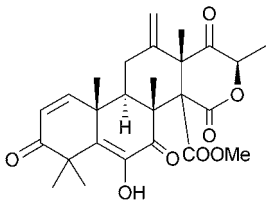
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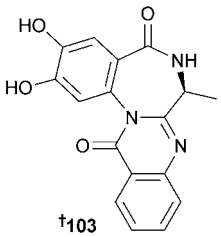
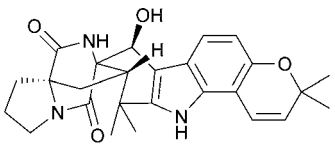
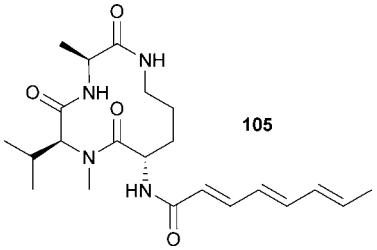
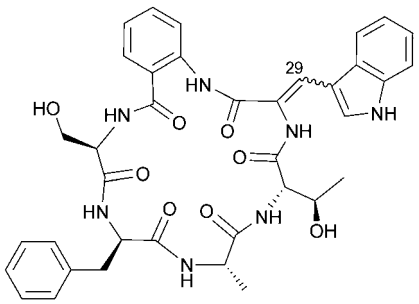

†103


†104

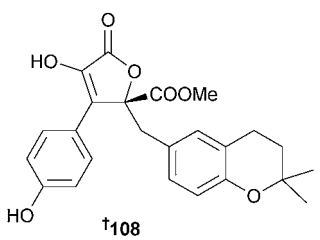

105

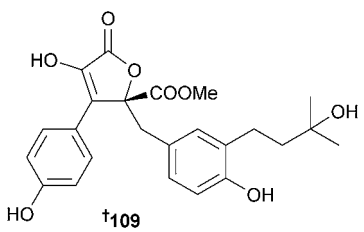
A heptacyclic alkaloid, 21-hydroxystephacidin **104**, was isolated from *Aspergillus ostianus* [unidentified sponge, (Pohnpei)],[133] while investigation of *Aspergillus sclerotiorum* [*Mycale* sp., (Ishigaki Is., Okinawa)] gave *N*-demethyl aspochracin **105**.[134]

The cyclic hexapeptides sclerotide A **106** and B **107** were isolated from *A. sclerotiorum* [Putian Sea Salt Field, (Fujian, China)] in a nutrient-limited hypersaline medium. Sclerotides A **106** and B **107** were photo-interconvertible. Both **106** and **107** displayed moderate activity against *C. albicans*, and **107** was weakly cytotoxic to HL-60 cells and inhibited *P. aeruginosa* growth.[135]


†106 (29*Z*)
†107 (29*E*)

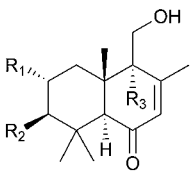
Investigation of *Aspergillus terreus* [*Sinularia kavarattiensis*, (Mandapam, India)] led to the aromatic butenolides aspernolide A **108** and B **109**. Aspernolide A **108** was first reported as a reaction product in the structural elucidation of the parent acid[136] from a terrestrial strain of *A. terreus*, but this is the first report from a marine source. Aspernolide B **109** and a known co-isolated butyrolactone I[137] (but here called aspernolide C) were unstable, and on storage converted to aspernolide A **108**.[138]


†108

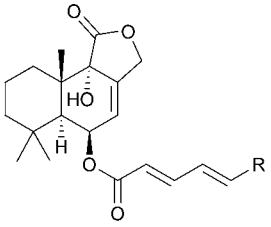

†109

Seven drimane sesquiterpenoids **110–116** were isolated from the culture broth of *A. ustus* [*Suberites domuncula*, (Adriatic Sea)]. Compounds **113** and **114** and the co-isolated, known sesquiterpenoid RES-1149-2[139] were cytotoxic to several tumour cell lines.[140] This was the first marine isolation of sesquiterpene RES-1149-2.[139]

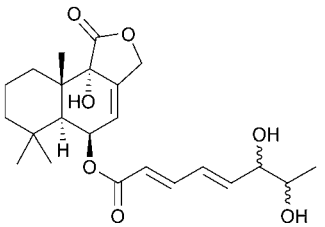
Published almost simultaneously with the previous report[140] were details of three drimane sesquiterpenes (ustusols A–C **110**, **117** and **118**), five drimane sesquiterpene esters (ustusolates A–E



110 R_1 = H, R_2 = R_3 = OH
111 R_1 = R_3 = OH, R_2 = H
112 R_1 = OH, R_2 = R_3 = H

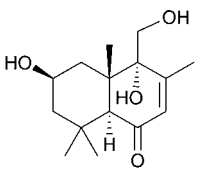


113 R = COOH
114 R = CHO

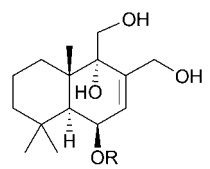


115
116

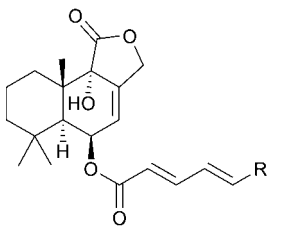
119–122 and **114**), and six benzofuran derivatives (ustusoranes A–F **123–128**) from *Aspergillus ustus* [rhizosphere soil of the mangrove *Bruguiera gymnorrhiza*, (Wenchang, Hainan Province, China)].[141] Ustusol A and ustusolate E were identical to two of the compounds **110** and **114** in the previous report.[140] Ustusorane E **127** displayed strong growth inhibition of HL-60 cells, ustusolates C **121** and E **114** exhibited moderate growth inhibition of A549 and HL-60 cells, and ustusolate A **119** showed weak growth inhibition of HL-60 and A549 cells.[141]



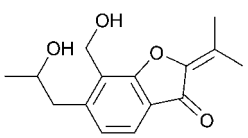
†**117**



118 R = Me
119 R =



120 R = (*E*) CH=CHCH$_2$CH(OH)Me
121 R = CH$_2$CH(OH)Me
122 R = CH(OMe)$_2$



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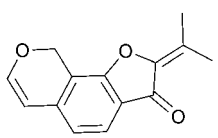

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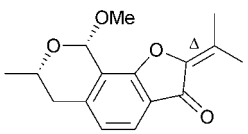
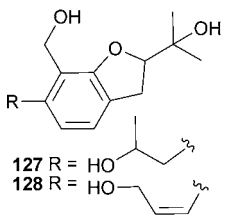
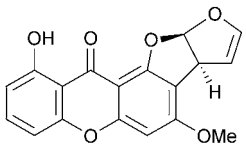


125
126 Δ saturated



127 R = HO
128 R = HO

Culture of *Aspergillus* sp. [seawater, (Quan-Zhou Gulf, China)] yielded asperxanthone **129** and asperbiphenyl **130**, inhibitors of Tobacco Mosaic Virus (TMV) replication.[142] The amide alkaloids **131** and **132** were characterised from an unidentified endophytic fungus [mangrove, *Acanthus ilicifolius*, (South China Sea)].[143]



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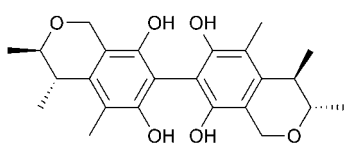

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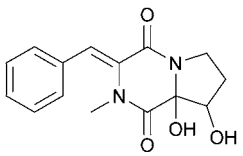

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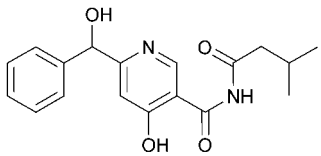
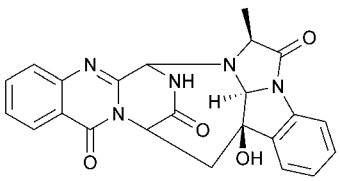


132

The alkaloid cottoquinazoline A **133** and the cyclopentapeptides, cotteslosin A **134** and B **135** were isolated from *Aspergillus versicolor* [sand, (Cottesloe, Western Australia)].[144]



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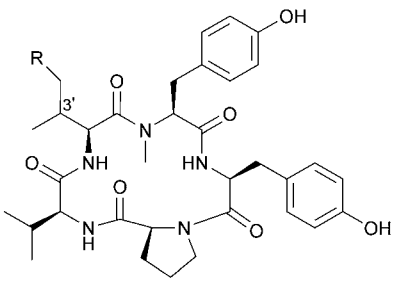


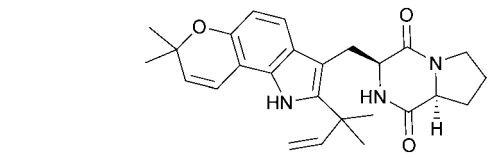
†**134** R = H
†**135** R = Me, (3′*S*)

Culture of *Aspergillus* sp. [*Mytilus edulis*, (Noto Peninsula, Sea of Japan)][145] gave notoamide E **136** which had previously been proposed[146] as an advanced precursor to notoamides A–D[145] and synthesised,[146] but had not been isolated. Biosynthetic studies of the producing organism indicated that notoamide E **136** was a short-lived metabolite and feeding experiments utilising synthetic, ^{13}C-labelled **136** showed incorporation into notoamides C,[145] D[145] and 3-*epi*-notoamide C.[146] These studies also produced three minor new alkaloids notoamides E2–E4 **137–139**.[147]

The same culture of *Aspergillus* that yielded notoamides A–D[145] was then further investigated and notoamides L–N **140–142**, and antipodal (−)-versicolamide B isolated. (+)-Versicolamide B had previously been isolated from a terrestrial species.[148] This example, along with (+)-[148] and (−)-notoamide B[145] and (+)[145] and (−)-stephacidin A,[148] led to a plausible biosynthetic pathway

involving a stereoselective indole oxidase.[149] Asymmetric total syntheses of both antipodes of versicolamide B have been achieved, utilising an intramolecular hetero-Diels–Alder reaction as a key step.[150]

Aureobasidin **143**, an ester with an unusual 4,6-dihydroxydecanoic acid residue, was isolated from culture of *Aureobasidium* sp. [seagrass, *Poseidonia oceanica*, (Moraira, Mediterranean Sea, Spain)] along with the known *Aureobasidium* metabolite, 3,5-dihydroxydecanoic acid.[151] Both compounds inhibited growth of *B. subtilis*, *E. coli* and *S. aureus*.[152] Culture of *Beauveria bassiana* [sponge, *Myxilla incrustans*, (Helgoland Is., Germany)] led to the moderately cytotoxic tetramic acid derivative, beauversetin **144**.[153] The known tetramic acid derivative



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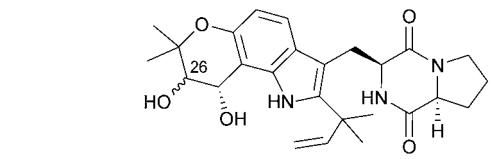
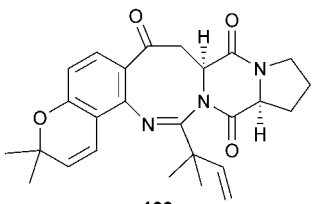


137 (26*R*)
138 (26*S*)



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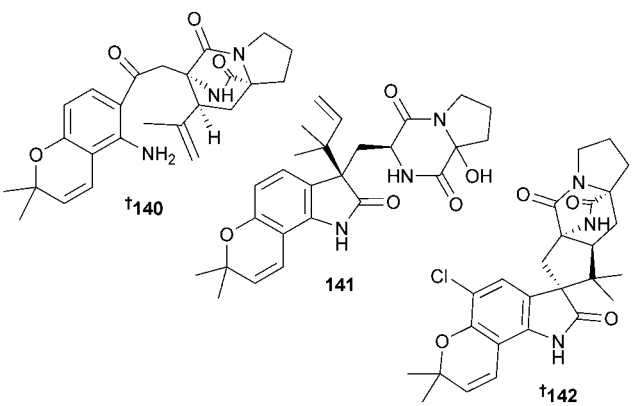
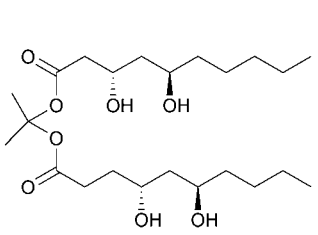


†**140**

141

†**142**



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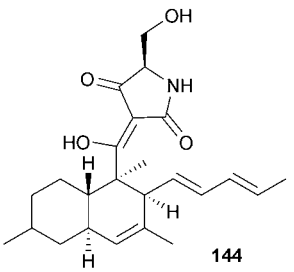


144

Sch210972[154] was isolated from the marine environment for the first time from *Microplodia* sp. [green alga, *Enteromorpha* sp., (Fehmarn Is., Baltic Sea)] and was an inhibitor of human leukocyte elastase (HLE) with moderate activity against *Bacillus megaterium*.[153]

Culture of *Chaetomium globosum*, originally isolated from a fish [*Mugil cephalus*, (Katsuura Bay, Japan)], and which had earlier yielded the azaphilones chaetomugilins A–F,[155,156] resulted in isolation of further members of the series, chaetomugilins G **145** and H **146**,[157] I–O **147–153**[158] and *seco*-chaetomugilins A **154** and D **155**.[159] The known terrestrial fungal metabolite chaetoviridin C[160,161] was also isolated and the absolute configuration established as **156**. All of the new chaetomugilins, except chaetomugilin M **151**, were cytotoxic. Chaetomugilin I **147** was selectively cytotoxic against a panel of 39 human cancer cell lines.[158]

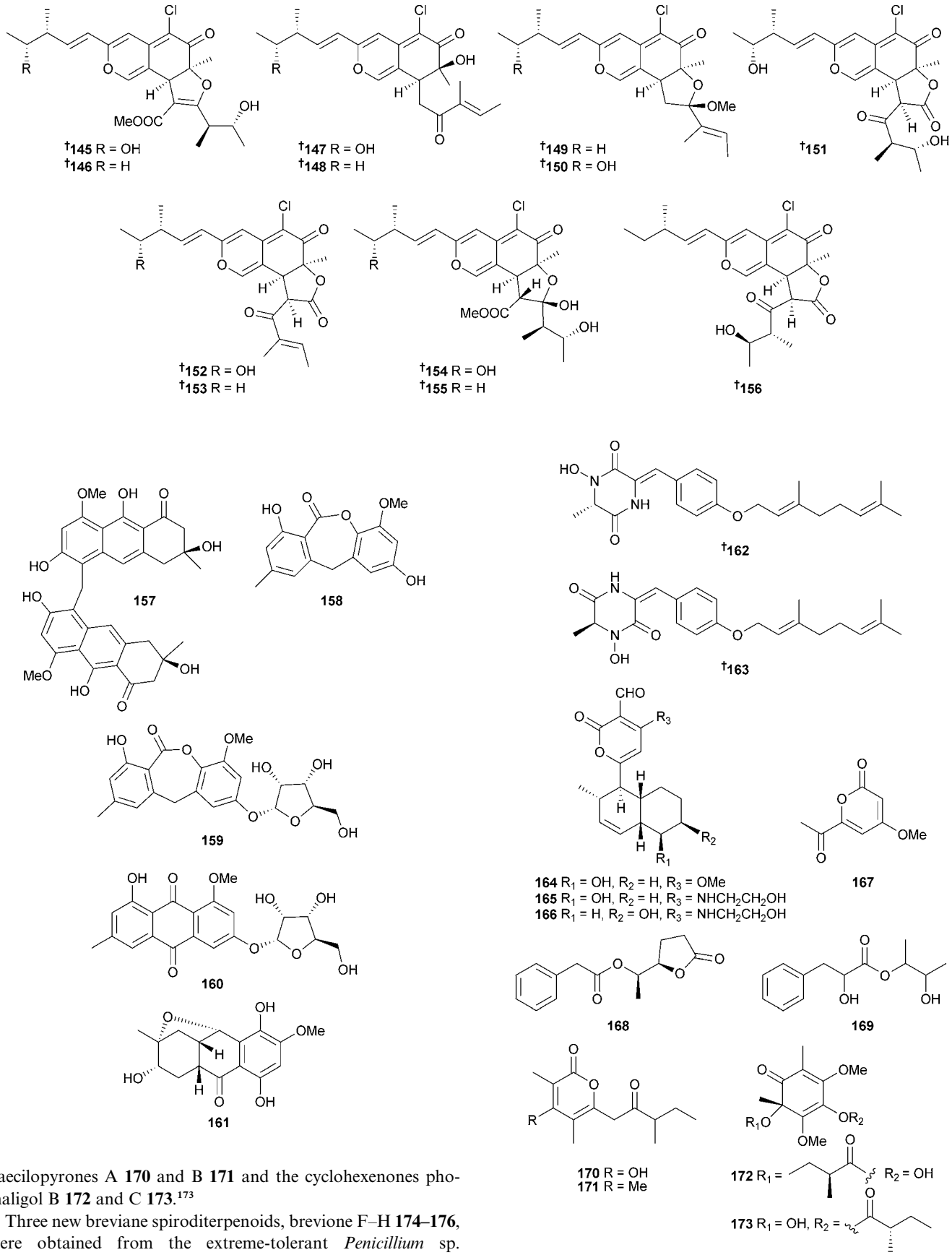
A bisdihydroanthracenone derivative (eurorubrin **157**), two seco-anthraquinone derivatives (3,2-*O*-methyl-9-dehydroxyeurotinone **158** and 4,2-*O*-methyl-4-*O*-(α-D-ribofuranosyl)-9-dehydroxyeurotinone **159**), and an anthraquinone glycoside (6,3-*O*-(α-D-ribofuranosyl)questin **160**), were isolated from *Eurotium rubrum* [stem tissue of the mangrove *Hibiscus tiliaceus*, (Hainan, Is., China)]. Compounds **158–160** displayed modest DPPH radical-scavenging activity, whilst the previously known co-isolated fungal metabolite 2-*O*-methyleurotinone[162] displayed strong activity.[163]

Fusaquinon A **161** is an anthraquinone derivative isolated from *Fusarium* sp. [mangrove sediment, (Zhuhai, China).[164] Two further compounds were isolated and designated as fusaquinons B and C. Seemingly, the enantiomers of these compounds have been published previously, and were designated tetrahydrobostrycin[165] and 1-deoxytetrahydrobostrycin[165] respectively, while an isomer of tetrahydrobostrycin has previously been isolated from the mangrove endophyte *Halorosellinia* sp.[166] by the same group as this current report. There are, however, discrepancies between the reported optical rotations for the compounds in all three papers, so the stereochemistries of these compounds require further clarification.

Two piperazine-2,5-dione derivatives, gliocladride A **162** and B **163**, were isolated from *Gliocladium* sp. [sea mud, (Rushan, China)]. Both compounds were moderately cytotoxic to HL-60, U937 and T47D cells, whilst the co-isolated, known compound, deoxymycelianamide,[167] was strongly cytotoxic to U937 cells. The name gliocladride was given to a different compound previously reported by the same authors from the same source,[168] but which lacked the C-6–C-7 double bond. Gliocladrides A **162** and B **163** are the *N*–OH derivatives of compounds PJ147 and PJ157 respectively, also previously reported by the same authors from the same source.[169] Inexplicably, none of the earlier work was cited in this current report.[170]

Of the nigrosporapyrones A–D **164–167** isolated from *Nigrospora* sp. [sea fan, *Annella* sp., (Similan Islands, Thailand)], nigrosporapyrone A **164** was moderately active against *S. aureus*,[171] while *Nigrospora sphaerica* [intertidal mud, (Nanhai Sea, China)] yielded 1-(5-oxotetrahydrofuran-2-yl)ethyl 2-phenylacetate **168** and 3-hydroxybutan-2-yl 2-hydroxy-3-phenylpropanoate **169**.[172]

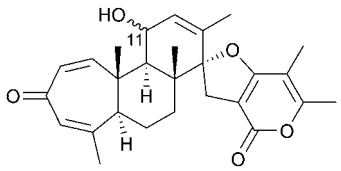
Examination of the culture broth of *Paecilomyces lilacinus*, [sponge, *Petrosia* sp., (Jeju Is., S. Korea)] led to the



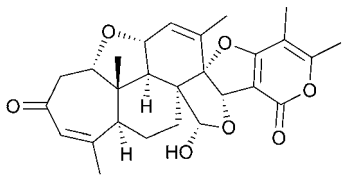
paecilopyrones A **170** and B **171** and the cyclohexenones phomaligol B **172** and C **173**.[173]

Three new breviane spiroditerpenoids, brevione F–H **174–176**, were obtained from the extreme-tolerant *Penicillium* sp.

[sediment from 5115 m, (East Pacific Ocean)], and were moderate inhibitors of HeLa cells, with brevione F **174** also inhibiting HIV-1 replication in C8166 cells. Brevione E[174] was also isolated, and while known from a terrestrial *Penicillium* sp., was the first isolation from a marine source.[175]

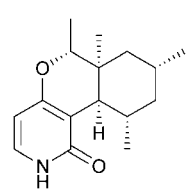


†**174** (11*S*)
†**175** (11*R*)

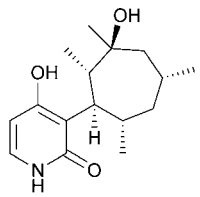


†**176**

A *Penicillium* sp. [brown alga *Xiphophora gladiata*, (Macrocarpa Point, New Zealand)] gave the 2-pyridone alkaloids **177** and **178**, of which **177** had been previously prepared as a derivative of the co-isolated *N*-hydroxypyridone antibiotic PF1140.[176] This represents the first isolation as a natural product.[177] Penicipyrone **179** and penicilactone **180** were isolated from *Penicillium* sp. [sea fan, *Annella* sp., (Similan Islands, Thailand)],[178] while the sesquiterpenoids JBIR-27 **181** and JBIR-28 **182** are eremophilane analogues isolated from *Penicillium* sp. [ascidian, *Didemnum molle*, (Ishigaki Is., Okinawa)]; **182** was moderately cytotoxic to HeLa cells.[179]



†**177**



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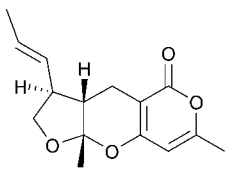

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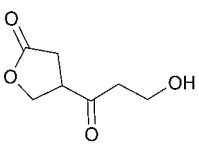

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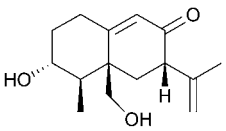

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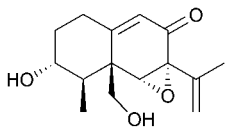
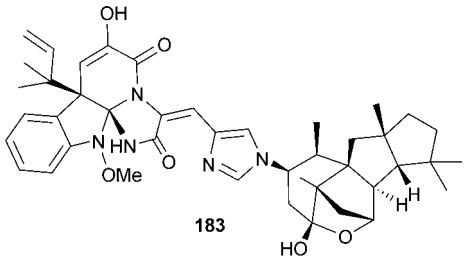


182

Ten new compounds, including the alkaloids meleagrins B **183** and C **184**, the diketopiperazine alkaloids roquefortines F **185** and G **186**, and the diterpenes conidiogenones B–G **187–192**, originated from *Penicillium* sp. [sediment, (5080 m, location not given]. All compounds were cytotoxic against a panel of four cancer cell lines, with conidiogenone C **188** potently cytotoxic to HL-60 and BEL-7402 cells.[180]

(3*R**,4*S**)-6,8-Dihydroxy-3,4,7-trimethylisocoumarin **193** was isolated from culture of an endophytic *Penicillium* sp. [roots of the mangrove *Bruguiera sexangula*, (Qinglan Port, Hainan, China)] and was moderately active against K562 tumour cells.[181] A *Penicillium* sp. [bark of the mangrove *Kandelia candel*, (Hong



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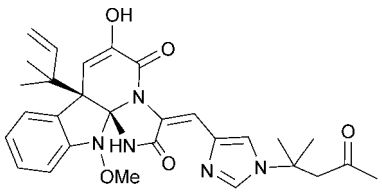

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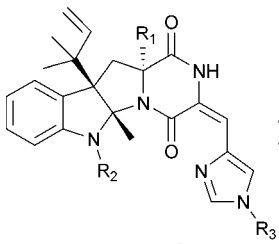
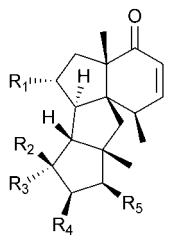
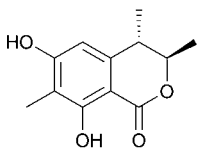


185 $R_1 = R_3 = H$, $R_2 = OMe$
186 $R_1 = OMe$, $R_2 = H$, R_3 =



187 $R_1 = R_4 = R_5 = H$, $R_2 = R_3 = Me$
188 $R_1 = R_3 = R_4 = R_5 = H$, $R_2 = CH_2OH$
189 $R_1 = R_4 = R_5 = H$, $R_2 = Me$, $R_3 = CH_2OH$
190 $R_1 = R_4 = H$, $R_2 = R_3 = Me$, $R_5 = OH$
191 $R_1 = R_5 = H$, $R_2 = R_3 = Me$, $R_4 = OH$
192 $R_1 = OH$, $R_2 = R_3 = Me$, $R_4 = R_5 = H$

Kong)] was the source of 7-hydroxyjanthinone **194**. This was the first marine occurence of the co-isolated janthinone,[182] a known metabolite from *Penicillium janthinellum* found as an endophyte of *Melia azedarach* (chinaberry).[183] Chromanone A **195** from a *Penicillium* sp. [green alga, *Ulva* sp., (Suez Canal, Egypt)] possessed a range of biological activities including cytochrome P450 1A (CYP1A) inhibition, glutathione S-transferases (GST) and epoxide hydrolase (mEH) induction and potent radical-scavenging activity against hydroxyl radicals.[184]



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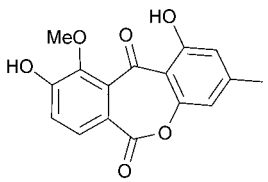

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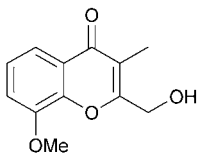
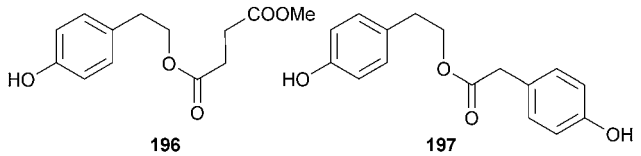


195

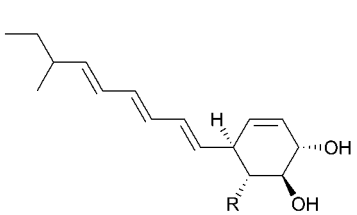
4-Hydroxyphenethyl methyl succinate **196** and 4-hydroxyphenethyl 2-(4-hydroxyphenyl)acetate **197** were obtained from *Penicillium griseofulvum* [mangrove, *Lumnitzera racemosa*,

(South China Sea)]. Both compounds were moderately active radical scavengers of the DPPH free radical and **197** was active against PC-3 prostate cancer cells.[185] Coincidentally, **197** was simultaneously isolated from terrestrial *Aspergillus phoenicis* as aspergillol B,[186] but confusingly, the name aspergillol had already been used to designate a different compound isolated from a marine strain of *Aspergillus versicolor*.[187]

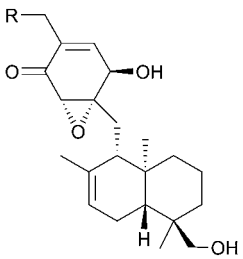


196 **197**

The polyketides spartinol A–D **198–201** came from the endophyte *Phaeosphaeria spartinae* [*Ceramium* sp., (North Sea, Büsum, Germany)].[188] Culture of *Phoma* sp. [sponge *Ectyplasia perox*, (Caribbean Sea, Dominica)] led to isolation of the prenylated polyketides epoxyphomalin A **202** and B **203**. Both compounds were active against a panel of 36 human tumour cell lines but epoxyphomalin A **202**, which was extremely potent, displayed significant selectivity toward 12 of the cell lines and possessed a unique cytotoxic selectivity pattern as determined by COMPARE analyses.[189]

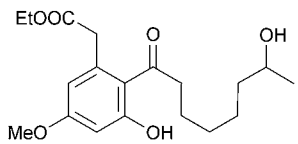


198 R = COCH(OH)Me
199 R = CH(OH)COMe
200 R = CH(OH)CH(OH)Me
201 R = COOH



202 R = OH
203 R = H

The polyketide ester **204**, isolated from *Phomopsis* sp. [mangrove, *Excoecaria agallocha*, (Dong, Hainan, China)], was cytotoxic to HEp-2 and HepG2 cells.[190] *Pichia membranificiens* [sponge, *Halichondria okadai*, (Izu Peninsula, Japan)] was the source of the indole derivatives **205** and **206**, modest DPPH radical scavengers. Synthesis of **205** indicated that the isolated natural product was scalemic in a 5 : 8 ratio of (*S*):(*R*) enantiomers.[191]



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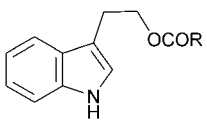
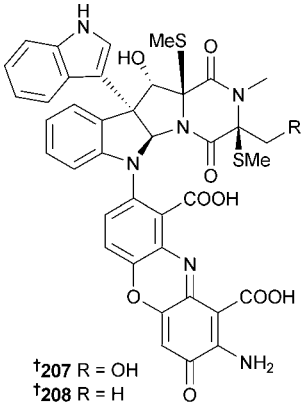


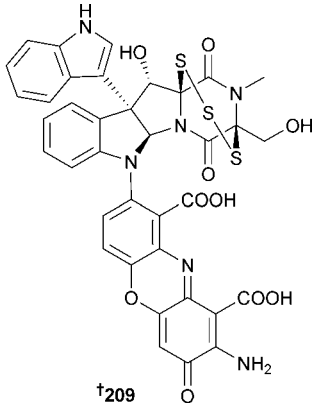
†**205** R = CH(OH)Me
206 R = $(CH_2)_4OH$

The alkaloids plectosphaeroic acid A–C **207–209** were isolated from *Plectosphaerella cucumerina* [sediments, (Barkley Sound, British Columbia)] as inhibitors of indoleamine 2,3-dioxygenase (IDO). The co-occurring, known terrestrial fungal metabolite T988 A[192] was also isolated from the marine environment for the first time.[193]

Culture of *Pestalotiopsis* sp. [mangrove leaves, *Rhizophora mucronata*, (Hainan Is., China)] produced the chromones

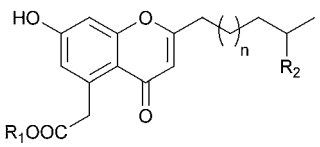


†**207** R = OH
†**208** R = H



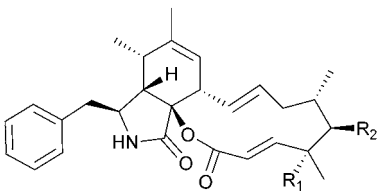
†**209**

pestalotiopsone A–F **210–215** and the known 7-hydroxy-2-(2-hydroxypropyl)-5-methylchromone,[194] originally isolated from rhubarb. This was the first isolation from a marine source. Pestalotiopsone F **215** was cytotoxic to L5178Y murine cancer cells.[195]



210 R_1 = Me, R_2 = H, n = 3
211 R_1 = Et, R_2 = H, n = 3
212 R_1 = R_2 = H, n = 3
213 R_1 = Me, R_2 = OH, n = 3
214 R_1 = Et, R_2 = OH, n = 3
215 R_1 = Me, R_2 = H, n = 1

Treatment of a culture of *Spicaria elegans* [sediment, (Jiaozhou Bay, China)] with the cytochrome P450 inhibitor metyrapone, initiated production of two deoxy-cytochalasins, 7-deoxy-cytochalasin Z_7 **216** (modestly cytotoxic) and 7-deoxy-cytochalasin Z_9 **217**.[196]

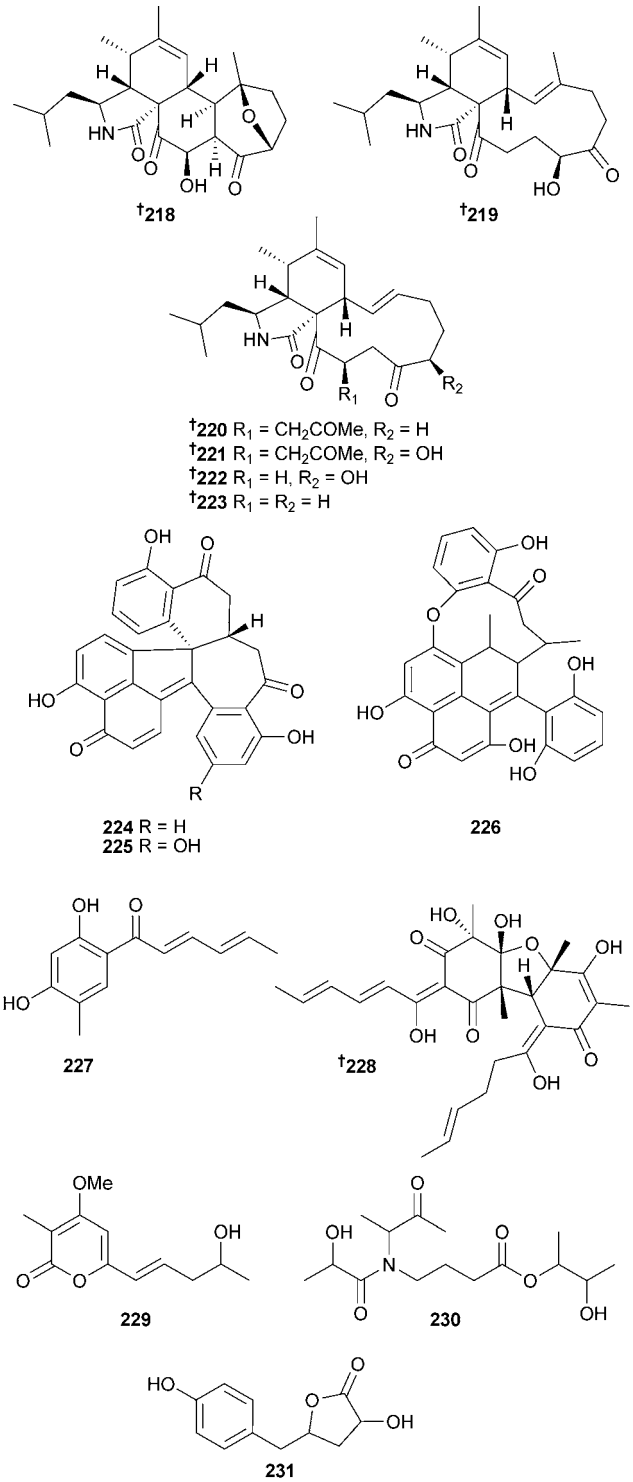


†**216** R_1 = H, R_2 = OH
217 R_1 = OH, R_2 = H

Using the same *Spicaria elegans* species, but with variation of the culture conditions in an OSMAC (one strain–many compounds) approach, the metabolites produced were greatly altered. These included the moderately cytotoxic spicochalasin A **218**, which has a unique pentacyclic ring system, and the aspochalasins M–Q **219–223**.[197]

Sporothrins A–C **224–226** were isolated from fermentation of *Sporothrix* sp. [bark of the mangrove *Kandelia candel*, (South China Sea)]. Sporothrins A and B exhibited moderate cytotoxicity to HepG2 cells, while sporothrin A **224** was a strong inhibitor of acetylcholinesterase. Based on gene sequencing, it was deduced that 1,3,6,8-tetrahydroxynaphthalene (T4HN) was a precursor in the biosynthesis of the sporothrins.[198]

A new sorbicillinoid, 6-demethylsorbicillin **227**, and a new bisorbicillinoid, 10,11-dihydrobisvertinolone **228**, were isolated



from a *Trichoderma* sp. [sediment, (Fujian province, China)]. Both exhibited moderate activities against HL-60 cells. A number of known sorbicillinoids and bisorbicillinoids were also isolated, some for the first time from the marine environment.[199]

A new pyranone derivative **229** was isolated from *Trichoderma viride* [sponge, *Agelas dispar*, (Dominica, Caribbean)].[200] The trivial name trichopyrone was proposed for **229** but this name had already been used to designate a metabolite from a terrestrial fungus.[201] *Trichoderma atroviride* [mangrove root sediment, *Ceriops tagal*, (South Sea intertidal zone, China)] was the source of compounds **230** and **231**.[202]

Asperelines A–F **232–237** are peptaibols from *Trichoderma asperellum* [sediment, (Penguin Is., Antarctica)] which are characterised by an acetylated *N*-terminus and a *C*-terminus with the uncommon prolinol residue. Absolute configurations were determined *via* a new method involving direct ^{1}H NMR spectroscopic comparison of the complexes formed between the chiral reagent Ru(D_4-Por*)CO and the amino acids from hydrolysis of the peptaibols against reference amino acid standards.[203] Fermentation of *Xylaria* sp. [seeds of a mangrove, (Mai Po, Hong Kong, China)] gave xylopyridine A **238** which had strong DNA-binding affinity to calf thymus (CT) DNA.[204]

Xylarisin A **239**, an [11]cytochalasin derivative from *Xylaria* sp. [sea fan, *Annella* sp., (Similan Is., Thailand)], was a weak inhibitor of both *S. aureus* and MRSA. (2*E*,4*S*)-2,4-Dimethyloct-2-enoic acid, a known synthetic compound,[205] was also isolated for the first time as a natural product.[206] The benzaldehyde derivatives **240** and **241** were isolated from a mangrove endophytic fungus [taxonomy of fungus and mangrove not given, (South China Sea coast)][207] and the acids **242** and **243** were obtained from culture of another unidentified mangrove endophyte (Zhanjiang sea area, China).[208] *Lyngbya bouillonii* (Milne Bay, Papua New Guinea) afforded the unusual cyclic depsipeptide, alotamide A **244**, with three contiguous peptidic residues and an unsaturated heptaketide. This compound had a unique calcium influx activation profile in murine cerebrocortical neurons.[209]

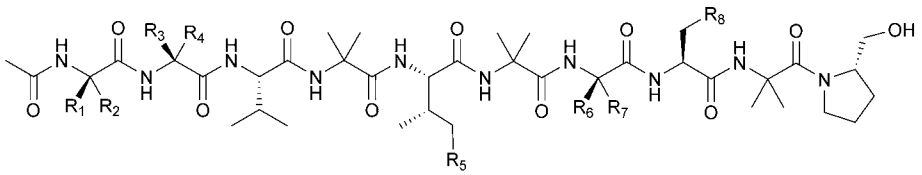
Grassystatins A–C **245–247** are linear peptides containing a statine unit, isolated from *L. confervoides* (Grassy Key and Key Largo, Florida). Grassystatins A **245** and B **246** selectively inhibited cathepsins D and E, whereas grassystatin C **247**, with two fewer residues, was less potent but still selective for cathepsin E.[210]

Chemical investigation of *L. confervoides* (Broward County, Fort Lauderdale, Florida) led to the largamides A–C **248–250**, unusual tiglic acid-containing cyclodepsipeptides that were moderate inhibitors of porcine pancreatic elastase activity *in vitro*.[211] These compounds, along with largamides D–H, were originally isolated from an *Oscillatoria* sp.[212] but the current isolation prompted a structural revision to replace the senecioic acid residue originally proposed with a tiglic acid residue.[213]

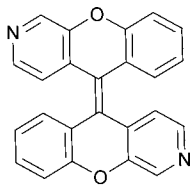
Another collection of *L. confervoides* (Port Everglades Inlet, Fort Lauderdale, Florida) yielded tiglicamides A–C **251–253**, also moderate inhibitors of porcine pancreatic elastase *in vitro*, along with largamides A–C.[214]

Tanikolide seco-acid **254** and tanikolide dimer **255** were isolated from a collection of *L. majuscula* (Tanikely Is., Madagascar). Tanikolide seco-acid **254** had been previously synthesised as an intermediate in the synthesis of tanikolide[215] but this was the first report as a natural product. Total synthesis of the three tanikolide dimer stereoisomers permitted elucidation of the stereochemistry of the dimer **255**, a selective inhibitor of the NAD^{+}-dependent cytoplasmic protein, human sirtuin type 2 (SIRT2).[216] The cyclodepsipeptide, hantupeptin A **256** was isolated from *L. majuscula* (Pulau Hantu Besar, Singapore) and was cytotoxic to MOLT-4 and MCF-7 cells.[217]

Desmethoxymajusculamide C **257** was isolated from *L. majuscula* (Kauviti Reef, Yanuca Is., Fiji) and was a potent and



†**232** $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = Me$, $R_8 = H$
†**233** $R_1 = R_8 = H$, $R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = Me$
†**234** $R_1 = R_2 = R_3 = R_4 = R_5 = R_7 = Me$, $R_6 = R_8 = H$
†**235** $R_1 = R_2 = R_3 = R_4 = R_6 = R_7 = Me$, $R_5 = R_8 = H$
†**236** $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = Me$, $R_8 = OH$
†**237** $R_1 = R_2 = R_5 = R_6 = R_7 = Me$, $R_3 = i\text{-Pr}$, $R_4 = R_8 = H$



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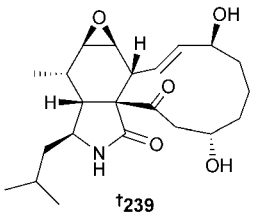
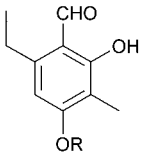
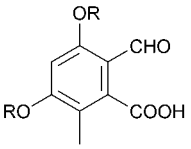


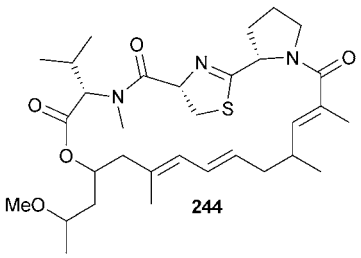
†**239**



240 R = Me
241 R = H



242 R = H
243 R = Me



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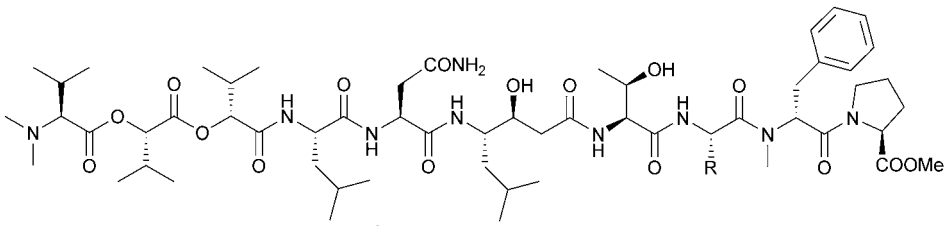
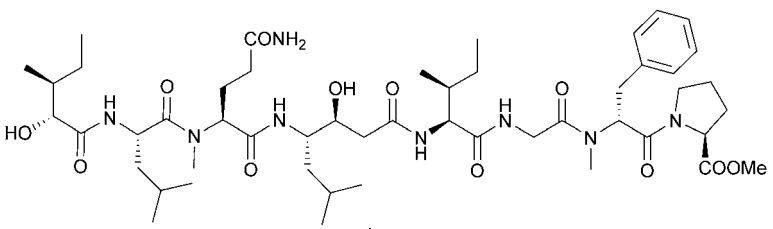
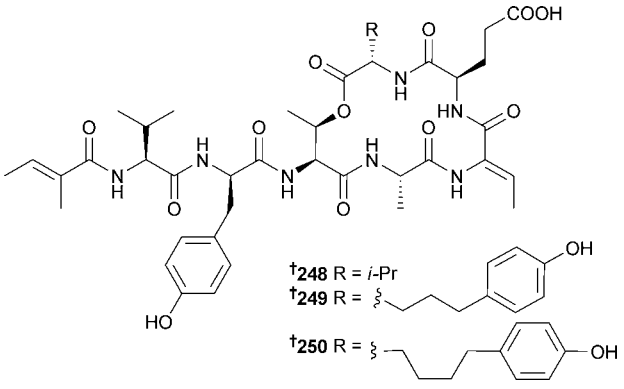
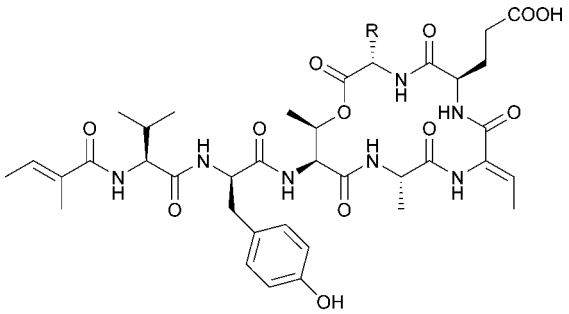


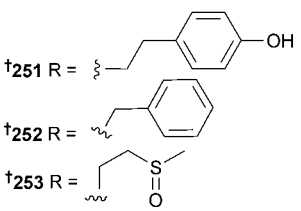
†**245** R = Me
†**246** R = Et

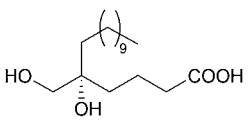


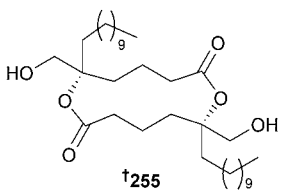
†**247**

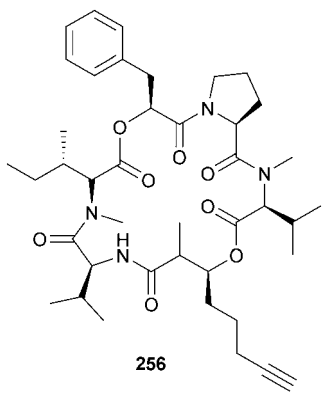




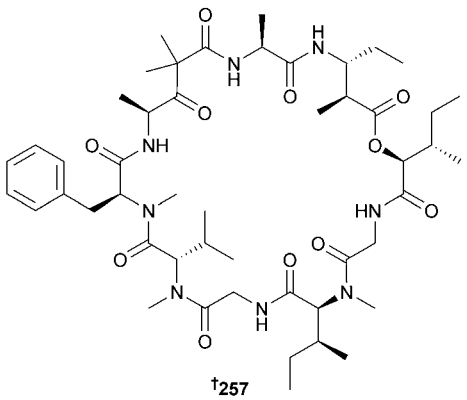




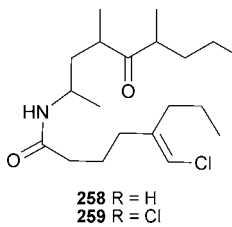


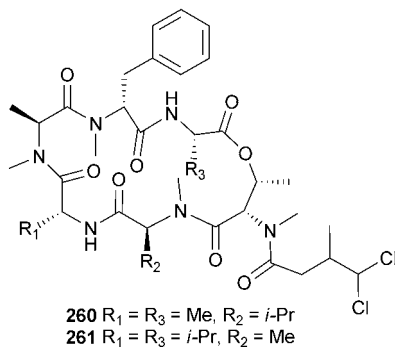


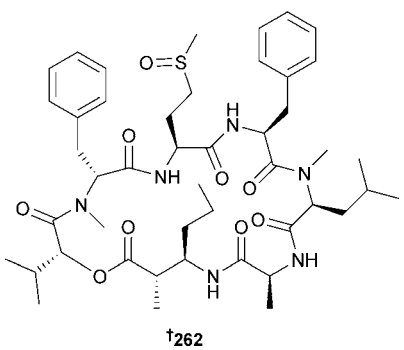
selective agent against HCT-116 through disruption of cellular microfilament networks. Interestingly, a linear version of **257**, generated through base hydrolysis, also possessed potent actin depolymerisation characteristics and solid tumour selectivity equivalent to **257**. Desmethoxymajusculamide C **257** was also active *in vivo* in HCT-116-bearing mice with severe combined immunodeficiency.[218]



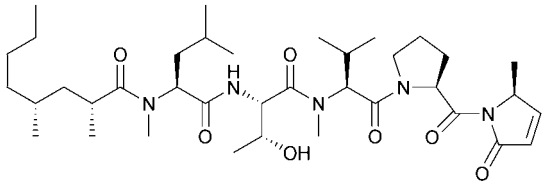
From *L. majuscula* (True Blue Bay, Grenada) two halogenated fatty acid amides, grenadamides B **258** and C **259**, and two depsipeptides, itralamides A **260** and B **261**, were isolated. The known depsipeptide carriebowmide[219] was isolated as the sulfone artefact, which on comparison with authentic carriebowmide led to a minor structural revision to **262**. Grenadamides B **258** and C **259** had marginal insecticidal activity against the beet armyworm (*Spodoptera exigua*), while itralamide B **261** was cytotoxic to HEK293 cells.[220]



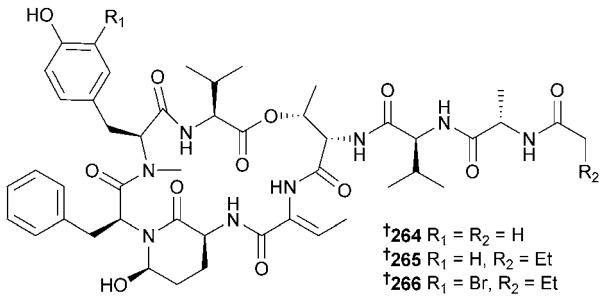




The linear peptide desacetylmicrocolin B **263** has been isolated from *Lyngbya cf. polychroa* (Hollywood, Florida) as a growth inhibitor of HT-29 and IMR-32 cells,[221] while extraction of *Lyngbya semiplena* (Tumon Bay, Guam) resulted in isolation of the cyclodepsipeptides lyngbyastatins 8–10 **264–266**, inhibitors of porcine pancreatic elastase.[222]

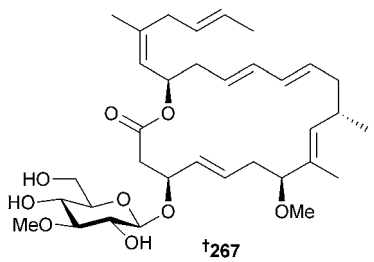


†263



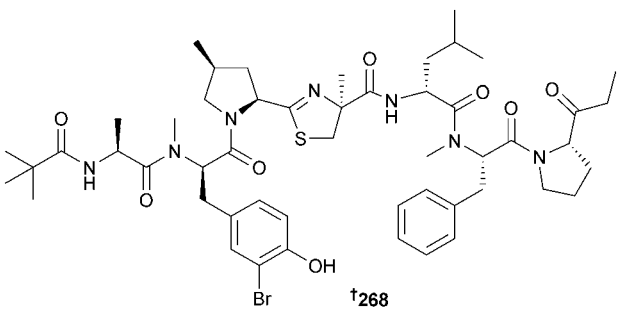
†264 $R_1 = R_2 = H$
†265 $R_1 = H$, $R_2 = Et$
†266 $R_1 = Br$, $R_2 = Et$

Chemical investigation of a collection of *Lyngbya* sp. (Okinawa) resulted in isolation of biselyngbyaside **267**, an 18-membered macrolide glycoside with broad-spectrum cytotoxicity in a human tumour cell line panel, likely by a novel mechanism as indicated by COMPARE analyses.[223]



†267

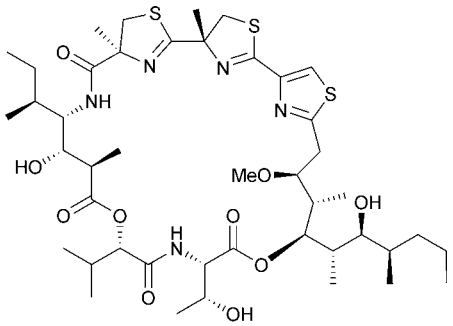
Bisebromoamide **268** was isolated from *Lyngbya* sp. (Okinawa), and was cytotoxic to HeLa S_3 cells and a panel of human cancer cell lines, in addition to exhibiting potent protein kinase inhibition.[224]



†268

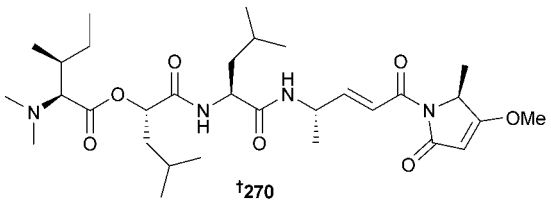
An assemblage of *Lyngbya majuscula* and *Phormidium gracile* (Hola Bay, Papua New Guinea) yielded hoiamide A **269**, a cyclic depsipeptide, of mixed peptide–polyketide biosynthetic origin, which was a partial agonist of site 2 on the voltage-gated sodium channel.[225]

The same *Symploca* sp. sample (Pillars, Key Largo, Florida) that produced largazole[226,227] was the source of symplostatin 4 **270**, a highly functionalised linear peptide with features from both dolastatin 10 and 15, but with modest activity only against



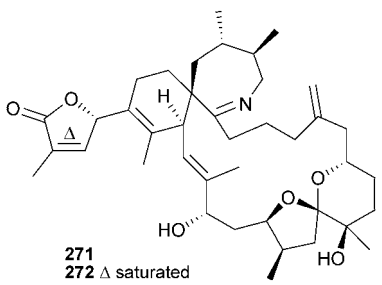
†269

HeLa and HT-29 cells and several orders of magnitude less potent than either dolastatin 10 or dolastatin 15 at disrupting cellular microtubules.[228] Symplostatin 4 **270** had the same planar structure as gallinamide A, isolated from *Schizothrix* sp. (Piedras Gallinas, Panama), and moderate activity against *Plasmodium falciparum*, *Leishmania donovani* and mammalian Vero cells.[229] The absolute configuration of gallinamide A was not fully determined, and NMR spectral comparison of the two metabolites indicated that they may be different.[228]



†270

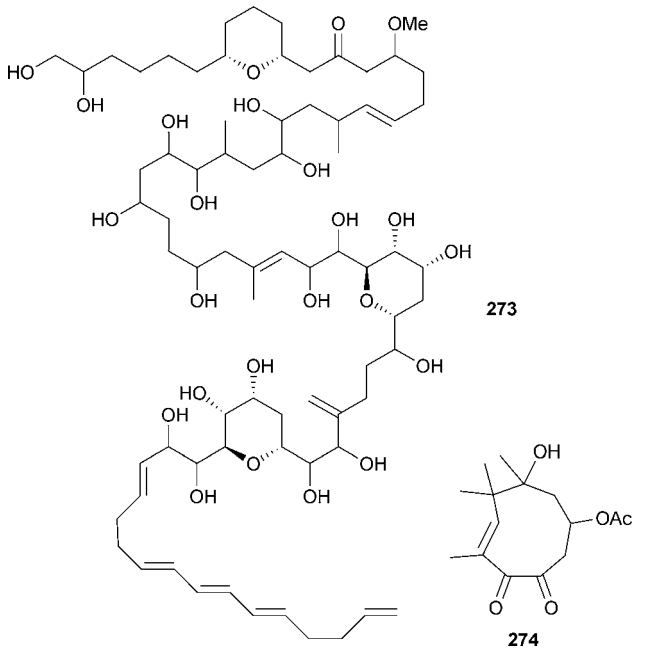
Spirolides H **271** and I **272** were isolated from culture of *Alexandrium ostenfeldii* (Ship Harbour, Nova Scotia) and are structurally distinct from other spirolides in that they contain a 5 : 6 dispiroketal ring system rather than the trispiroketal ring system characteristic of previously isolated spirolides. Spirolide H **271** displayed only extremely weak toxicity in a mouse bioassay, in contrast to previously isolated spirolides.[230] Analysis of ROE and geometrical constraints, the latter derived from ^{1}H-^{1}H and ^{1}H-^{13}C coupling constants, combined with molecular dynamics and molecular mechanics calculations led to the assignment of the full relative configuration of 13,19-didesmethylspirolide C.[231,232] The analysis also identified three major conformations of the toxin present as an equilibrium in solution.



271
272 Δ saturated

Carteraol E **273**, a polyhydroxyl metabolite isolated from *Amphidinium carterae* [seaweed washings, (southern coast of Taiwan)], was a potent ichthyotoxin, in addition to being active against *Aspergillus niger*.[233] Cooliatin **274**, an unusual

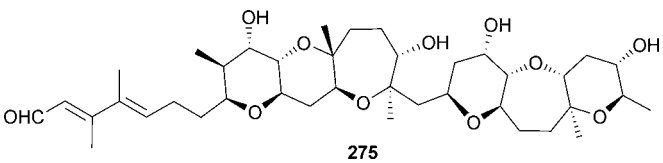
dioxocyclononane, was isolated from *Coolia monotis* [coastal seaweeds, (Hainan Is., China)].[234]



273

274

The polyether brevisin **275** was isolated from *Karenia brevis* (Wilson's 58 clone) and has an unprecedented structure that consists of two separate fused polyether ring assemblies linked *via* a methylene group. Brevisin **275** inhibited the binding of brevetoxin-3 to voltage-sensitive sodium channels in rat brain synaptosomes.[235]



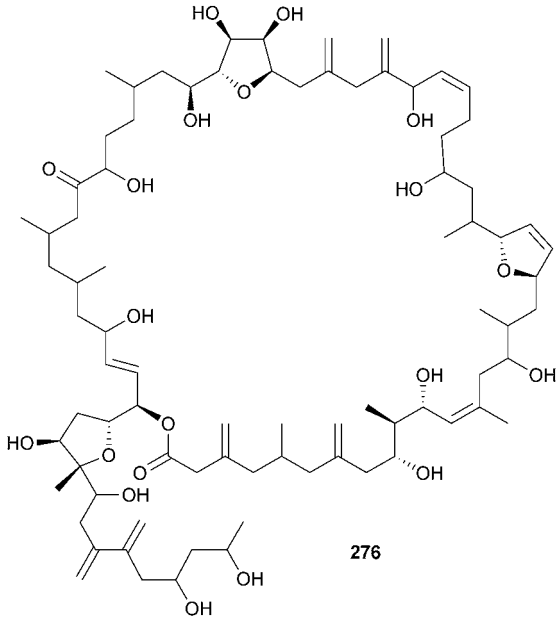
275

Culture of *Prorocentrum belizeanum* (source not given) led to the polyunsaturated, polyhydroxylated macrocycle, belizeanolide **276**, and the open-chain form, belizeanolic acid **277**. Both compounds had significant antiproliferative activities against several human solid tumour cell lines.[236]

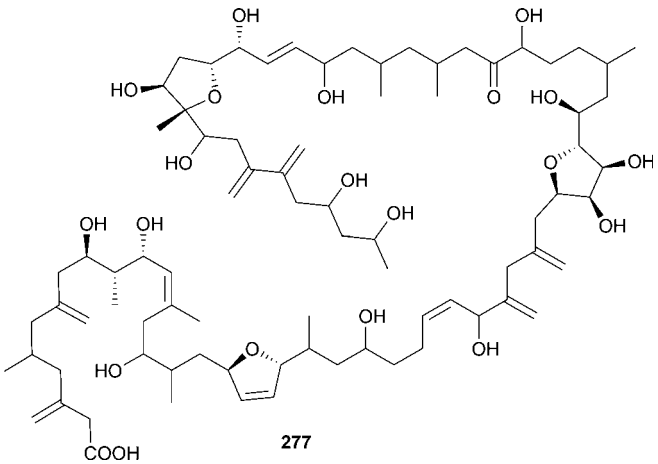
Formosalides A **278** and B **279**, 17-membered ring macrolides, were isolated from culture of *Prorocentrum* sp. [seaweed washings, (South Bay, Taiwan)].[237]

A *Symbiodinium* sp. [flatworm, *Amphiscolops* sp., (Sesoko Is., Okinawa)] was the source of the long carbon-chain compounds, symbiospirol A–C **280–282**, with symbiospirol A **280** inhibitory against L-phosphatidylserine-induced PKC activation.[238]

Aspergillides A and B are cytotoxic macrolides isolated from *Aspergillus ostianus*.[239] Enantioselective synthesis of the proposed structure of aspergillide A indicated that revision of that structure to that proposed for aspergillide B **283** was necessary. The structure of aspergillide A as originally published was incorrect, but the actual structure was unclear.[240] Subsequently, the original researchers, assisted by X-ray analysis, published a structural revision of both compounds to establish aspergillide A as **284** and aspergillide B as **283**.[241] Total synthesis



276



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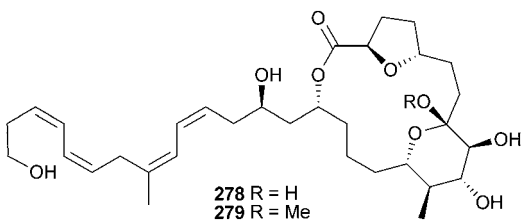
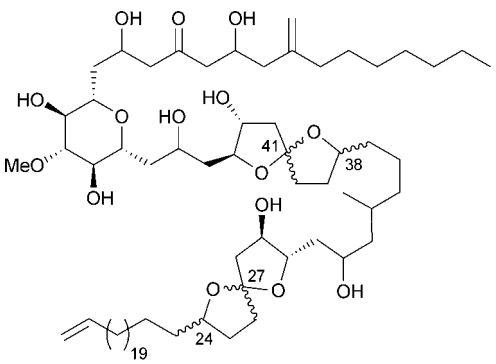
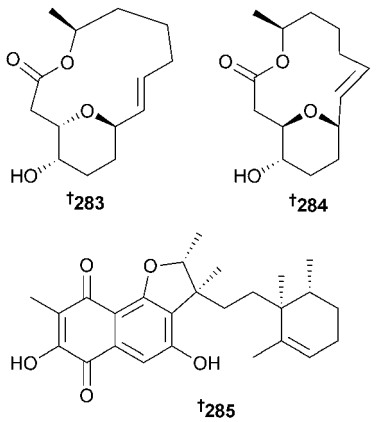


278 R = H
279 R = Me

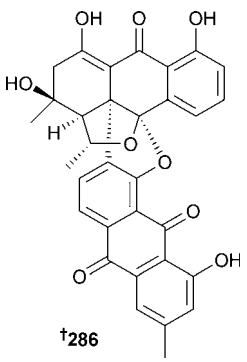


280 (24*R*,27*S*,38*R*,41*S*)
281 (27*R*,41*S*)
282 (27*S*,41*R*)

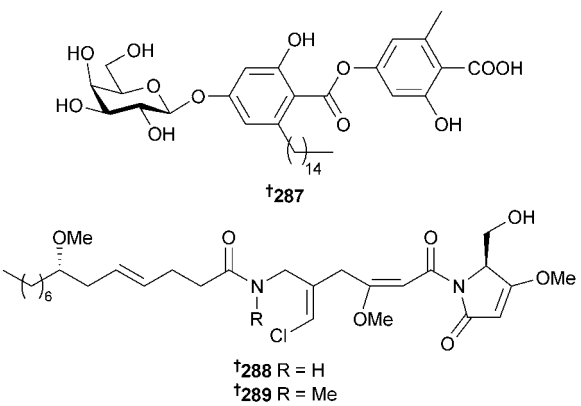
of aspergillide C, also from *Aspergillus ostianus*,[239] was accomplished from a commercially available chiral glycidol derivative.[242] The structure of neomarinone, a furanonaphthoquinone, isolated from a marine filamentous bacterium[243] was revised after a biosynthetic study and NMR analysis.[244] The total synthesis of neomarinone (utilising a regioselective Diels–Alder reaction) has now been achieved, and established the absolute configuration as **285**.[245]



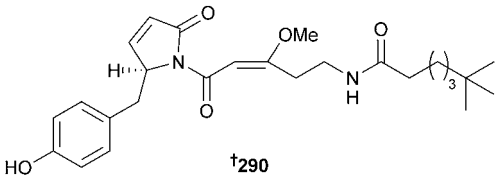
Total synthesis of both isomers of the bisanthraquinone antibiotic BE-43472B, originally isolated from *Streptomyces* sp. found in a cyanobacterium associated with the ascidian *Ecteinascidia turbinata*,[246] was achieved *via* a cascade sequence initiated by an intermolecular Diels–Alder reaction, and defined the absolute configuration of the natural product as **286**.[247,248]



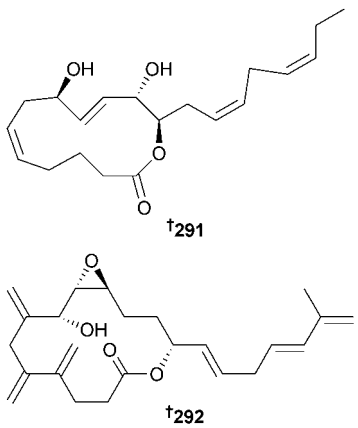
Aquastatin A, previously isolated from *Fusarium aqueductuum*,[249] has now been isolated from the marine environment (*Cosmospora* sp. [sediment, (Gejae Is., S. Korea)] and the absolute configuration determined (**287**).[250] Malyngamides O and P were originally isolated from the sea hare *Stylocheilus longicauda*,[251] whilst malyngamides Q and R were isolated from the cyanobacterium *Lyngbya majuscula*.[252] All four metabolites have now been synthesised *via* a flexible and convergent route, which established the configurations of malyngamides Q and R as **288** and **289** respectively.[253,254]



Ypaomide was isolated as a herbivore-feeding deterrent from the cyanobacterium *Lyngbya majuscula*.[255] An enantioselective synthesis of the (*R*)-enantiomer established that the natural product was the (*S*)-enantiomer **290**.[256]



Total synthesis of amphidinolactone A from the cultured dinoflagellate *Amphidinium* sp. [flatworm, *Amphiscolops* sp.],[257] was accomplished *via* a ring-closing metathesis reaction and established the absolute configuration (**291**).[258] A further member of the series, amphidinolide V,[259] was also synthesised utilising a ring-closing alkyne metathesis, again establishing the absolute configuration **292**.[260,261]



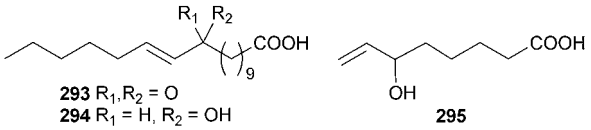
Amphidinolide Q, isolated from the same *Amphidinium* sp.,[262,263] has been stereoselectively synthesised by a scheme that combined Julia coupling, Myers alkylation, and Yamaguchi lactonisation.[264] Caboxamycin, a known intermediate in the synthesis of benzoxazole carboxamides,[265] has been described as a natural product for the first time following isolation from *Streptomyces* sp. [deep-sea sediment, (Canary Basin, Atlantic Ocean)]. Caboxamycin was an inhibitor of Gram-positive bacteria and a moderate inhibitor of several cancer cell lines.[266] Methyl 3-(3-oxocyclopent-1-enyl)propionate was isolated for the first time as a natural product from *Trichoderma atroviride* [sediment, roots of *Ceriops tagal*, (South China Sea)][267] but had previously been synthesised.[268] A number of bile acid derivatives were isolated from culture of *Psychrobacter* sp. [*Stelletta* sp., (Geoje Is., S. Korea)]. Of these, 3-dimethoxy-12α-hydroxycholanic acid was a new derivative, but assumed to be an artefact. 3-Dimethoxy-7-ketocholanic acid,[269] while known, was isolated

from a natural source for the first time. It too may also be an artefact. Finally, 12α-hydroxy-3-ketocholanic acid[270] and 12α-hydroxy-3,7-diketocholanic acid,[271] while known, were isolated from a marine source for the first time.[272] Culture of *Halobacillus salinus* [sea grass, (South Kingstown, Rhode Is., USA)] produced *N*-(2′-phenylethyl)isobutyramide,[273] a known inhibitor of quorum sensing-regulated behaviour in Gram-negative bacteria, but isolated from a marine source for the first time.[274] Known fungal metabolites pyripyropene A, B and D[275] were isolated from *Aspergillus* sp. [sediment, (Gokasyo Gulf, Japan] as selective antiproliferative substances against human umbilical vein endothelial cells (HUVECs). Pyripyropenes B and D were isolated from the marine environment for the first time.[276] Marinoquinoline A, a pyrroloquinoline from the marine gliding bacterium *Rapidithrix thailandica*,[277] exhibited strong inhibition of acetylcholinesterase. Two related pyrrole derivatives, 3-(2′-aminophenyl)pyrrole[278] and 2,2-dimethylpyrrolo-1,2-dihydroquinoline, were isolated from two other strains of *R. thailandica*, but the quinoline was proposed as an artefact of the pyrrole, which was isolated from a natural source for the first time.[279] Culture of an unidentified fungal strain isolated from a sea salt pan in Australia resulted in the first marine-based isolation of 3-*O*-methylfunicone,[280] a selective inhibitor of mammalian Y-family DNA polymerases (pols) and growth suppressor of HCT-116 and HeLa cells.[281] *N*-Methyl-2-indolecarboxamide, a known synthetic compound,[282] was isolated from a natural source for the first time as a metabolite of *Cladosporium cladosporiodes* [*Cliona* sp., (Los Molles, Chile)][283] while 2,2′-dithiobis-benzothiazole, a known plant metabolite,[284] was isolated from the marine environment for the first time from an unidentified endophytic fungus [mangrove, (South China Sea)].[285] The known terrestrial fungal siderophore fusigen[286] was isolated from the marine environment for the first time from the fungus *Aureobasidium pullulans* [sea saltern, (Yellow Sea, China)] as a growth inhibitor of *Vibrio anguillarum* and *V. parahaemolyticus*.[287] Sporolide B, a halogenated macrolide from the actinomycete *Salinispora tropica*,[288] was synthesised by a convergent strategy featuring a ruthenium-catalysed [2 + 2 + 2] cycloaddition reaction,[289] while synthesis of bacillamide 3, originally isolated from *Bacillus endophyticus* [hypersaline microbial mat, (Bahamas)],[290] was accomplished from D-alanine.[291] The total synthesis of emericellamide B, a metabolite of the fungus *Emericella* sp. produced during co-culture with the actinomycete *Salinispora arenicola*,[292] was achieved by a flexible, convergent strategy.[293] Gymnastatins F[294] and Q,[295] metabolites of the fungus *Gymnascella dankaliensis* (*Halichondria japonica*), were synthesised *via* a biomimetic route from the corresponding spirodienone derivatives.[296] The first[297] of several[298–300] total syntheses of brevisamide, a cyclic ether alkaloid from the dinoflagellate *Karenia brevis*,[301] was achieved in 21 linear steps from *cis*-but-2-ene-1,4-diol.[297] A series of synthetic studies established the configurations of various fragments of symbiodinolide, a polyol macrolide from the symbiotic marine dinoflagellate *Symbiodinium* sp.[302] For example, a stereoselective synthesis of the C-23–C-34 bis-epoxide fragment of symbiodinolide and related diastereomers led to configurational revision to (26*S*,27*R*,28*R*,29*S*,30*R*,32*S*),[303] while synthesis of the C-14–C-23 fragment established the configurations (17*S*,18*R*,21*R*).[304] Synthesis of the C-33–C-42 fragment established the configurations (36*S*,40*S*),[305,306] and also the absolute configuration of the C-1′–C-25′ fragment.[307] Xyloketal B, one of a series of ketals isolated from the mangrove fungus *Xylaria* sp.,[308] protected HUVECs against oxidised low density lipoprotein (LDL)-induced cell injury,[309] in addition to giving protection of rat pheochromocytoma (PC12) cells in an *in vitro* oxygen glucose deprivation (OGD) model of ischemic stroke.[310] Beneficial effects appear to be associated with these free radical-scavenging and antioxidant properties.[310] The known diketopiperazines Sch54796[311] and Sch54794[311] were isolated from *Penicillium* sp. [mangrove species not given, (South China Sea)] as inhibitors of laryngeal cancer hep2 and hepatoma hepG2 cell lines.[312] Fermentation of an unidentified marine fungus (source not given) yielded a number of known metabolites of which decarboxydihydrocitrinone[313] was inhibitory to MRSA.[314] Mycalamide A, a metabolite of the sponge *Mycale hentscheli*,[315] and pederin, isolated from *Paederus* spp. rove beetles,[316] are structurally similar polyketides. Three methyltransferases, part of a previously isolated set of genes from a bacterial endosymbiont, were incubated with mycalamide A to produce a non-natural hybrid compound, 18-*O*-methylmycalamide A which possessed increased cytotoxicity, providing evidence that invertebrates can obtain defensive metabolites from bacterial symbionts.[317] This work was carried out on the 10 μg scale, with the identity of the product derived from the ^{1}H NMR spectrum acquired in a capillary NMR probe. Most of the enzymes responsible for spiroketal formation and epoxidation in griseorhodin A[318] biosynthesis were identified through generation of 14 gene-deletion variants of the biosynthetic gene cluster isolated from a *Streptomyces* sp. (*Aplidium lenticulum*).[319] *Streptomyces maritimus* produces the enterocin family of polyketides.[320] Priming the enterocin biosynthetic enzymes with unnatural substrates led to *ex vivo* multienzyme syntheses of 24 unnatural 5-deoxyenterocin and wailupemycin F and G analogues, of which 18 were new.[321] Feeding experiments using ^{13}C-labelled sodium acetate precursors revealed that all 25 carbon atoms in the skeleton of aspergiolide A, a metabolite of the filamentous fungus *Aspergillus glaucus*,[322,323] were derived from labelled acetate.[324] The effects of biosynthetic pathway specific inhibitors and precursors on aspergiolide A production were investigated in a novel strategy involving simultaneous feeding of both, which resulted in greatly enhanced aspergiolide A production.[325] Biosynthetic studies of curacin A, a metabolite of mixed polyketide-peptideorigin from the cyanobacterium *Lyngbya majuscula*,[326] revealed an unprecedented decarboxylative chain termination mechanism involving a module containing adjacent sulfotransferase (ST) and thioesterase (TE) catalytic domains.[327] Studies on the biotransformation of bromosesquiterpenes in the fungi, *Rhinocladiella atrovirens*[328] and *Rhinocladiella* sp. from the Okinawan brown alga *Stypopodium zonale*,[329] indicated that the former fungus converted aplysistatin into 5α-hydroxyaplysistatin, 5α-hydroxyisoaplysistatin and 9β-hydroxyaplysistatin, whilst the latter fungus, transformed aplysistatin, palisadin A and 12-hydroxypalisadin B to 3,4-dihydroaplysistatin and 9,10-dehydrobromopalisadin A.[330]

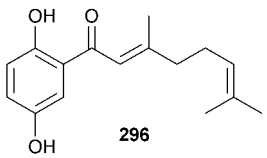
4 Green algae

The chemistry of the abundant and relatively easy to collect members of the phylum Chlorophyta continues to be underrepresented. In 2009 there were only 30 papers published, with

the majority being descriptive, or dealing with polysaccharide chemistry. A bioactivity-directed analysis of *Ulva fasciata* (Aabu-Qir, Mediterranean coast, Egypt) characterised three new unsaturated fatty acids **293–295** and a further ten known non-polar metabolites identified by GC–MS.[331]



The ubiquitous monoterpene loliolide[332] was found in thirteen red, brown and green algae from the Black Sea. This was the first report of loliolide from green algae.[333] Debromocymopolone, **296** was isolated from *Cymopolia barbata* (Fairy Hill Beach, Jamaica), and is the first non-halogenated cymopol isolated.[334]

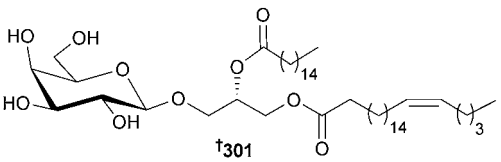


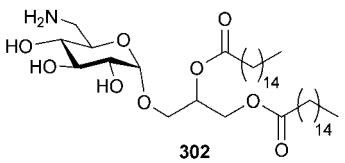
A significant find was the discovery of two new cyclic depsipeptides from *Bryopsis pennata* (Kahala Bay, Ohau, Hawaii). These were 5-OHKF **297** and norKA **298**, and join the other seventeen congeners of the kahalide family that have to date been isolated from *B. pennata* or molluscs of the genus *Elysia*. Interestingly, 5-OHKF **297** showed no antitumour properties, in keeping with the importance of the aliphatic group in the known compounds KF **299** and isoKF **300**.[335] Six known sterols were identified from *Chaetomorpha basiretorsa*.[336] In each case this was the first discovery of these compounds from that genus.

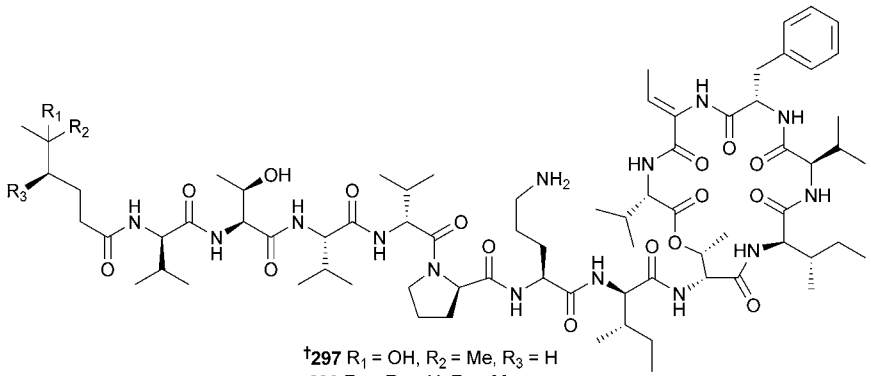
The biological roles of two well-known *Caulerpa* metabolites have been examined. Both natural (+)-caulerpenyne and the synthetic enantiomer inhibited microtubule formation, with the (−) enantiomer having a lower IC_{50} for inhibition of tubulin polymerisation.[337] In this recent study, (−)-caulerpenyne was demonstrated to bind slowly to tubulin in a non-covalent and poorly reversed fashion, but not at the colchicine, Taxol® or *Vinca*-alkaloid binding sites.[338] Caulerpin, a *Caulerpa* sp. pigment,[339] but also found in *Chondria* sp.[340] has been established as an inhibitor of mitochondrial respiration at complex 1, suppressing hypoxic activation of HIF-1, an important target in anticancer drug discovery.[341] The first syntheses of two *Caulerpa taxifolia* metabolites, taxifolione and taxifolial D, were reported and the surprising (*Z*) configuration for taxifolial D confirmed.[342] Metabolomics technology was successfully applied in a proof-of-principle study to assess environmental risk factors using the unicellular *Scendesmus vacuolatus* as test organism.[343]

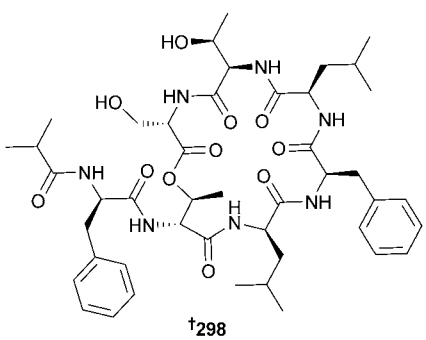
5 Brown algae

The majority of the new metabolites from brown algae each year were terpenoid, or part terpenoid in origin. In 2009 well over half of the ~60 papers published were descriptive in nature, or dealt with sulfated polysaccharide (fucoidan) chemistry. Eicosapentaenoic acid, isolated for the first time from *Zonaria tournefortii* (Tipaza, Algeria), was proposed as the biosynthetic precursor for the co-occuring acylphloroglucinols and chromone derivatives.[344] The diacylglycerol **301** was reported from *Zonaria diesingiana* (unspecified location, South China Sea),[345] while ishigoside **302** was isolated from *Ishige okamurae* (Busan, S. Korea). The free-radical-scavenging activity of ishigoside **302** was evaluated using an ESR technique.[346]

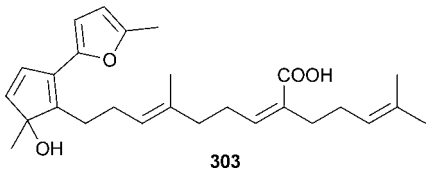






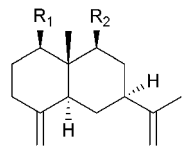


A bioactivity study of the fibrinolytic properties of *Sargassum fulvellum* (East Sea, China), selected from 700 samples, identified the bioactives as the known diacylglycerols MOGG and POGG. This was the first isolation of these compounds from a marine source.[347] In another large survey, 342 species of marine alga were screened against the bacterium *Propionibacterium acnes*, and the bacteriostatic compound sargafuran **303** was isolated from *Sargassum macrocarpum* (Japan). Sargafuran, a novel compound 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.[348]

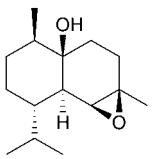


303

Two brominated selinane sesquiterpenoids **304** and **305** and five known sesquiterpenes were isolated from *Dictyopteris divaricata* (Yantan, Shandong Province, China).[349] This same alga was also the source of the cadinane sesquiterpenes **306** and **307**, and six other known cadinanes.[350,351]



304 R_1 = Br, R_2 = H
305 R_1 = H, R_2 = Br



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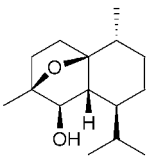
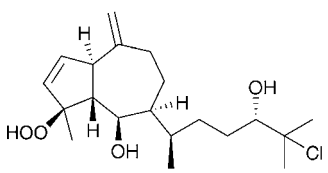


307

Hydroperoxides have rarely been found in algae: two examples, dictyohydroperoxide, **308** and hydroperoxyacetoxycrenulide **309**, were isolated from *Dictyota dichotoma* (Troitsa Bay, Sea of Japan, Russia) along with 15 other known diterpenoid and steroidal secondary metabolites.[352]



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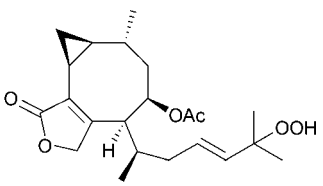
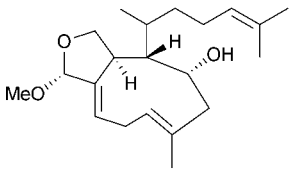


309

In a study of a Mediterranean *Dictyota* sp. (Le Brusc Lagoon, France), a new xenicane **310** and three new dolabellanes **311–313** were characterised in addition to seven previously reported diterpenoids. A study was carried out on the antifouling properties of the more abundant of this series against *Pseudoalteromonas* sp.[353] Despite differences in the magnitude of the optical rotation, the absolute configuration of the xenicane diterpenoid (−)-4-hydroxydictyolactone **314** from *Dictyota ciliolata*[354] has been determined from synthesis *via* an enantiocontrolled route utilising the *B*-alkyl Suzuki reaction to incorporate the (*E*)-alkene in a direct ring closure.[355]

The inhibitory activity of two known dolastanes from *Dictyota cericornis* (Baia da Ribeira, Brazil) against mammalian Na^+K^+-ATPase was evaluated.[356] Seven new members of the rare 2,6-



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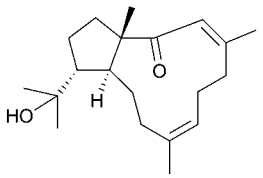

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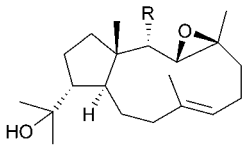
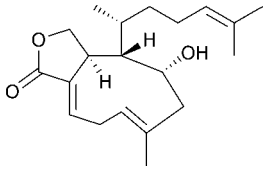
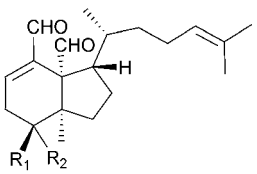


312 R = OH
313 R = H

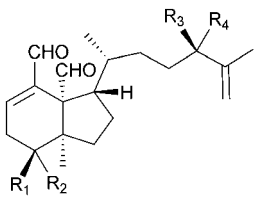


†**314**

cyclo-xenicane skeleton, **315–321**, were obtained from *Dilophus fasciola* (Cap Zebib, Tunisia) and *D. spiralis* (Elafonissos Island, Greece). Xenicane **315** was isolated from *D. spiralis* and **316–321** from *D. fasciola*. In addition, seven previously reported metabolites were isolated.[357]

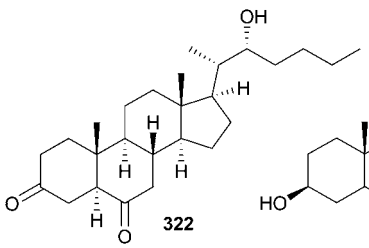


315 R_1 = R_2 = H
316 R_1 = OH, R_2 = H
317 R_1 = H, R_2 = OH

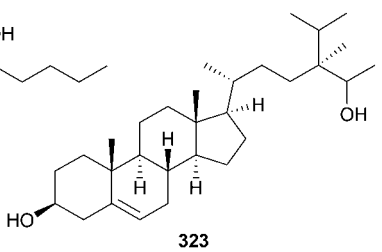


318 R_1 = R_4 = OH, R_2 = R_3 = H
319 R_1 = R_3 = OH, R_2 = R_4 = H
320 R_1 = R_3 = H, R_2 = R_4 = OH
321 R_1 = R_4 = H, R_2 = R_3 = OH

A brassinosteroid-related compound **322** was isolated from *Cystoseira myrica* (Fayed, Egypt) in an investigation centered on the cytotoxic activity of the extract against two human cancer cell lines.[358] *Cytoseira compressa* (Tunisia) was the origin of the sterol saoussazine **323**, discovered along with fucosterol,[359] while from *Sargassum fusiforme* (location not specified) six known sterols and two known glycolipids were reported. For both glycolipids this was the first isolation from this genus.[360]



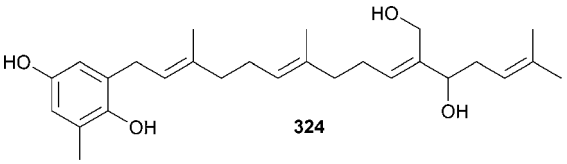
322



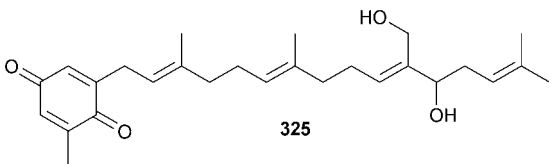
323

Three new meroditerpenoids, **324–326**, along with four known metabolites, were isolated from *Sargassum fallax* (Port Phillip Bay, Australia).[361]

Eight known compounds and two new meroditerpenoids **327** and **328**, which included a halogenated derivative **328**, from *Stypopodium flabelliforme* (Hanga Roa, Easter Island) were characterised as the derived peracetates. This is the first occurrence of a halogenated *Stypopodium* metabolite.[362]



324



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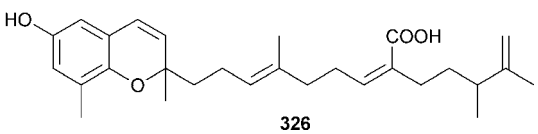

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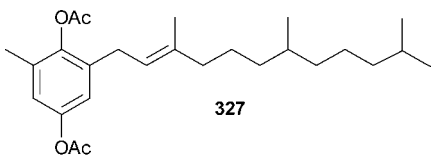

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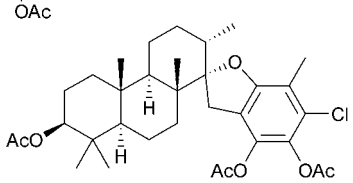
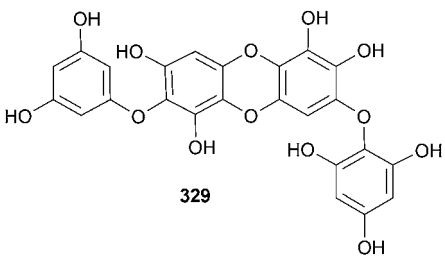


328

The absolute configuration of (−)-stypotriol was determined, as the triacetate, by application of vibrational CD spectroscopy. This was the first direct assignment of configuration as this previously had relied on the several syntheses, from chiral substrates, of (−)-stypoldione, the air-oxidation product. With 300 electrons, this is to date the largest natural product successfully studied by VCD.[363] A reassignment of configuration has been reported for the meroditerpenoids from a Korean *Sargassum siliquastrum*,[364] and requires revision of the C-13′ configuration for six of the structures.[365] The alga *Leathsia nana* was a rich source of bromophenols,[366] and six compounds have now been evaluated *in vitro* against eight human tumour cell lines and protein tyrosine kinase (PTK) (with over-expression of *c-kit*). All compounds were modestly cytotoxic and three were strong inhibitors of PTK.[367] Use of an antioxidant assay led to the isolation of the phlorotannin diphlorethohydroxycarmalol **329** from the abundant Japanese alga *Ishige okamurae*. ESR techniques were used to establish the radical-scavenging activity of **329**.[368] In addition to having radical-scavenging activity, **329** was a potent inhibitor of α-glucosidase and α-amylase, with possible potential as a functional food or nutraceutical for diabetes.[369]

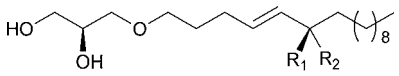


329

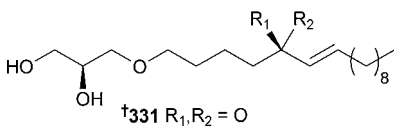
The antioxidant and anti-inflammatory properties of phlorotannins from *Ecklonia stolonifera* and *E. cava* have been investigated.[370,371] In further studies, the suppressive effects of eckstolonol[372] and phlorofucofuroeckol A[373] (*E. stolonifera*) on FcεRI expression (antiallergenic) was examined,[374] and the role of two phlorotannins from *E. cava* in inducing apoptosis in MCF-7 cells evaluated.[375]

6 Red algae

The number of new compounds reported from red algae in 2009 has recovered from a marked reduction in 2008 to levels more typical for the previous years. Six weakly cytotoxic 1-glyceryl ethers, ceratodictyols A–F **330–335**, were obtained from a mixed assemblage of the red alga *Ceratodictyon spongiosum* and the sponge *Haliclona cymaeformis* (Kurosaki, Japan). These 1-alkylglyceryl ethers were unusual in having oxygenation in the alkyl chain.[376]

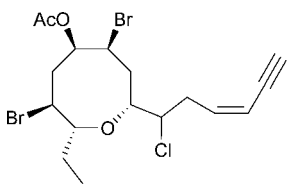


†**330** R_1,R_2 = O
332 R_1 = H, R_2 = OH
333 R_1 = OH, R_2 = H

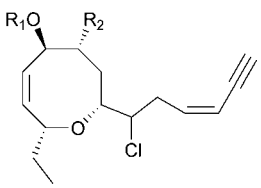


†**331** R_1,R_2 = O
334 R_1 = H, R_2 = OH
335 R_1 = OH, R_2 = H

A collection of *Laurencia grandulifera* (Loutraki Bay, Crete) yielded five lauthisan derivatives **336–340**, some of which showed modest antistaphylococcal activity.[377] In a separate report, five C_{15} tetrahydrofuran-containing acetogenins **341–345** and a linear biosynthetic precursor **346** were described from this same collection of *L. grandulifera*.[378]

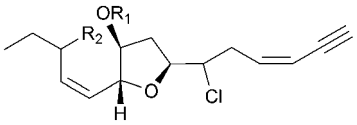


336

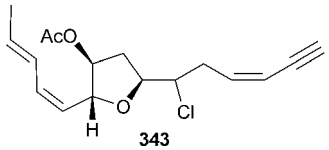


337 R_1 = Ac, R_2 = OAc
338 R_1 = Ac, R_2 = OH
339 R_1 = H, R_2 = OAc
340 R_1 = Ac, R_2 = Br

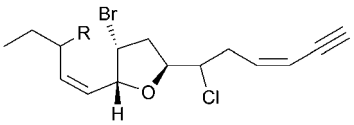
Neurymenolides A **347** and B **348** are two α-pyrone macrolides isolated from *Neurymenia fraxinifolia* (Taveuni, Fiji). Neurymenolide A, which consists of quickly interchanging atropisomers, had moderate potency against MRSA, VREF strains and a range of tumour cell lines. Neurymenolide B showed only modest MRSA activity.[379] *Plocamium cornutum* (Kalk Bay, S.



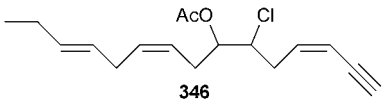
341 R_1 = Ac, R_2 = Cl
342 R_1 = H, R_2 = OH



343

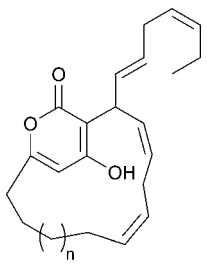


344 R = Br
345 R = OMe

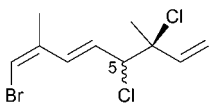


346

Africa) was the source of five antiplasmodial (to a chloroquine-sensitive strain of *Plasmodium falciparum*) halogenated monoterpenes, of which the two new ones **349** and **350** were the least active.[380]

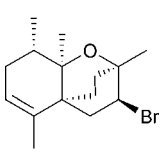


347 n = 3
348 n = 5

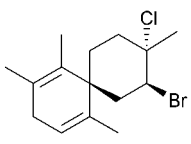


349 (5*S**)
350 (5*R**)

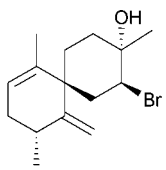
Several rearranged chamigrane sesquiterpenes were obtained from *Laurencia composita* (Nanji Is., China). Two, 2-bromospironippol **351** and laurencomposidiene **352**, were new. Confusingly, **351** was named as laurencomposene elsewhere in this paper.[381] It was suggested that the occurrence of rearranged chamigranes in *L. composita* but not in *L. okamurai* could provide a useful chemotaxonomic marker to distinguish these two similar species, but this argument is not supported by the report, by the same authors, of laurenokamurin **353** in *L. okamurai* (Weihai coastline, China).[382]



351

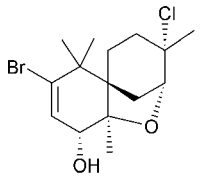


352



353

L. saitoi (Shandong Province, China) yielded the halogenated chamigranes **354** and **355**, together with **356** and **357** as an inseparable 1 : 1 mixture.[383] Another collection of *L. saitoi* (Hainan coastline, China) provided three sesquiterpenes **358–360** and the norsesquiterpene **361**.[384]



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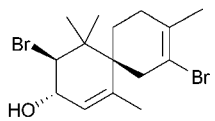

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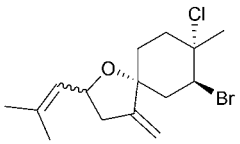

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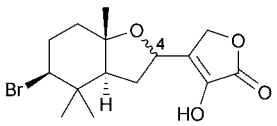
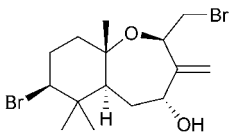
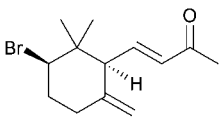
357



358 (4*S**)
359 (4*R**)

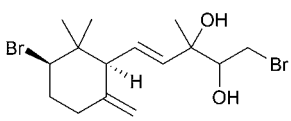


360



361

The new sesquiterpene **362**, along with fifteen other known sesquiterpenes, was obtained from *L. similis* (Sanya Bay, China).[385] The brominated diterpene neorogioltriol **363**, which has analgesic properties, was obtained from *L. glandulifera* (Kefalonia Is., Greece),[386] while *Sphaerococcus coronopifolius* (Corfu Is., Greece) yielded the neodolabellane diterpenes sphaerollane I **364** and II **365**, together with the sphaeroane diterpene **366**.[387]



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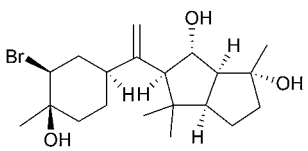
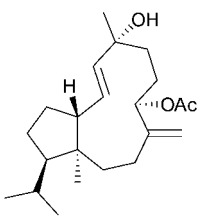
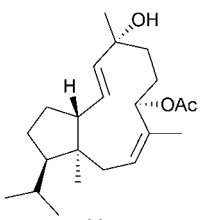


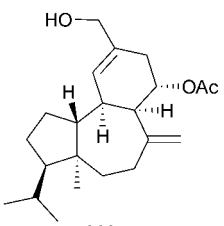
363



364



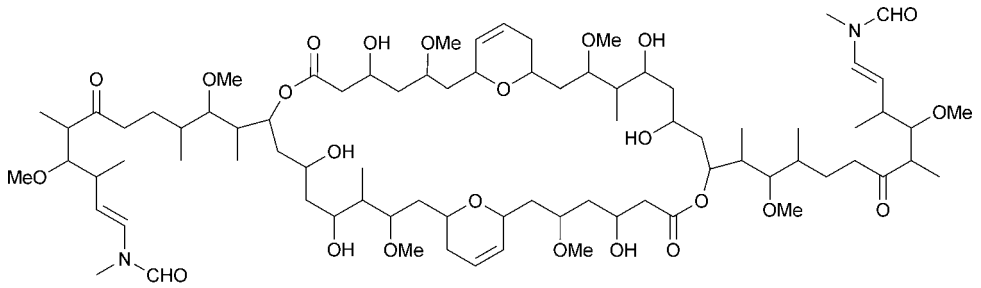
365



366

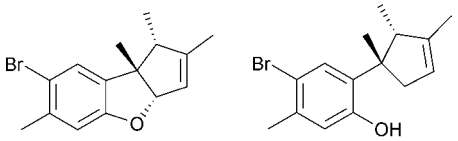
The metamorphosis-enhancing macrodiolide, luminaolide **367**, was isolated from the crustose coralline alga *Hydrolithon reinboldii*. Based on the similarity of this compound to others previously reported from cyanobacteria, it was speculated that luminaolide may be produced by epiphytic bacteria on the surface of the *H. reinboldii*.[388]

In a study on the phytochemical profiling of *Laurencia filiformis* (St. Paul's Beach, Australia) by conventional and HPLC-NMR methods, new aromatic sesquiterpenes cycloisoallolaurinterol **368**



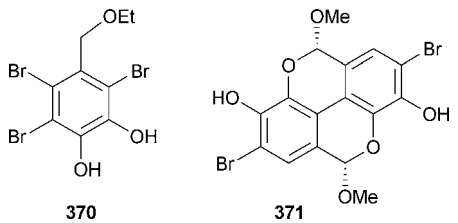
367

and isoallolaurinterol **369** were isolated.[389] It was suggested that these may have been formed as artefacts from allolaurinterol. Several other known compounds were also characterised in this study, including filiformin,[390] for which the first X-ray diffraction study was secured.



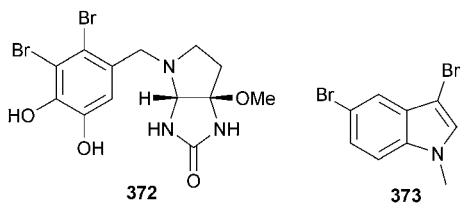
368 369

The weakly antimicrobial bromoether **370** was isolated from *Symphyocladia latiuscula* (Qingdao, China).[391] The bromophenol **371** was obtained from *Polysiphonia urceolata* (Yantai, China) and characterised by spectroscopic techniques and DFT theoretical analysis.[392]

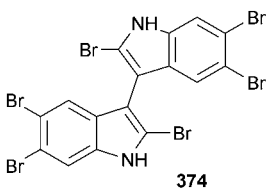


370 371

By using a novel 'stacked HSQC mask' dereplication strategy on partially purified mixtures from algal extracts, a new nitrogenous bromophenol, colensolide A **372**, was identified from *Osmundaria colensoi* (Northland, New Zealand).[393] Two



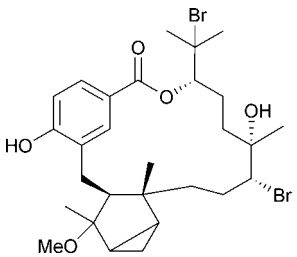
372 373



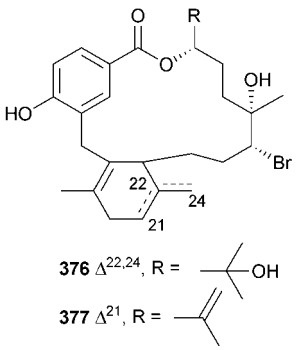
374

bromoindole alkaloids **373** and **374** were isolated from *Laurencia similis* (Sanya Bay, China).[394]

A further study on *Callophycus serratus* (Yanuca, Fiji) has yielded an additional suite of unusual antimalarial diterpene-benzoate macrolides, bromophycolides J–Q **375–382**. These bromophycolides also showed a range of moderate to strong antimicrobial and anticancer activities.[395]

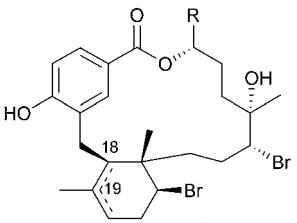


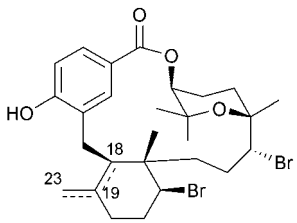
375



376 $\Delta^{22,24}$, R = OH

377 Δ^{21}, R =





378 Δ^{18}, R =

379 Δ^{19}, R =

380 Δ^{19}, R = Br

381 $\Delta^{19,23}$

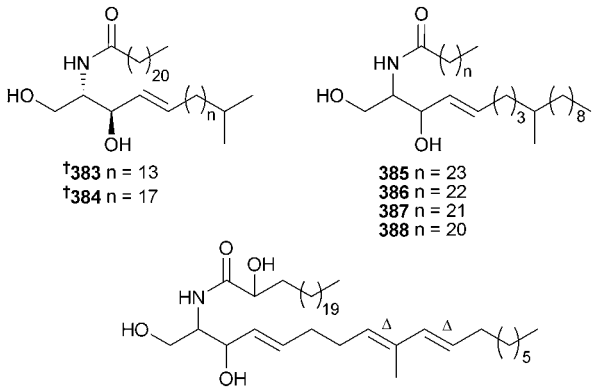
382 Δ^{18}

The biologically active halophenol 2,2′,3,3′-tetrabromo-4,4′,5,5′-tetrahydroxydiphenylmethane, originally from *Rhodomela larix*,[396] was synthesised along with a series of related halogenated bis(hydroxyphenyl)methanes in a study of antimicrobial activities.[397] The syntheses of four analogues of the oxylipin agardhilactone (*Agardhiella subulata*)[398] has resulted in a revision of the absolute configuration of this compound.[399] Radioactive ^{82}Br was used in a study of the biosynthesis of laurencin, laureatin and other brominated metabolites in some

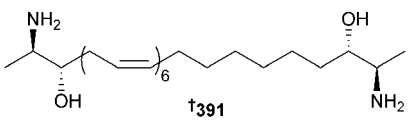
Laurencia species.[400] Reactive desorption electrospray mass spectrometry (DESI-MS) is a promising technique and permits MS experiments under ambient environmental condition. In this example, three bromophycolides, implicated as antimicrobial defense compounds, were directly detected on the surface of *Callophycus serratus*.[401] This technique is applicable to a wide range of surface types, not just red alga.

7 Sponges

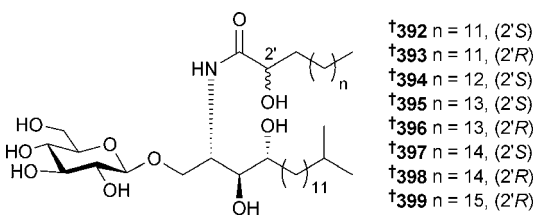
The number of new compounds reported from sponges in 2009 (287) is similar to that in each of the previous few years. The alkyl amino alcohol halaminol A (*Haliclona* sp.)[402] induced rapid larval settling in ascidians but prevented their subsequent metamorphosis. For the larvae of other phyla, halaminol A inhibited settlement, and was toxic.[403] Iotrochotamides I **383** and II **384** were isolated from *Iotrochota purpurea* (Pulau, Indonesia).[404] A *Haliclona* species (Jeddah, Saudi Arabia) yielded a series of cytotoxic sphingolipids, **385–390**.[405]



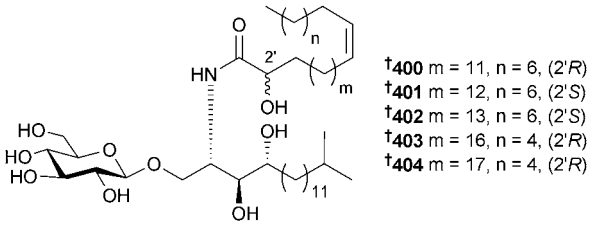
The absolute configuration of leucettamol A **391** (*Leucetta microrhaphis*)[406] was determined by a deconvolution of superimposed exciton coupled circular dichroism spectra of a hydrogenated *N*,*N*′,*O*,*O*′-benzoyl derivative.[407] Leucettamol A was previously claimed as a racemate due to its undetectable optical rotation.[406]

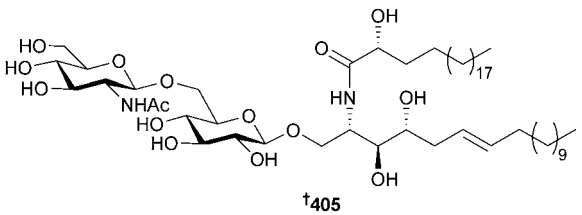


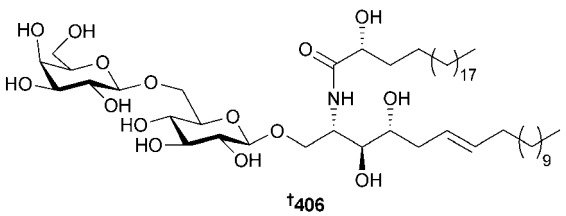
A *Haliclona* (*Reniera*) species (Ulleung Is., S. Korea) contained a series of glucocerebrosides, renierosides C_1–C_3, C_5–C_{14} **392–404**.[408]

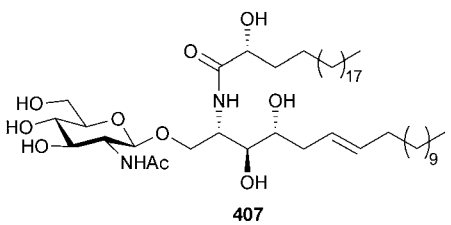


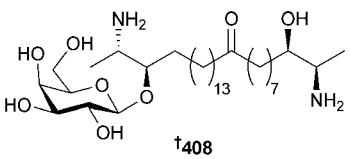
Amphiceramides A **405** and B **406** and the related *N*-acetylglucoside **407** were obtained from *Amphimedon compressa* (Key Largo, Florida).[409] *Rhizochalina incrustata* (Madagascar) yielded the bipolar sphingolipid isorhizochalin **408**.[410]



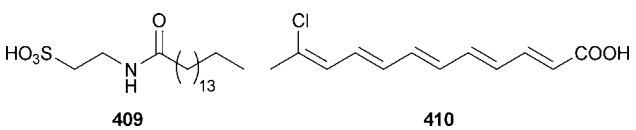




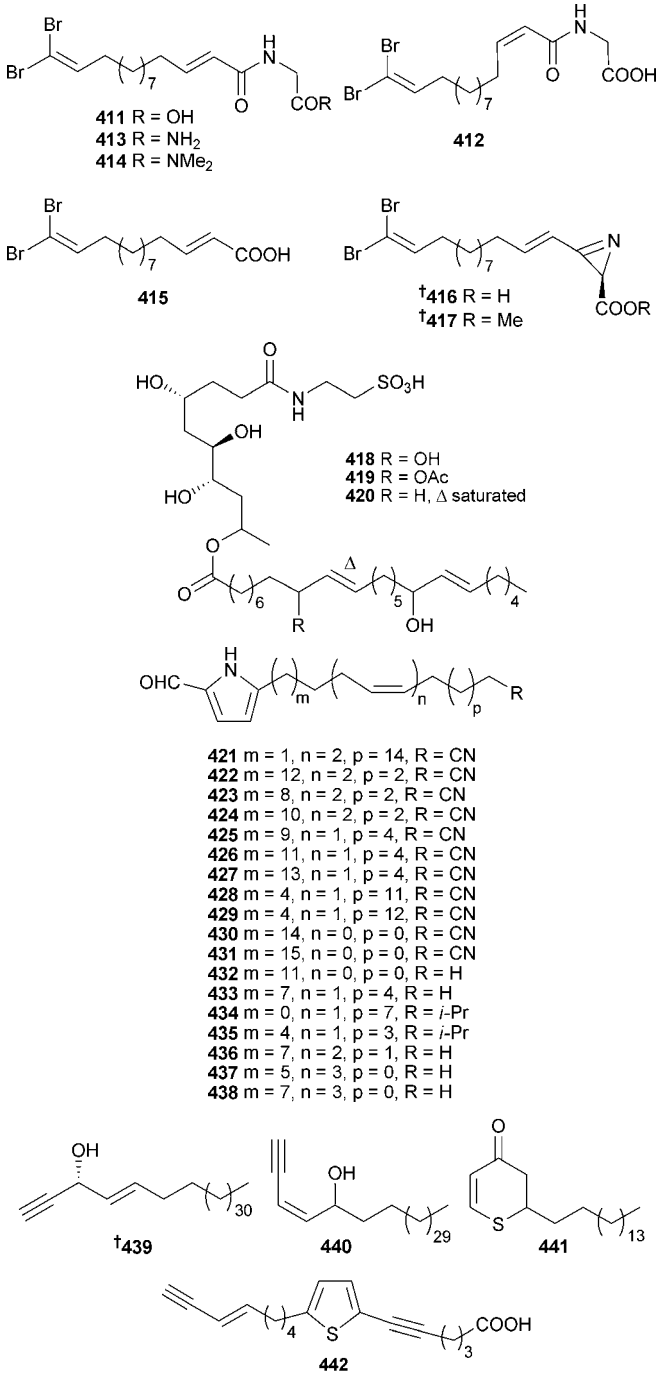




The taurine derivative 2-palmitamidoethane sulfonic acid **409** was isolated from *Haliclona* sp. (Hainan Is., China).[411] A series of glycerol ethers **348–353** isolated from the sponge/red alga assemblage *Haliclona cymaeformis*/*Ceratodictyon spongiosum* is described in the previous section of this review. *Theonella swinhoei* (Sulawesi, Indonesia) yielded aurantoic acid **410**.[412]



The bromine-containing motualevic acids A–F **411–416** and (4*E*)-(*R*)-antazirine **417**, isolated from *Siliquariaspongia* sp. (Motualevu Reef, Fiji), were active against MRSA.[413]



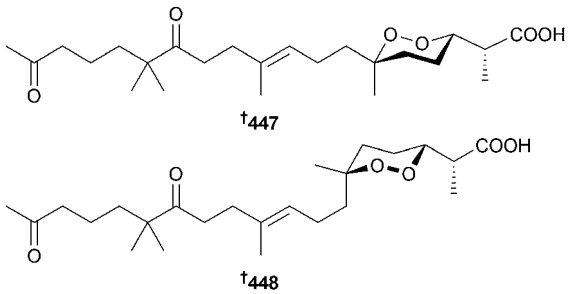
The carteriosulfonic acids A–C **418–420**, isolated from *Carteriospongia* sp. (San Miguel Is., Philippines), were inhibitors of the kinase GSK-3β.[414]

A series of long-chain-substituted pyrroles, mycalenitriles 4–14 **421–431** and mycalazals 14–20 **432–438**, inhibited HIF-1 activation in human breast tumour cells.[415]

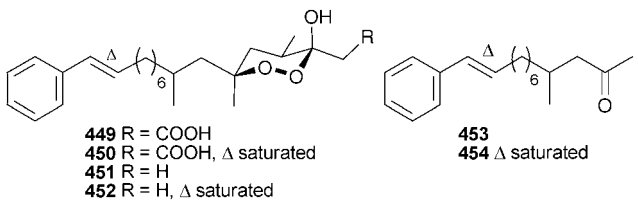
Jaspine B (*Jaspis* sp.)[416] inhibited sphingomyelin synthase in human melanoma cells, thereby increasing ceramide levels and thus triggering apoptosis which accounts for the compound's reported cytotoxicity.[417] The cytotoxic acetylenes **439** and **440** and the unusual dihydrothiopyranone **441** were obtained from *Reniochalina* sp. (Chuuk, Micronesia).[418] A weakly cytotoxic and weakly antimicrobial thiophene **442** was obtained from the calcareous sponge *Paragrantia cf. waguensis* (Okinawa).[419]

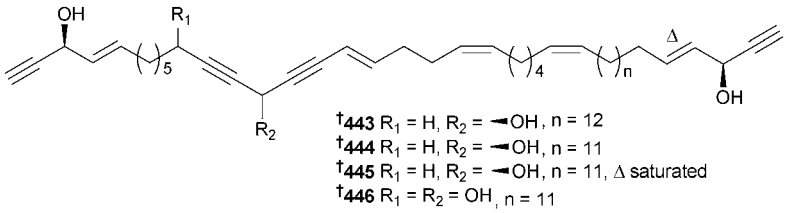
A *Petrosia* species, collected by dredging (150 m, Kurose Hole, Hachijo Is., S. Korea), contained the cytotoxic neopetroformynes A–D **443–446**.[420]

Diacarnus bismarckensis (Sanaroa, Papua New Guinea) yielded *ent*-(−)-muqubilone **447** and (+)-muqubilone B **448**, active against *Trypanosoma brucei* (African sleeping sickness).[421]

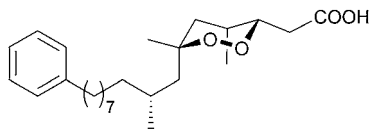


The absolute configuration of muqubilone (*Diacarnus erythraeanus*)[422] was assigned by the establishment of absolute configuration of **447**. The aromatic peroxides **449–452** and compounds **453** and **454** were isolated from *Plakortis* sp. (Orote Peninsula, Guam); **449–452** were weakly active against *S. aureus*.[423]

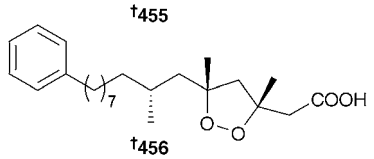




Plakinic acids I **455** and J **456** were obtained from *Plakortis halichondrioides*, and absolute configurations determined from CD curves by degradation and liposomal ordering of naphthamide derivatives.[424] Melophlins P, Q and R (*Melophlus* sp.)[425] have been synthesised,[426] as have plakortethers F[427] and G[427] (*Plakortis simplex*).[428]

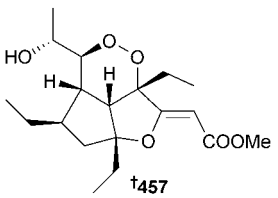


†**455**

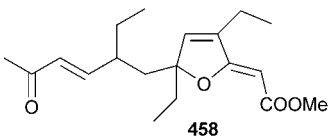


†**456**

The antimalarial gracilioethers A–C **457–459** were isolated from *Agelas gracilis* (Oshima-Shinsone, Japan). Compounds **458** and **459** were generally cytotoxic, while **458** was also active against *Leishmania major*.[429] (+)-Spiculoic acid (*Plakortis angulospiculatus*)[430] has been synthesised.[431] Total synthesis[432] has established the absolute configuration of tedanalactam **460** (*Tedania ignis*),[433] and syntheses of bengazoles C and E (*Jaspis* sp.)[434] have been reported.[435]



†**457**



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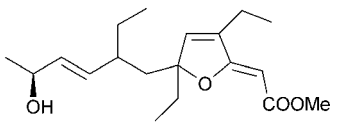

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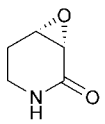
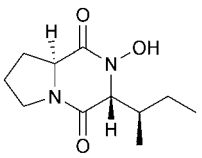
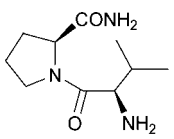


†**460**

A total synthesis of theopederin B (*Theonella* sp.)[436] has also been achieved using an SmI_2-promoted Reformatsky reaction.[437] A *Callyspongia* species (Hainan Is., China) yielded callyspongidipeptide A **461** and the related dipeptide **462**.[438]



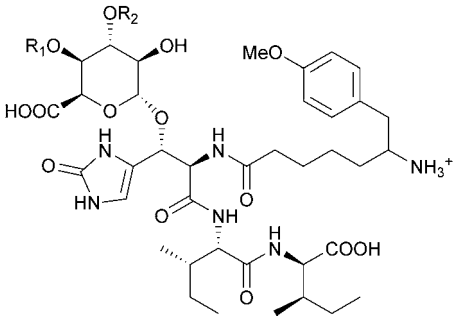
†**461**



†**462**

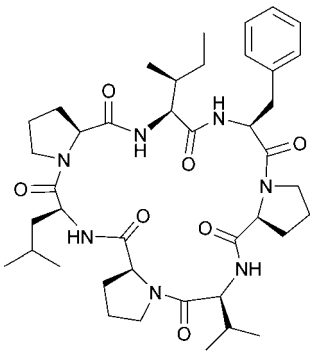
Citronamides A **463** and B **464**, isolated from *Citronia astra* (Day Reef, Queensland, Australia), were moderately active against *S. cerevisiae* (baker's yeast).[439]

The proline-rich cyclic peptides rolloamide A **465**, **466** and B **467** were obtained from *Eurypon laughlini* (Rollo Head, Dominica). Rolloamide A was cytotoxic and existed as two conformers with independent sets of NMR resonances attributable to *cis* **465** and *trans* **466** conformers around one of the

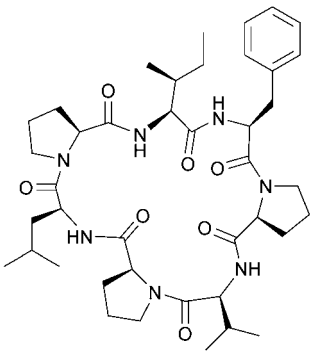


463 R_1 = H, R_2 = $CONH_2$
464 R_1 = $CONH_2$, R_2 = H

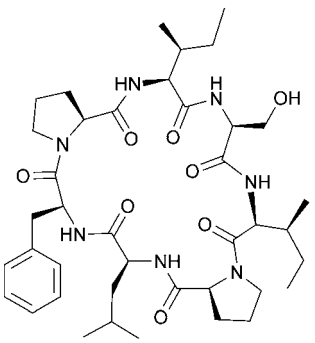
proline residues. Rolloamide B, while showing some evidence of a minor conformer, was determined to be predominantly the all-*cis* conformer.[440] *Prosuberites laughlini* (Aguadilla, Puerto Rico) contained a cytotoxic tryptophan-containing cyclic peptide, euryjanicin A **468**. While an X-ray analysis revealed all-*cis* conformers, there was NMR spectral evidence of another form in solution.[441]



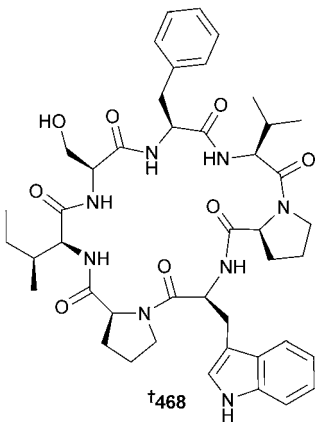
†**465**



†**466**

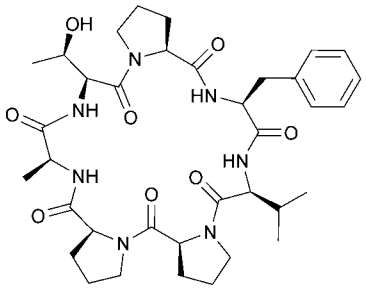


†**467**



†**468**

In a subsequent report by the same research group, the isolation of euryjanicins B–D **469–471** from the same sponge was reported.[442] The reported structure of euryjanicin C **470** is identical to the previously reported rolloamide B **467** in all respects except for a *trans* instead of a *cis* rotamer of one proline residue. Since the NMR data were recorded in different solvents, it is unclear whether the two reports represent the same structures.



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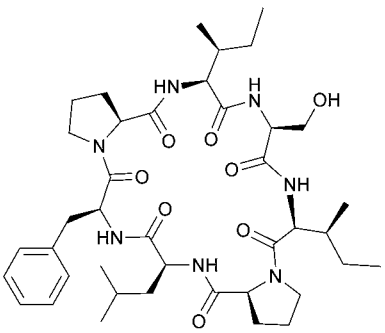

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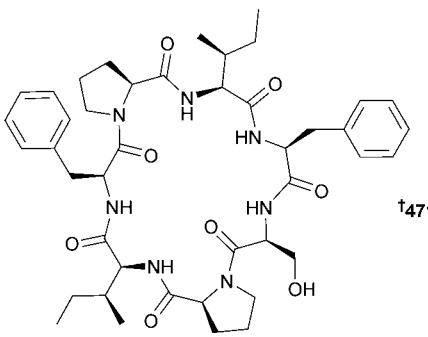
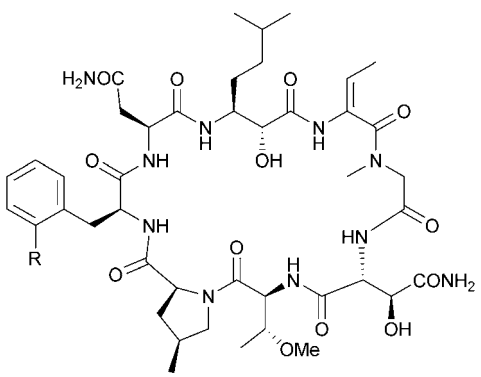


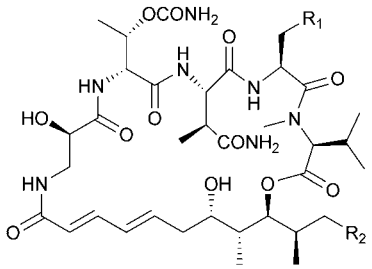
†471

The cyclic peptides perthamide C **472** and D **473**, isolated from *Theonella swinhoei* (Vangunu Is., Solomon Is.), were anti-inflammatory in a mouse oedema model, while lacking cytotoxicity.[443]

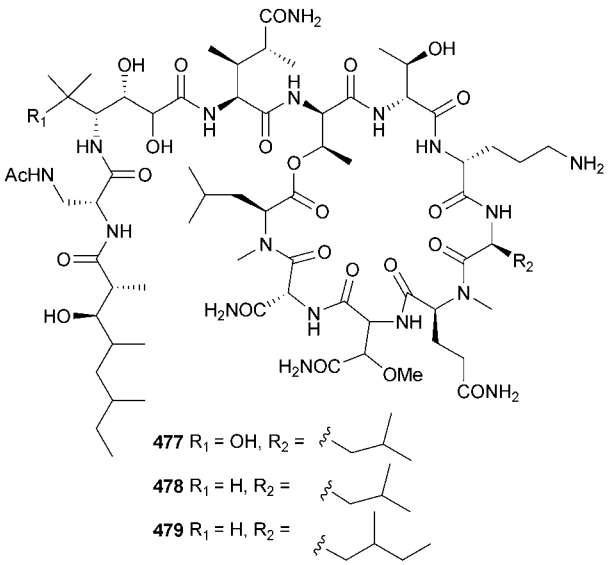


472 R = OH
473 R = H

An enantiomeric synthesis of stylisin 1 (*Stylissa caribica*)[444] has been reported.[445] Halicylindramide A (*Halichondria cylindrata*)[446] was synthesised enantiospecifically.[447] *Siliquariaspongia mirabilis* (Sulawesi, Indonesia) has yielded two classes of polyketide-containing cyclic peptides, celebeside A–C **474–476** and theopapuamides B–D **477–479**. Celebeside A **474** inibited HIV-1 proliferation, while the theopapuamides were cytotoxic.[448]

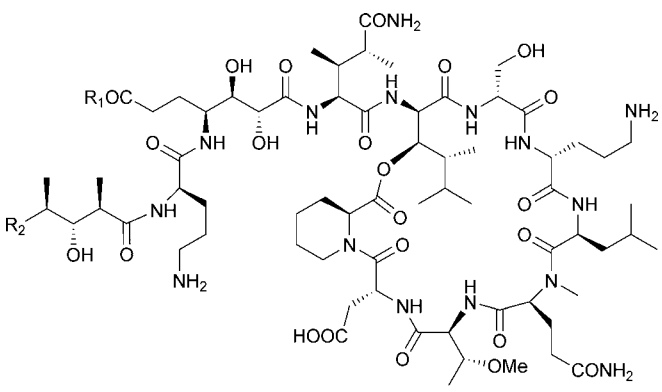


474 $R_1 = OPO_3^{2-}$, R_2 = Et
475 $R_1 = OPO_3^{2-}$, R_2 = Me
476 R_1 = OH, R_2 = Et



477 R_1 = OH, R_2 =
478 R_1 = H, R_2 =
479 R_1 = H, R_2 =

Nine new homophymines, B–E **480–483** and A1–E1 **484–488**, isolated from *Homophymia* sp. (New Caledonia), were potently antiproliferative to HL60 cells.[449]

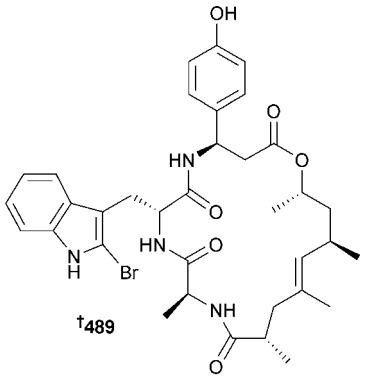


480 R_1 = OH, R_2 = *i*-Pr
481 R_1 = OH, R_2 =
482 R_1 = NH_2, R_2 =
483 R_1 = OH, R_2 =
484 R_1 = NH_2, R_2 =

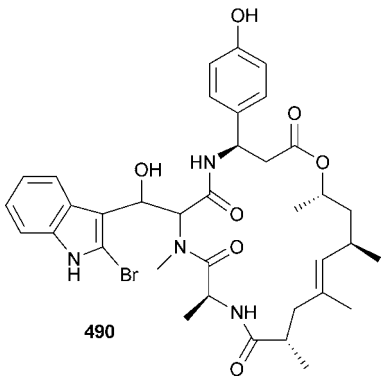
485 R_1 = NH_2, R_2 = *i*-Pr
486 R_1 = NH_2, R_2 =
487 R_1 = NH_2, R_2 =
488 R_1 = NH_2, R_2 =

Total syntheses of the tryptophan-containing peptides kapakahine B and F (*Cribrochalina olemda*)[450,451] have been

reported.[452] *Jaspis splendans* (Vanuatu) contained the cytotoxic jaspamides M–P **489–492**.[453]



†**489**



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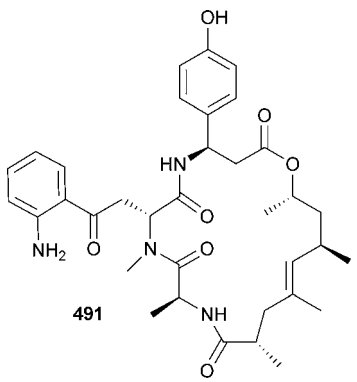

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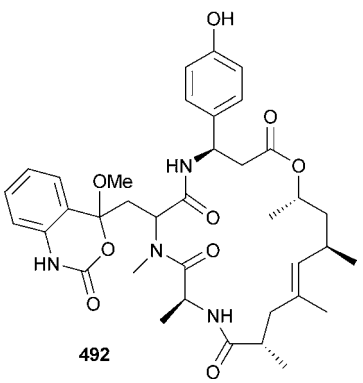
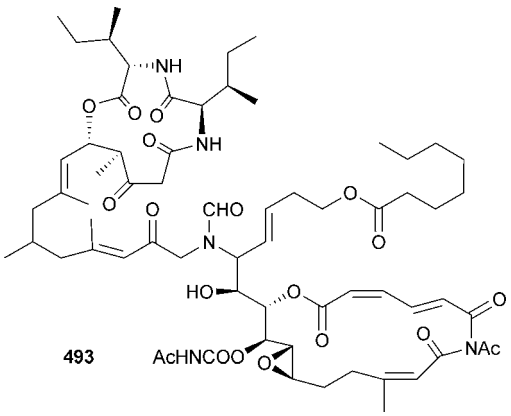


492

The nitrogenous bismacrolide tausalarin C **493**, isolated from *Fascaplysinopsis* sp. (Salary Bay, Madagascar), was anti-proliferative towards leukaemia cells.[454] In the same study, the relative configuration of salarin A **494** (*Fascaplysinopsis* sp.)[455] was determined by X-ray analysis. Pateamine (*Mycale* sp.)[456] has been shown to bind to eIFAIII and inhibit nonsense-mediated decay of messenger RNA.[457] The structure of hemi-phorboxazole A **495**, isolated from *Phorbas* sp. (Australia), was established from a total sample of 16.5 μg using a cryogenic capillary NMR probe.[458] A total synthesis has also been reported establishing absolute configuration. Unlike other members of the series, it was not bioactive.[459] From the same specimen of *Phorbas* sp. (Australia) the chlorocyclopropyl-bearing macrolide muironolide A **496** was isolated. The configuration of the chlorocyclopropyl appendage was determined *via* degradation and synthesis.[460]



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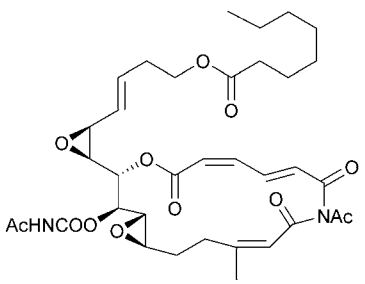

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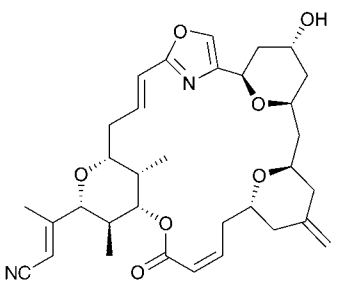
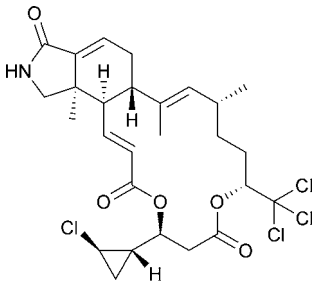


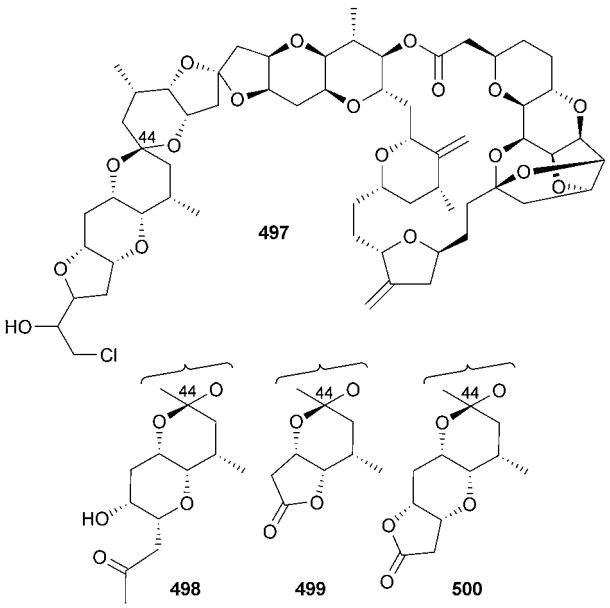
495

Zampanolide, originally isolated from *Fasciospongia rimosa* (Cape Zampa, Okinawa),[461] has recently been re-isolated from *Cacospongia mycofijiensis* ('Eua, Tonga) and found to be a potent microtubule-stabilising agent.[462] The synthesis of its natural (+) enantiomer has also been reported.[463] Neolaulimalide (*Fasciospongia rimosa*)[464] and isolaulimalide (*Hyattella* sp.),[465] congeners of the potent microtubule-stabilising laulimalide, have



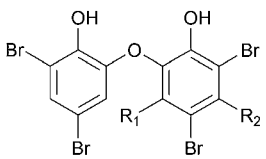
†496

been synthesised. Neolaulimalide was shown to have potent microtubule stabilising activity.[466] Four potently cytotoxic halichondrin B congeners, B-1140 **497**, B-1092 **498**, B-1020 **499** and B-1076 **500**, were obtained from a large collection of *Lissodendoryx* sp. (Kaikoura, New Zealand), with their structures being determined on the nanomole scale using a capillary NMR probe.[467]

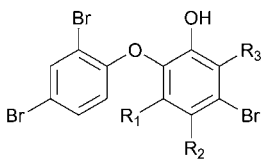


497 498 499 500

The diphenyl ethers **501** and **502** were isolated from *Dysidea* (*Lamellodysidea*) *herbacea* (Vim Levu, Fiji) while **503** and **504** were isolated from *Dysidea granulosa* (Milne Bay, Papua New Guinea). All were mild inhibitors of Bcl-2 activity.[468]

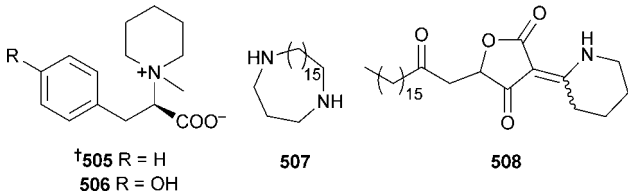


501 R_1 = Br, R_2 = H
502 R_1 = H, R_2 = Br



503 R_1 = Cl, R_2 = H, R_3 = Br
504 R_1 = Br, R_2 = OMe, R_3 = H

The modified amino acids axiphenylalaninium **505** and axityrosinium **506** were obtained from *Axinella polypoides* (Marseille, France).[469] A mildly cytotoxic cyclic diamine, 1,5-diazacyclohenicosane **507**, was isolated from *Mycale* sp. (Lamu Is., Kenya).[470] Plakoridine C **508**, obtained from *Plakortis* sp. (Manzamo, Okinawa), was a racemic and also a 1 : 1 *cis*/*trans* mixture of isomers.[471]

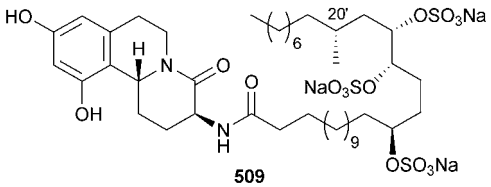


†**505** R = H
506 R = OH

507

508

The potent α-glucosidase inhibitors, schulzeine A–C (*Penares schulzei*),[472] have been synthesised, revising the C-20′ configuration of schulzeine A **509** from (*S*) to (*R*).[473] A biomimetic synthesis of pyrinadine A (*Cribrochalina* sp.)[474] confirmed the assigned *trans* azoxy functionality and suggested a hydroxylamine origin.[475] The alkylpyridinium salts pachychaline D **510**, didehydropachychaline A **511**, norpachychaline A **512** and dinorpachychaline A **513** were isolated from *Callyspongia* sp. (Martinique). A biogenic scheme linking these and other alkylpyridine metabolites to the presumed precursor norspermidines was also presented.[476]



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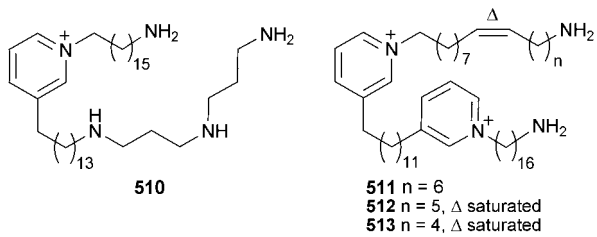
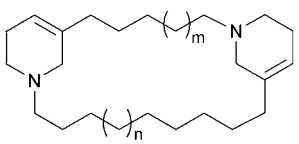


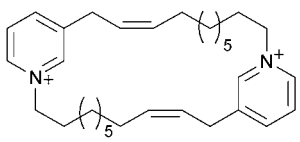
510

511 n = 6
512 n = 5, Δ saturated
513 n = 4, Δ saturated

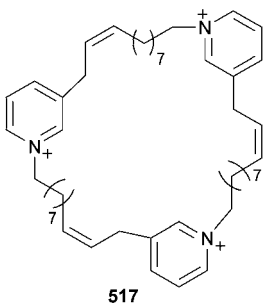
The Arctic sponge *Haliclona viscosa* (Kongsfjorden, Svalbard) was the source of haliclamines E **514** and F **515**; structures were established by MS analysis and synthesis of model compounds.[477] The weakly cytotoxic cyclic alkylpyridinium salts **516** and **517** were obtained from *Haliclona* sp. (Pacific Coast,



514 m = 5, n = 2
515 m = 7, n = 3



516



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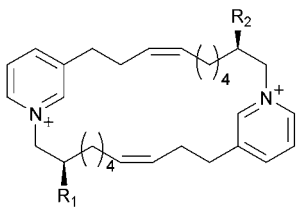


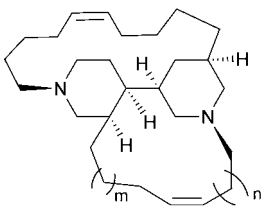
518 R_1 = R_2 = H
†**519** R_1 = R_2 = Me
†**520** R_1 = Me, R_2 = H

Guatemala).[478] Njaoaminiums A–C **518–520** were isolated from *Reniera* sp. (Pemba Is., Tanzania); **519** showed weak cytotoxicity.[479]

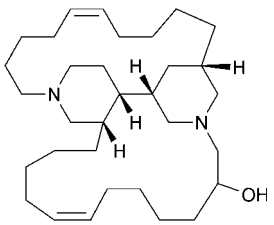
The ecological role of alkylpyridinium alkaloids was investigated for *Amphimedon chloros*, from which halitoxin (*Haliclona* sp.)[480] and amphitoxins (*Amphimedon compressa*)[481] were isolated. These compounds were selectively toxic towards saltwater bacteria, but not those associated with *A. chloros*.[482] The absolute configurations of the tetracyclic haliclonacyclamines A **521** and B **522** (*Haliclona* sp.)[483] were determined by X-ray analysis. Interestingly, they have opposite signs of rotation but are of the same enantiomeric series.[484] The related 22-hydroxyhaliclonacyclamine B **523**, isolated from *Haliclona* sp. (Flores Is., Indonesia), together with haliclonacyclamines A and B, were active against TB-causing *Mycobacterium smegmatis* and *M. bovis* under both aerobic and hypoxic conditions.[485]

The moderately cytotoxic and antibacterial haliclonin A **524** was isolated from *Haliclona* sp. (Jeju Is., S. Korea).[486]

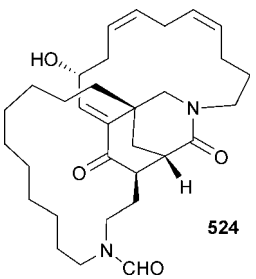
The cytotoxic manzamine-type alkaloids zamamidine A **525** and B **526** were isolated from *Amphimedon* sp. (Seragaki, Okinawa).[487] In a subsequent report the same group has described zamamidine C **527** with antitrypanosomal and antimalarial activity along with the related 3,4-dihydro-6-hydroxy-10,11-epoxymanzamine A **528** and 3,4-dihydromanzamine J *N*-oxide **529**.[488,489]



521 m = 4, n = 3
522 m = 2, n = 5



523



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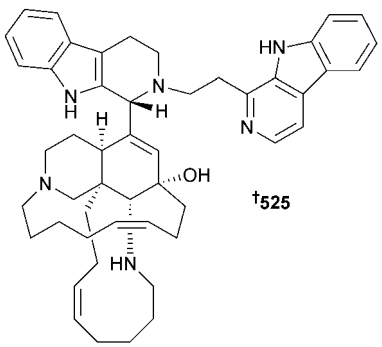
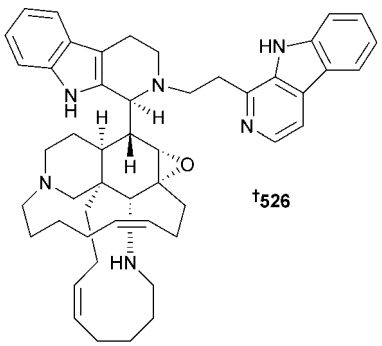
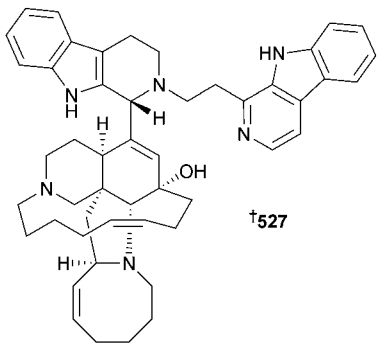


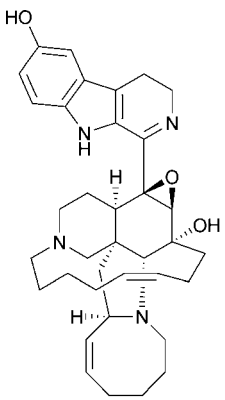
†**525**



†**526**



†**527**



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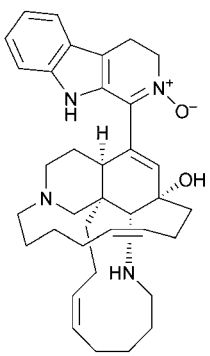
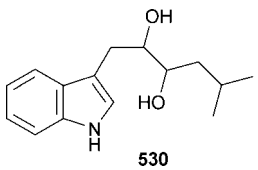


†**529**



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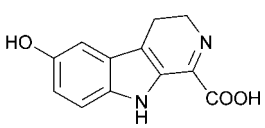

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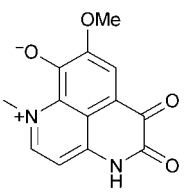

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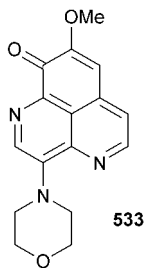


533

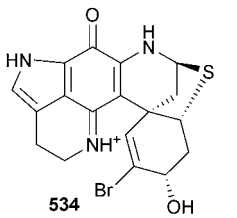
An *Axinella* species (Sanya, Hainan Is., China) yielded the indole alkaloid **530**.[490] A *Hyrtios* species (Chuuk, Micronesia) contained 1-carboxy-6-hydroxy-3,4-dihydro-β-carboline **531**.[491] Aaptanone **532** was isolated from *Aaptos aaptos* (Cu Lao Re Is., Vietnam).[492] An inibitor of EGF-induced malignant transformation of murine epidermal cells, 3-*N*-morpholinyl-9-demethyl(oxy)aaptamine **533**, was isolated from *Aaptos* sp. (Vang Fong Bay, Vietnam).[493]

Tsitsikammamine A (Latrunculiidae)[494] has been synthesised.[495] The discorhabdin congeners (+)-dihydrodiscorhabdin A **534**, (+)-debromodiscorhabdin A **535** and (+)-discorhabdin X **536** were isolated from *Higginsia* sp. (South Australia).[496] The structure of dihydrodiscorhabdin A was subsequently revised from **534** to the epimeric **537**.[497,498]

(+)-Dihydrodiscorhabdin L **538** was isolated from *Spongosorites* sp. (South Australia).[496] *Latrunculia* (*Biannulata*) *wellingtonesis* (Wellington, New Zealand) yielded the cytotoxic (6*R*,8*S*)-1-thiomethyldiscorhabdin G*/I **539** and both enantiomers of 16a,17a-dehydrodiscorhabdin W **540**.[497]

A synthesis of neolamellarin A (*Dendrilla nigra*)[499] has been reported.[500] A series of bromopyrroles, acanthamides A–D **541**–**544**, and the related **545** and **546**, were isolated from *Acanthostylotella* sp. (Bali, Indonesia).[501]

(*Z*)-Axinohydantoin and (*Z*)-debromoaxinohydantoin (*Stylotella aurantium*)[502] have been synthesised.[503] Syntheses of ceratamines A and B (*Pseudoceratina* sp.)[504] have been reported.[505] The antibacterial and antifungal nagelamides Q **547** and R **548** were isolated from *Agelas* sp. collected from Seragaki and Unten-Port, Okinawa, respectively.[506]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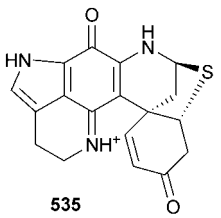
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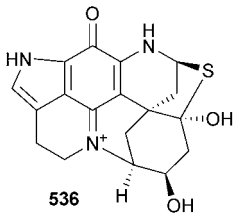
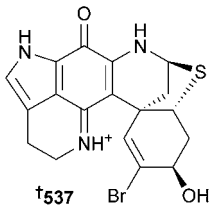
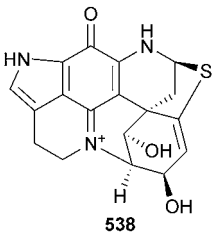

536


†**537**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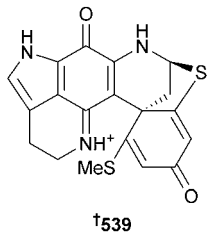
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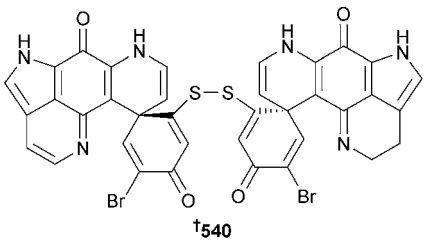
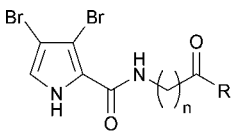
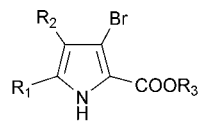
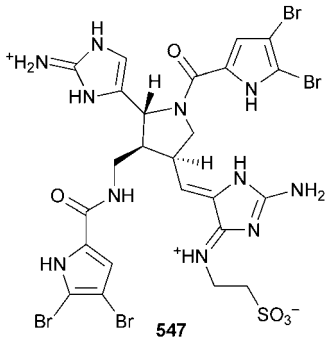

†**540**


541 n = 3, R = OMe
542 n = 2, R = OMe
543 n = 2, R = OEt
544 n = 3, R = OEt


545 R_1 = H, R_2 = Br, R_3 = Me
546 R_1 = Br, R_2 = R_3 = H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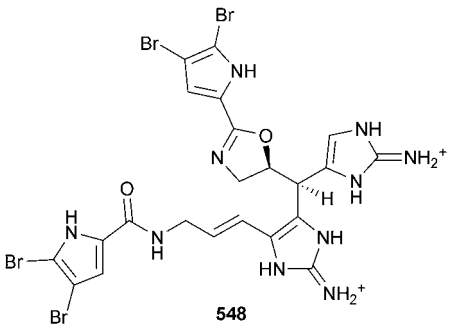
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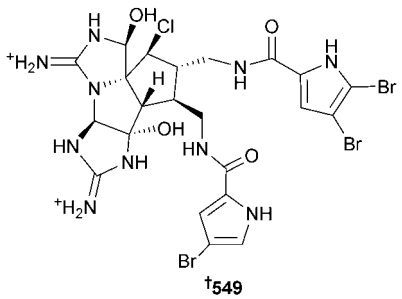
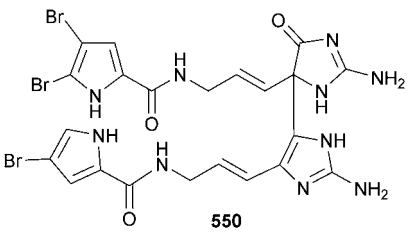
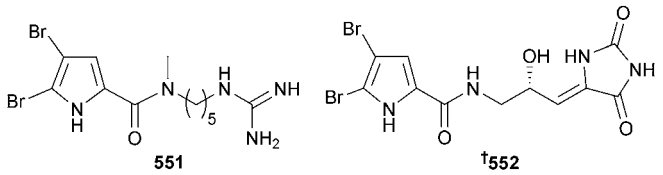
(−)-Dibromophakellin (*Phakellia flabellata*)[507] has been obtained from *Acanthella costata* (Sykes Reef, Great Barrier


†**549**

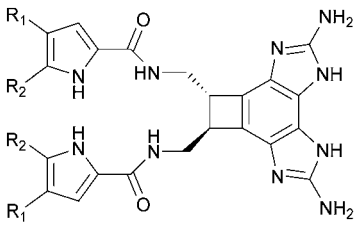

550

Reef) and was an α_{2B} adrenoceptor agonist.[508] The enantiomer, (+)-dibromophakellin, has been synthesised.[509] Nagelamides O **549** and P **550** and mukanadins E **551** and F **552** were isolated from several collections of *Agelas* sp. (Okinawa). Nagelamide O **549** was weakly antibacterial, nagelamide P **550** was isolated as a racemate, and mukanadin F **552** was weakly antifungal.[510]

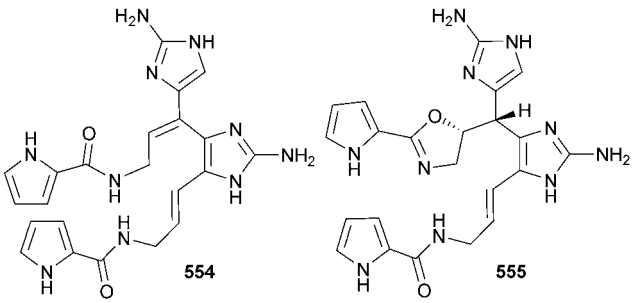


551 **†552**

Benzosceptrin A **553** and nagelamides S **554** and T **555** were isolated from *Agelas cf. mauritiana* (Guadalcanal, Solomon Is.) while benzosceptrin B **556** was isolated from *Phakellia* sp. (New Caledonia).[511] Benzosceptrin C **557** was isolated from *Agelas* sp. (Unten-Port, Okinawa).[512] The reported structure of nagelamide D (*Agelas* sp.)[513] has been synthesised, but the spectral data differ slightly from the natural compound.[514]



553 $R_1 = R_2 = H$
556 $R_1 = Br$, $R_2 = H$
557 $R_1 = R_2 = Br$

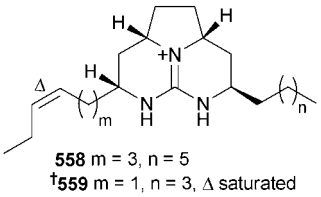


554 **555**

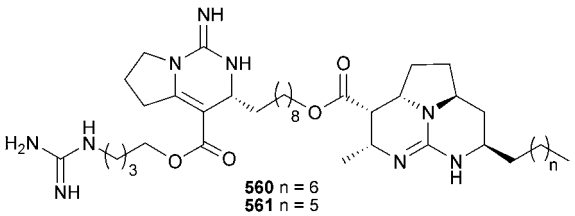
Merobatzelladines A **558** and B **559**, with activity against bacteria, *Plasmodium falciparum* (malaria) and *Trypanosoma brucei brucei* (sleeping sickness), were isolated from *Monanchora* sp. (Amami-Oshima, Japan).[515,516] Norbatzelladine A **560**, dinorbatzelladine A **561**, dinordehydrobatzelladine A **562**, dinorbatzelladine B **563** and dihomodehydrobatzelladine C **564** were isolated from *Monanchora arbuscula* (Martinique), while norbatzelladine L **565** and clathriadic acid **566** were isolated from *Clathria calla* (Guadeloupe). All compounds were cytotoxic.[517]

The bromotyrosine alkaloid content of *Aplysina* sp. (Croatia) was different between deep-water and shallow-water individual specimens. These differences were stable to transplantation and artificial culture.[518] Clavatadines C–E **567–569**, from *Suberea clavata* (Queensland, Australia), weakly inhibited serine protease factor XIa.[519]

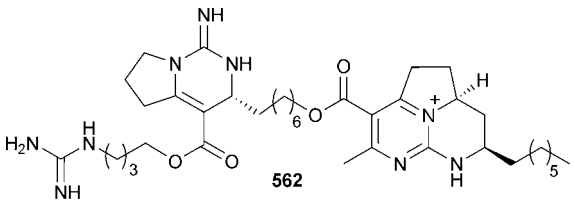
Moloka'iamine (*Pseudoceratina arabica*)[520] has been synthesised.[521] In an independent study the related alkaloid moloka'iamide, originally isolated along with moloka'iamine,[520] has also been synthesised.[522] The cytotoxic bromotyrosine dimer-



558 m = 3, n = 5
†559 m = 1, n = 3, Δ saturated



560 n = 6
561 n = 5



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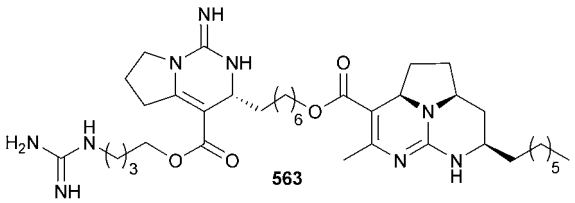

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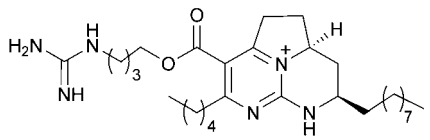

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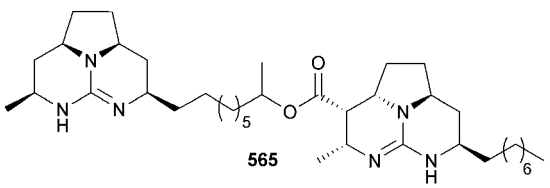

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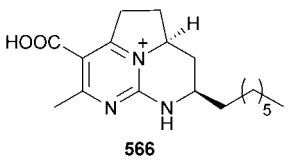
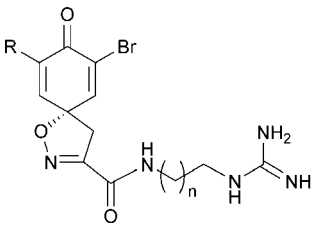


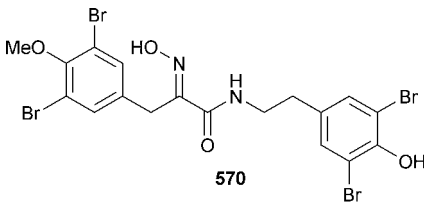
566



567 R = Br, n = 3
568 R = Br, n = 4
569 R = H, n = 3

derived alkaloid, JBIR-44 **570**, was obtained from *Psammaplysilla purpurea* (Kinwan Bay, Okinawa).[523] The non-selective pyruvate phosphate dikinase (PPDK) inhibitor

19-hydroxyaraplysillin-I N^{20}-sulfamate **571** was isolated from *Ianthella flabelliformis* (Shelburne Bay, Queensland, Australia).[524]



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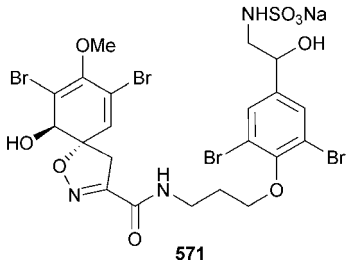
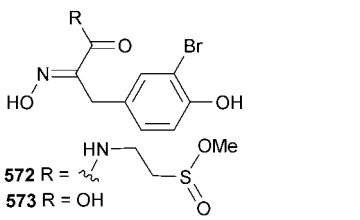
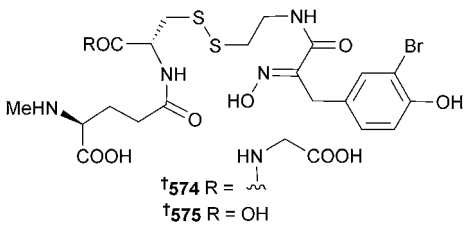


571

The structure of psammaplin I (*Pseudoceratina purpurea*)[525] has been revised from a sulfone to a sulfinate ester **572**. This paper also reported the isolation of the related compounds **573**–**575** from *P. purpurea*.[526]

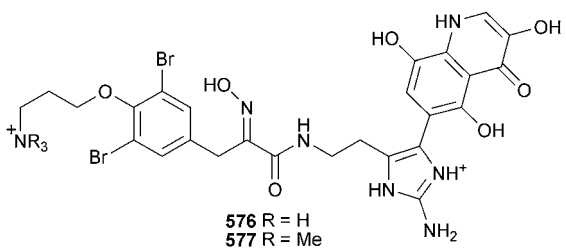


572 R = ~
573 R = OH

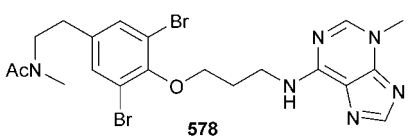


†**574** R = ~
†**575** R = OH

Tyrokeradine A **576** and the antimicrobial tyrokeradine B **577** were isolated from a Verongid sponge (Kerama Is., Okinawa).[527] The cytotoxic aphrocallistin **578** was isolated from the hexactinellid *Aphrocallistes beatrix* collected by submersible (Fort Pierce, Florida). It was also synthesised and found to cause G_1 arrest.[528]

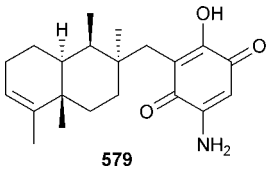


576 R = H
577 R = Me

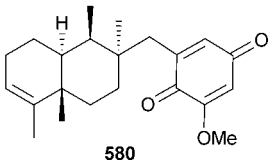


578

The merosesquiterpenoid dysideamine **579**, isolated from *Dysidea* sp. (Indonesia), was neuroprotective against iodoacetic acid-induced cell death in mouse neurons.[529] *Dysidea villosa* (Hainan Is., China) yielded the human protein tyrosine phosphatase 1B (hPTB1B) inhibitor 21-dehydroxybolinaquinone **580**.[530]

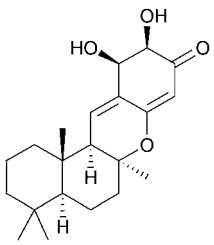


579

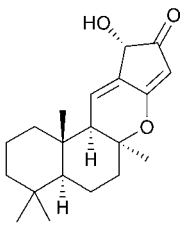


580

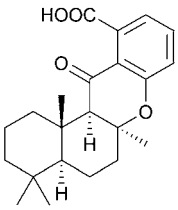
Puupehanol **581** was isolated from *Hyrtios* sp. (Papua New Guinea); the absolute configuration was determined from extensive calculated ECD spectra. Interestingly, a simple application of the octant rule predicted the wrong configuration.[531] 20-*epi*-Hydroxyhaterumadienone **582** and 15-oxo-puupehenoic acid **583** were isolated from *Hyrtios* sp. (Pocklington Reef, Papua New Guinea).[532]



†**581**

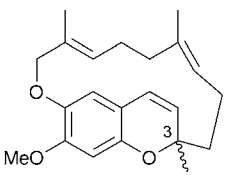


†**582**

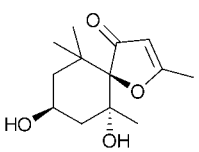


583

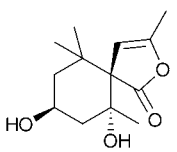
A racemic synthesis of smenochromene D and subsequent chiral separation has shown that (−)-smenochromene D **584** (*Smenospongia* sp.)[533] and (+)-likonide B **585** (*Hyatella* sp.)[534] are enantiomers, and suggests that neither of the original isolations were enantiopure.[535] Dysidine (*Dysidea* sp.)[536] promoted glucose uptake in cells, probably by inhibition of protein tyrosine phosphatase PTP1B.[537] A *Spheciospongia* species (Sanya, Hainan Is., China) yielded the norterpenoids spheciospongone A **586** and B **587**.[538]



†**584** (3*S*)
†**585** (3*R*)



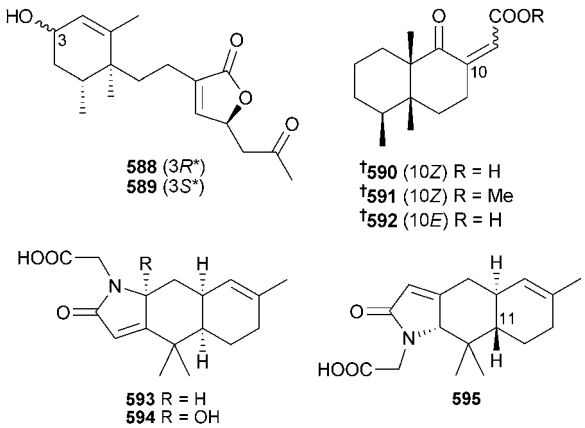
†**586**



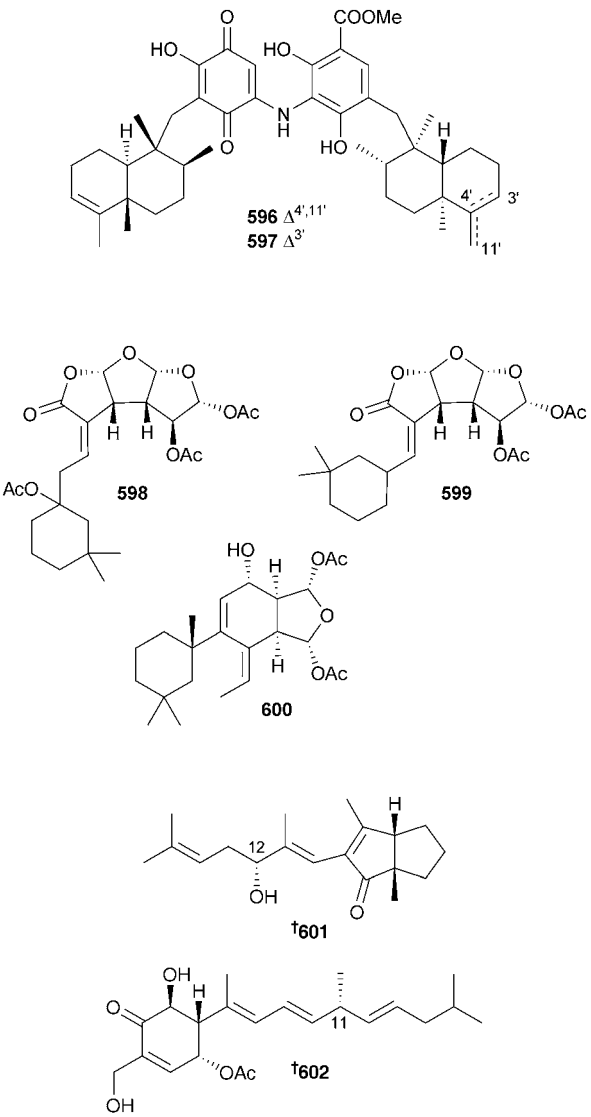
†**587**

Dysifragilisins A **588** and B **589** were isolated from *Dysidea fragilis* (Sanya, Hainan Is., China), but the authors of the report suggest that they were artefacts of acetone extraction, as they were not detected in a chloroform extraction of the sponge.[539] Aignopsanoic acid **590**, the methyl ester **591**, and iso-aignopsanoic acid **592** were isolated from *Cacospongia mycofijiensis* (Kimbe Bay, Papua New Guinea); **590** and **591** were

moderately active against *Trypanosoma brucei*.[540] The nitrogenous isopyrodysinoic acid **593**, 13-hydroxyisopyrodysinoic acid **594** and pyrodysinoic acid B **595** were obtained from *Dysidea robusta* (Bahia, Brazil).[541]



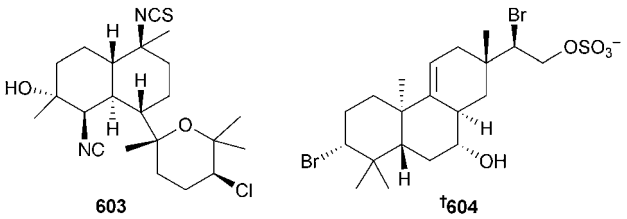
Nakijiquinones E **596** and F **597** were obtained from *Spongia* sp. (Unten-Port, Okinawa).[542]



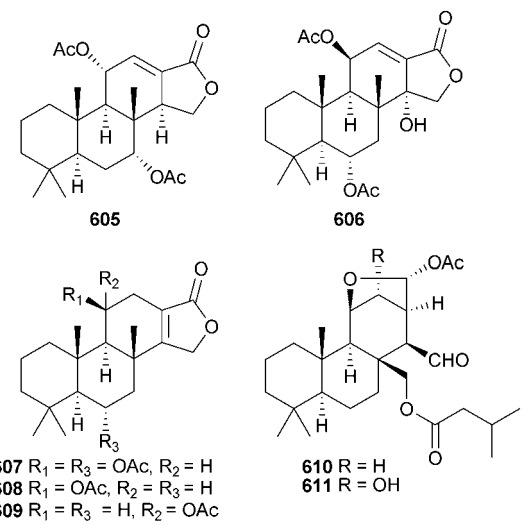
The cytotoxic norditerpenoids, gracilins J–L **598–600**, were isolated from *Spongionella* sp. (West Angaur, Philippines), of which **600** was active against protein tyrosine kinase EGF-R.[543]

A synthesis of xestenone **601** (*Xestospongia vanilla*)[544] established the relative configuration at C-12 and the absolute configuration,[545] while synthesis of phorbasin C **602** (*Phorbas* sp.)[546] established the relative configuration at C-11 as well as the absolute configuration.[547]

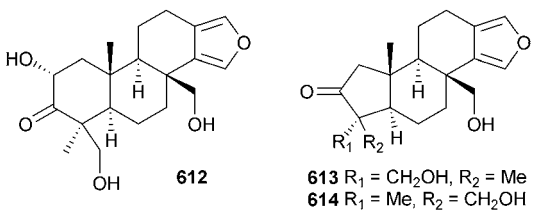
The moderately cytotoxic 10-*epi*-kalihinol X **603** was obtained from *Acanthella* sp. (Yalong Bay, Hainan Is., China).[548] *Tedania ignis* (Sweeting Cay, Grand Bahama Is.) yielded tedanol **604**, which was anti-inflammatory in mice.[549]



Dysidea cf. arenaria (Okinawa) contained a series of spongian diterpenoids **605–611**, of which **606**, **610** and **611** were cytotoxic.[550]

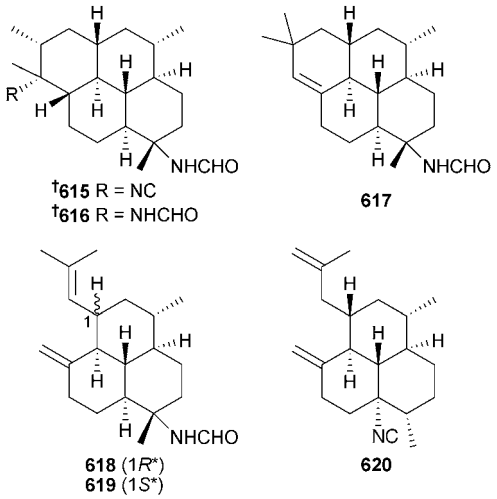


Isospongiatriol **612**, and 3-nor-spongianones A **613** and B **614** were isolated from *Spongia* sp. (Fiji).[551]

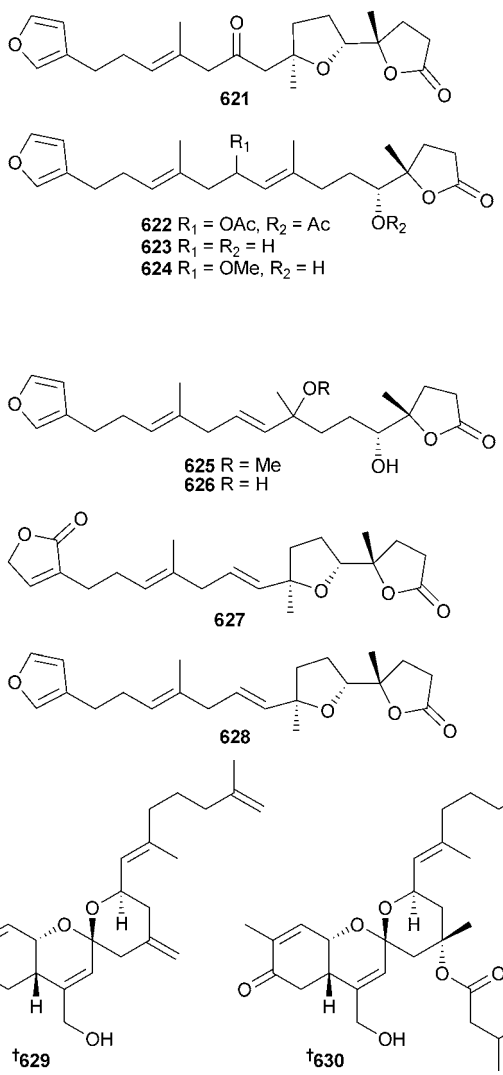


A series of weakly antiplasmodial amphilectane diterpenoids **615–619** were isolated from *Cymbastela hooperi* (Kelso Reef, Queensland, Australia).[552] A *Ciocalapata* species (Koh-Tao, Thailand) yielded 8-isocyanoamphilecta-11(20),15-diene **620**.[553]

The enantiomer of agelasine F (*Agelas nakamurai*)[554] has been synthesised, confirming the absolute configuration of the natural

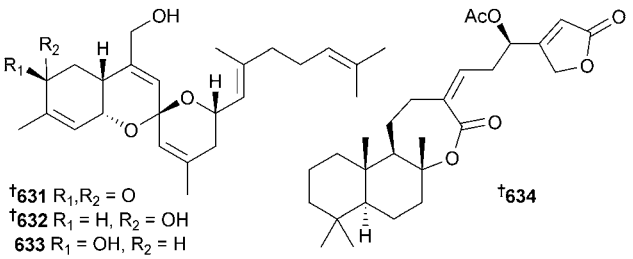


enantiomer.[555] The norsesterterpenoids irciformonin E–K **621–627** were isolated from *Ircinia formosana* (Taiwan), of which irciformonin I was found to inhibit peripheral blood mononuclear cell proliferation. In the same study irciformonin A (*Ircinia formosana*)[556] was re-isolated and the structure revised to **628**.[557]

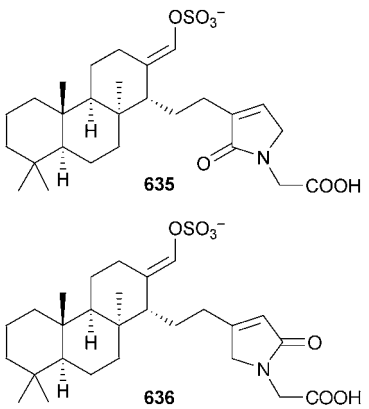


Palinurin (*Ircinia variabilis*)[558] has been synthesised.[559] The unusual spirosesterterpenoids alotaketal A **629** and B **630** were isolated from *Hamigera* sp. (Milne Bay, Papua New Guinea) and found to activate the cAMP cell signalling pathway.[560]

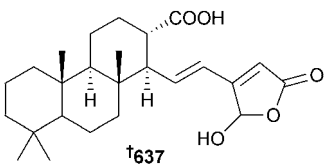
The closely related, moderately cytotoxic phorbaketals A–C **631–633** were isolated from *Phorbas* sp. (Gageo Is, S. Korea).[561] An enantioselective synthesis of luffalactone **634** (*Luffariella variabilis*)[562] established the absolute configuration.[563]



Coscinolactams A **635** and B **636**, isolated from *Coscinoderma mathewsi* (Vangunu Is., Solomon Is.), were moderately anti-inflammatory and inhibited PGE_2 and NO production in cells.[564]

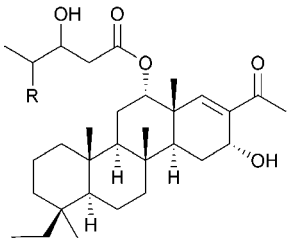


A synthesis of petrosaspongiolide R **637** (*Petrosaspongia nigra*)[565] from (−)-sclareol established the absolute configuration.[566] Antifouling activity has been reported[567] for the sesterterpenoids (7*E*,12*E*,20*Z*)-variabilin (*Sarcotragus* sp.),[568] cavernosolide (*Fasciospongia cavernosa*)[569] and lintenolide A (*Cacospongia cf. linteiformis*).[570] The scalarane-type sesterterpenoids **638–641** were isolated from *Carteriospongia foliascens* (Sulawesi, Indonesia); compounds **638**, **640** and **641** inhibited human Ras-converting enzyme (hRCE protease).[571]

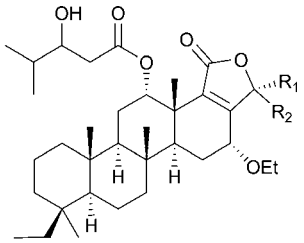


The rearranged sesterterpenoid similan A **642** and the related scalaranoids **643–645** were obtained from *Hyrtios gumminae* (Similan Is. Andaman Sea, Thailand); **645** was weakly cytotoxic.[572]

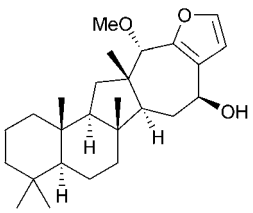
Phyllofolactone L **646**, cytotoxic phyllofenone D **647** and phyllofenone E **648** were isolated from *Phyllospongia foliascens* (Yongxing Is., China).[573]



638 R = Me
639 R = H



640 R_1 = OH, R_2 = Me
641 R_1 = Me, R_2 = OH



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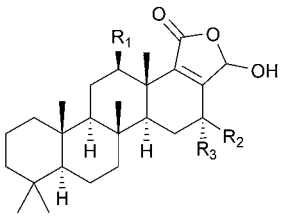
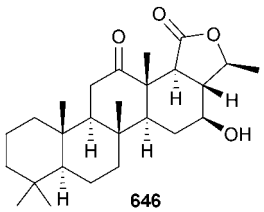


643 R_1 = OH, R_2 = OAc, R_3 = H
644 R_1 = OAc, R_2 = R_3 = H
645 R_1 = R_3 = OH, R_2 = H



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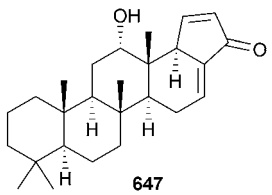

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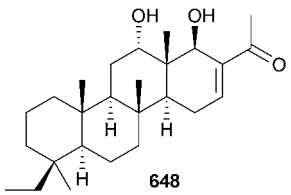

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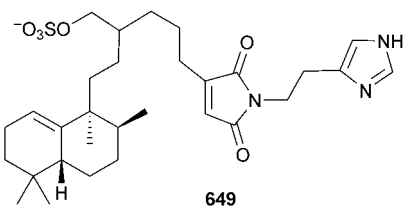

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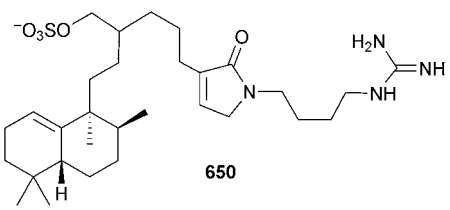

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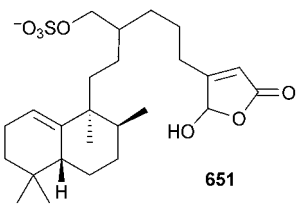
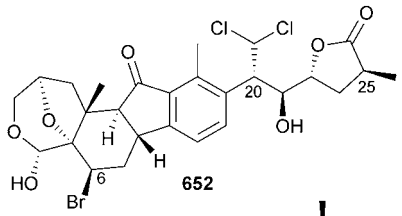


651

Heteronemin acetate,[574] 12-*O*-deacetyl-19-deoxyscalarin[575] and sesterstatin-5[576] (*Hyrtios erecta*), were synthesised from heteronemin isolated from *Hyrtios* sp. (American Samoa).[577] Scalarolide (*Spongia idia*)[578] has been synthesised.[579] The antimicrobial sesterterpenoid alkaloids 19-oxofasciospongine A **649**, fasciospongine C **650** and 25-hydroxyhalisulfate 9 **651** were isolated from *Fasciospongia* sp. (Palau).[580]

A synthesis of the nor-steroid nakiterpiosin **652** (*Terpios hoshinota*)[581] revised the relative configurations at C-6, C-20 and C-25 and established the absolute configuration.[582] The steroid **653** originated from *Axinella* sp. (Sanya, Hainan Is., China).[490]



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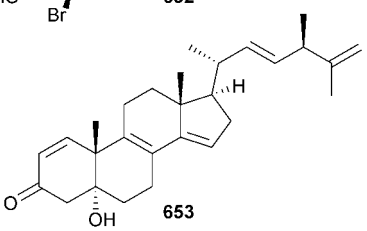
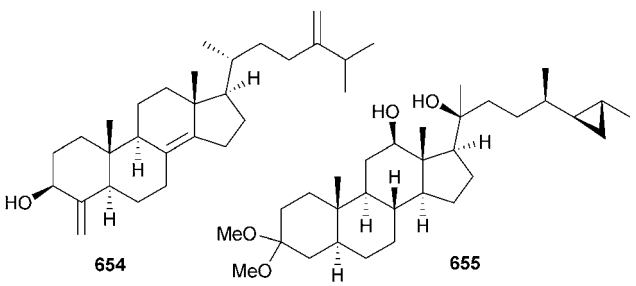
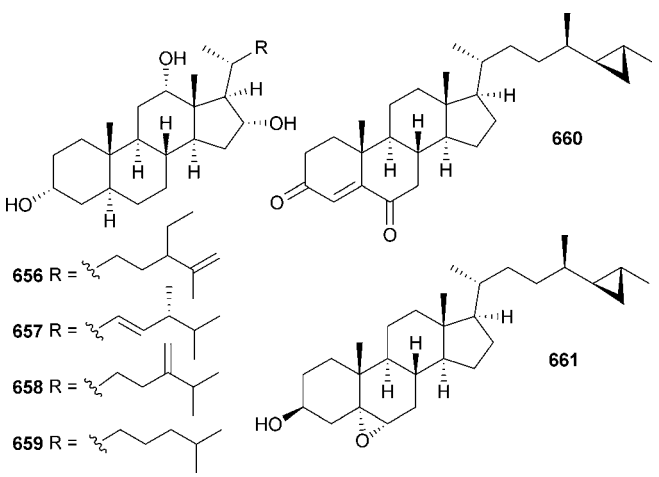


653

Theonella swinhoei (Sulawesi, Indonesia) was the source of dehydroconicasterol **654**.[412] Aragusteroketal B **655** was isolated from *Ianthella* sp. (Namyet Is., Vietnam).[583]



654 **655**

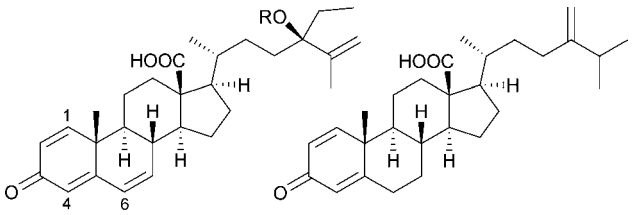


656 R =
657 R =
658 R =
659 R =

660 **661**

A *Psammoclema* species (Nelson Bay, NSW, Australia) contained the antiproliferative steroids **656–659**.[584] Petrosterol-3,6-dione **660** and 5,6α-epoxy-petrosterol **661**, isolated from *Ianthella* sp. (Namyet Is., Vietnam), were cytotoxic and caused apoptosis.[585]

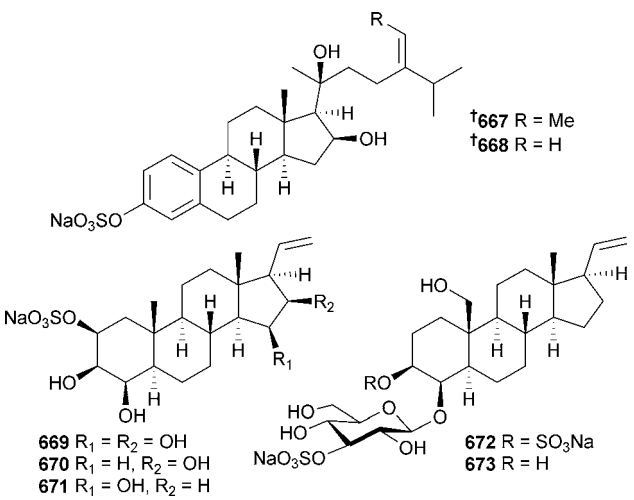
The norselic acids A–E **662–666**, isolated from *Crella* sp. (Norsel Point, Palmer Station, Antarctica), were weakly antimicrobial and antifeedants to mesograzers.[586]



662 R = H
663 R = H, 5αH, Δ^4,Δ^6 saturated
665 R = H, Δ^1,Δ^6 saturated
666 R = Ac

664

Haplosamate A (*Xestospongia* sp.)[587,588] was shown to be a cannabinoid receptor binder by saturation transfer double-difference NMR spectroscopy.[589] Geodisterol-3-*O*-sulfite **667** and 29-demethylgeodisterol-*O*-sulfite **668**, isolated from *Topsentia* sp. (Chuuk, Micronesia), reversed efflux pump-mediated fluconazole resistance in the yeasts *S. cerevisiae* and *C. albicans* but had no antimicrobial activity.[590] Ptilosteroids A–C **669–671** and ptilosaponosides A **672** and B **673** were isolated from *Ptilocaulis spiculifer* (New Georgia Is., Solomon Is.).[591]



†**667** R = Me
†**668** R = H

669 R_1 = R_2 = OH
670 R_1 = H, R_2 = OH
671 R_1 = OH, R_2 = H

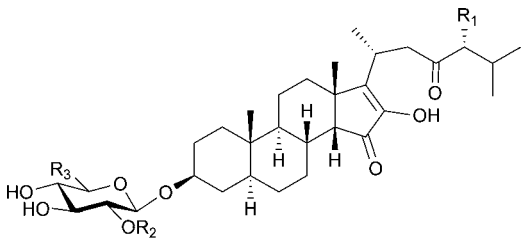
672 R = SO_3Na
673 R = H

The steroidal glycosides pandaroside A–D **674–677** and the methyl esters of pandarosides A **678**, C **679** and D **680** were obtained from *Pandaros acanthifolium* (Martinique).[592]

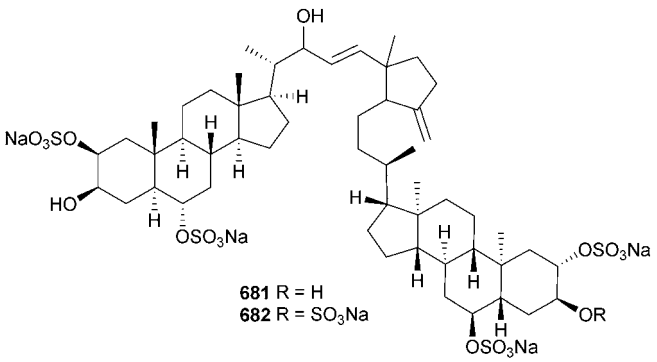
The bis-steroids fibrosterol sulfate A–C **681–683**, were isolated from *Lissodendoryx* (*Acanthodoryx*) *fibrosa* (Coron Is., Philippines); **682** and **683** were found to inhibit protein kinase C ζ (PKCζ).[593]

Phorbas amaranthus (Key Largo, Florida) yielded the amaroxocanes A **684** and B **685**, of which **685** was also found to deter feeding by bluehead wrasse.[594]

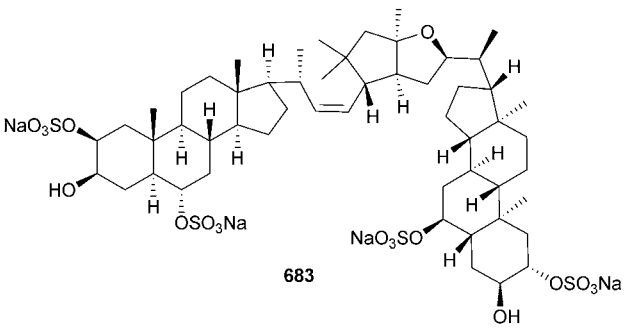
The sipholane-type triterpenoids **686**, sipholenone E **687**, sipholenols J–M **688–691**, siphonellinols D **692** and E **693** and



674 R_1 = Et, R_2 = 1β-glucose, R_3 = COOH
675 R_1 = Et, R_2 = H, R_3 = COOH
676 R_1 = H, R_2 = 1β-glucose, R_3 = COOH
677 R_1 = R_2 = H, R_3 = COOH
678 R_1 = Et, R_2 = 1β-glucose, R_3 = COOMe
679 R_1 = H, R_2 = 1β-glucose, R_3 = COOMe
680 R_1 = R_2 = H, R_3 = COOMe



681 R = H
682 R = SO_3Na



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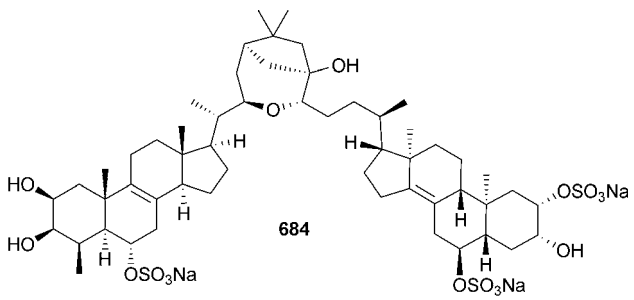

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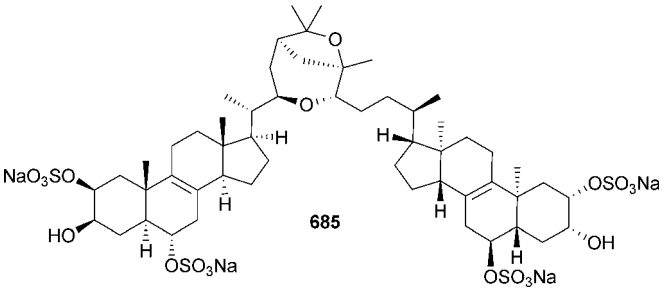
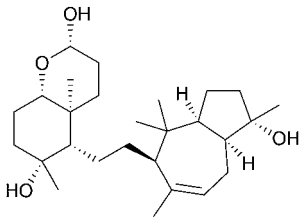


685

siphonellinol hydroperoxide **694** were obtained from *Callyspongia* (*Siphonochalina*) *siphonella* (Hurghada, Red Sea, Egypt). In the same report the structure of sipholenol I **695** (*S. siphonella*)[595] was revised.[596]



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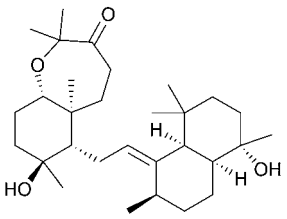

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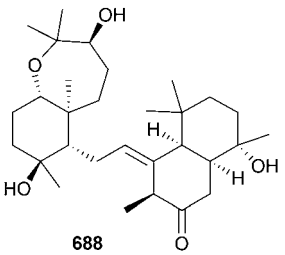

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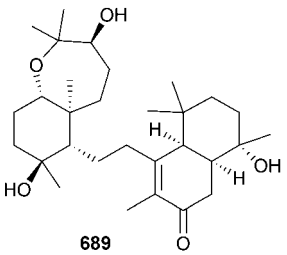

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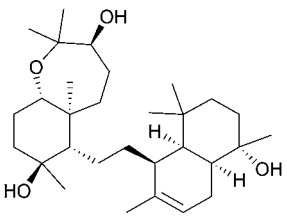

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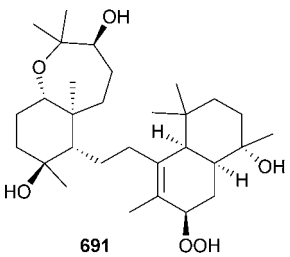

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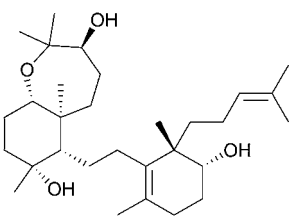

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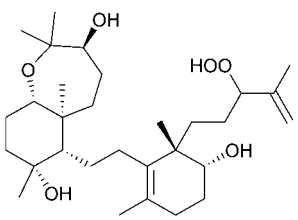

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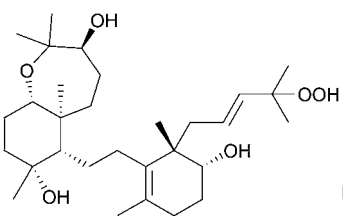

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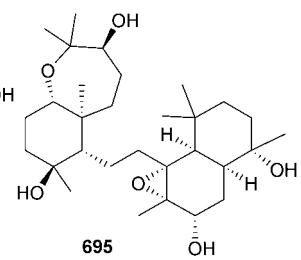
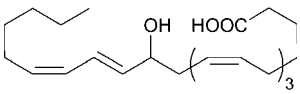


695

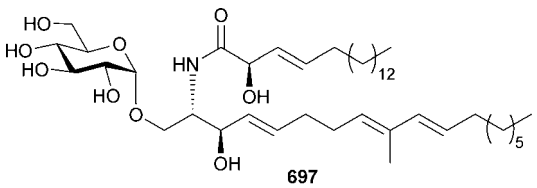
8 Cnidarians

There was a pronounced decline in the number of new metabolites reported from cnidarians compared with previous years. The total content of mycosporine-like amino acids in six species of stony coral (Eastern Coast, Red Sea) was approximately three times greater in summer than winter, an observation in keeping with the suggested putative ecological roles as UV-protectants.[597] Oxylipin **696**, isolated by bioassay-directed fractionation (*Sinularia numerosa*, Kagoshima Prefecture, Japan), inhibited tube-formation in a human endothelial cell line model of angiogenesis.[598]



696

Cerebrosides sarcoehrenosides A **697** and B **698** were isolated from *Sarcophyton ehrenbergi* (Dongsha Is., Taiwan) and reduced expression of pro-inflammatory inducible nitric oxide synthetase (iNOS) in a murine macrophage cell line.[599]



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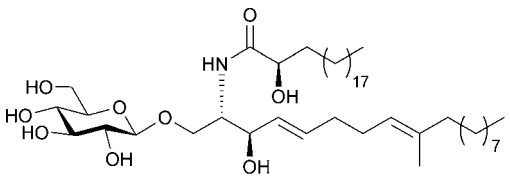
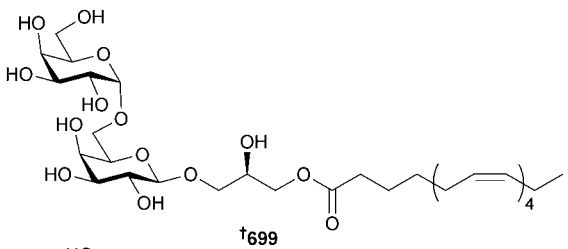
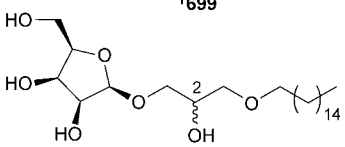


698

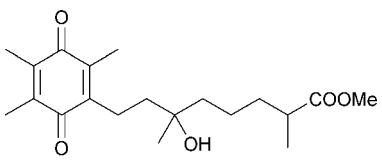
A South China Sea collection of *S. infundibuliforme* yielded the glycosylglycerols sarcoglycosides A–C **699–701**, which were mildly toxic to *Artemia salina*.[600]



†**699**



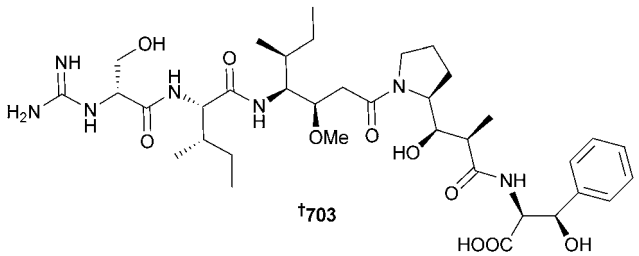
†**700** (2*S*)
†**701** (2*R*)



702

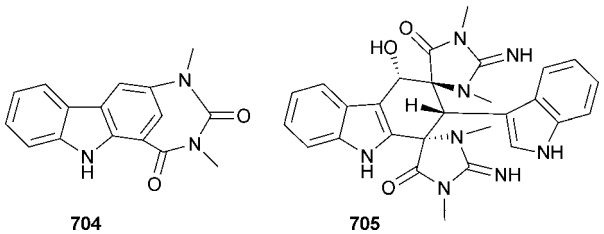
The meroterpenoid sarcophytonone **702**, isolated from *Sarcophyton crassocaule* (Lingshui Bay, Hainan Province, South China Sea), also exhibited mild toxicity to *Artemia salina*.[601]

Asymmetric synthesis of the originally proposed structure of the cytotoxic hydroid (*Gymnangium regae*) pentapeptide gymnangiamide[602] requires that the configuration of the terminal α-guanidino-serine residue be reassigned from L- to D- as shown (**703**).[603]



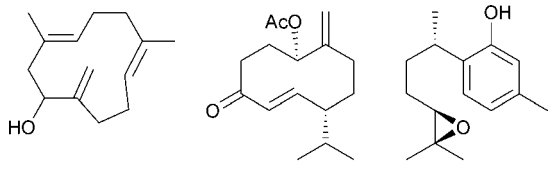
†**703**

A highly strained cyclo-1,3-carbazole structure **704** (antipathine A) was deduced for a metabolite isolated from the black coral *Antipathes dichotoma* (Sanya, Hainan Province, South China Sea).[604] Cycloaplysinopsin C **705**, a dimeric alkaloid isolated from the hard coral *Tubastraea* sp. (Hanish Is., Yemen), had micromolar antimalarial activity towards both chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum*.[605]



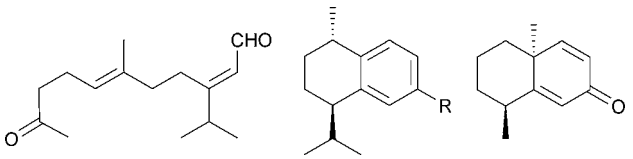
704 **705**

In addition to a number of xeniaphyllane diterpenes (see later), the norhumulene gibberosin N **706** was isolated from a Taiwanese collection of *Sinularia gibberosa*.[606] Nor-sesquiterpene **707** was isolated from *Nephthea* sp. (Sibuan Is., Sabah, Malaysia).[607] (+)-(7*S*,10*R*)-10,11-Epoxycurcuphenol **708**, previously reported as a semi-synthetic derivative of (+)-curcuphenol,[608] has been isolated as a natural product from *Echinomuricea* sp. (Taiwan).[609]

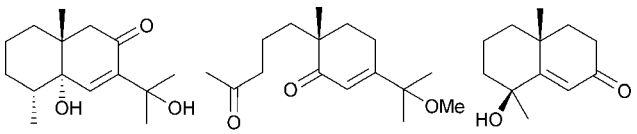


706 **707** †**708**

The *sec*-germacrane sesquiterpene **709** was isolated from *Nephthea chabroli* (Siaoliouciou Is., Taiwan), whilst a specimen of *N. erecta* (Green Is., Taiwan) yielded the unusual antibacterial mercaptan-containing sesquiterpene erectathiol **710**.[610] In separate publications, sesquiterpenes **711** and **712**[611] and the mildly cytotoxic eudesmanoid and nor-eudesmanoid sesquiterpenes **713–715**[612] were also reported from extracts of *N. erecta* collected at the same Taiwanese location.

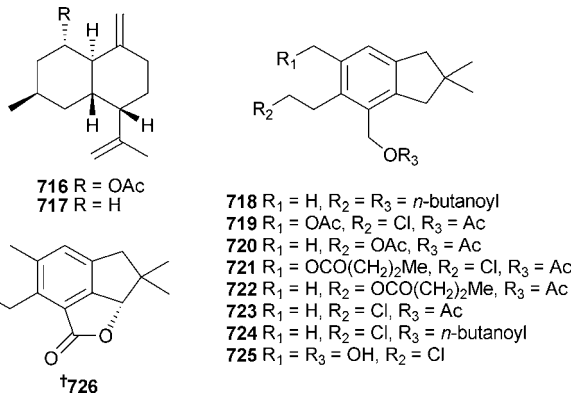


709 †**710** R = CH_2SH †**712** R = CHO **711**



713 †**714** **715**

In addition to a range of known diterpene and steroidal metabolites, two examples of the rare bulgarane-skeleton sesquiterpenes, alcyonicene **716** and deacetoxy-alcyonicene **717**, were isolated from the soft coral *Alcyonium antarcticum* (Terra Nova Bay, Antarctica).[613] A deep-sea dredging campaign in the Western Weddell Sea, Antarctica, afforded specimens of *A. grandis* from which new congeners **718–726** of the alcyopterosin family of sesquiterpenes were purified.[614] Methanolysis of lactone **726** provided an alcohol, enabling assignment of absolute configuration.

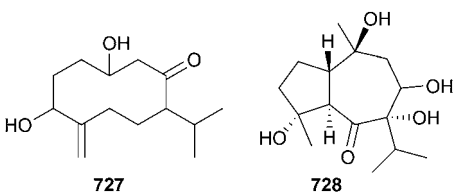


716 R = OAc
717 R = H

718 R_1 = H, R_2 = R_3 = *n*-butanoyl
719 R_1 = OAc, R_2 = Cl, R_3 = Ac
720 R_1 = H, R_2 = OAc, R_3 = Ac
721 R_1 = $OCO(CH_2)_2Me$, R_2 = Cl, R_3 = Ac
722 R_1 = H, R_2 = $OCO(CH_2)_2Me$, R_3 = Ac
723 R_1 = H, R_2 = Cl, R_3 = Ac
724 R_1 = H, R_2 = Cl, R_3 = *n*-butanoyl
725 R_1 = R_3 = OH, R_2 = Cl

†**726**

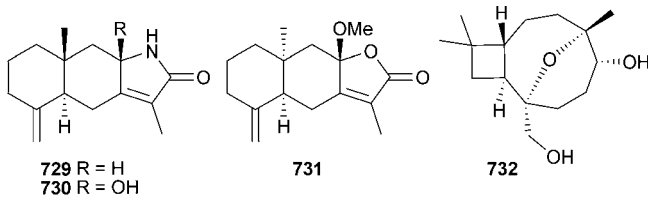
Nor-sesquiterpene nephthediol **727** and bicyclic sesquiterpene nephthetetraol **728** were isolated from *Nephthea* sp. (Bay of Sanya, Hainan Is., South China Sea).[615]



727 **728**

Taenialactams A **729** and B **730** and taenialactone A **731**, close analogues of terrestrial sesquiterpenes, were reported from extracts of *Cespitularia taeniata* (Green Is., Taiwan).[616] Two separate publications have reported the isolation of caryophyllane skeleton sesquiterpenes; rumphellolide H **732**, previously noted from the plant *Cyperus longus*[617] (and as a semisynthetic product from caryophyllene oxide),[618] and rumphellolide I **733**, from *Rumphella antipathies* (Southern coast,

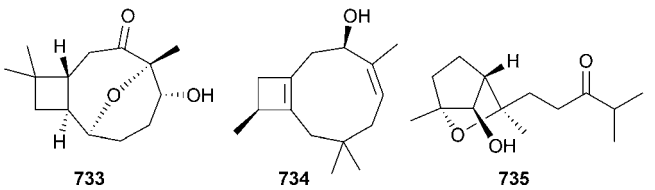
Taiwan).[619,620] The carbon skeleton of capillosanol **734** (*Sinularia capillosa*, Dongsha Atoll, Taiwan) is novel while the highly condensed, nor-sesquiterpene structure of the mildly cytotoxic chabranol **735**, (*Nephthea chabroli*, Siaoliouciou Is., Taiwan), is likely derived from oxidative demethylation of a sesquiterpene precursor.[621]



729 R = H
730 R = OH

731

732



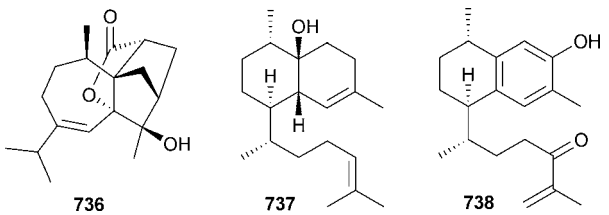
733

734

735

Methyl 5-[(1′*E*,5′*E*)-2′,6′-dimethylocta-1′,5′,7′-trienyl]furan-3-carboxylate (*Sinularia capillosa*)[622] induces apoptosis *via* a caspase-dependent pathway in the THP-1 leukaemia cell line.[623] Extensive *in vitro* and *in vivo* evaluations of the soft coral sesquiterpene metabolite $\Delta^{9(12)}$-capnellene-8β,10α-diol[624] and a monoacetate derivative established inhibition of interferon-γ-stimulated expression of inducible nitric oxide synthase and cyclooxygenase-2, and so represent lead compounds in the development of new treatments of neuroinflammatory effects.[625] An examination of the sesquiterpene chemistry of over 100 individuals of five of the six known species of soft corals of the genus *Plexaurella* has determined that there was no correlation between species and chemistry, nor was there any correlation between location or depth and chemistry.[626] The structure of an unusual antineuroinflammatory C_{18} terpene metabolite nanolobatolide **736**, isolated from a Taiwanese collection of *Sinularia nanolobata*, was established.[627] The proposed biogenesis of **736** was by Diels–Alder addition of acrylic acid to a guaiane-sesquiterpene. Further investigation of extracts of *Pseudopterogorgia elisabethae* (San Andrés Is., Colombia) yielded four diterpenes, elisabethadienol **737**, 7-hydroxyerogorgiaenone **738**, 7,14-erogorgiaenediol **739**, and elisabethin A acetate **740**, a norditerpene sandresolide C **741**, a bisnorditerpene elisabethin G **742** and the C_{15}-rearranged metabolite elisabethin H **743**. Elisabethin H was proposed to be a pentanorditerpene, and was modestly antimycobacterial with antineuroinflammatory activities. Sandresolide C **741** was mildly antimalarial with no significant cytotoxicity.[628]

The pseudopterosins, diterpene glycoside metabolites of *P. elisabethae*, undergo oxidation and proton transfer, eliciting an intramolecular ring closure that leads to a dramatic change in conformation, which is possibly relevant to the well known anti-inflammatory activity of this class.[629] Nine examples of eunicellin-diterpenes, simplexins A–I **744–752**, were isolated from *Klyxum simplex* (Dongsha Atoll, Taiwan).[630] Simplexin E reduced iNOS and COX-2 protein expression in macrophage cells, while simplexins A and D only had an effect on iNOS protein expression. Cultivated specimens of *K. simplex* afforded the closely related diterpenes klysimplexins A–H **753–760**.[631]



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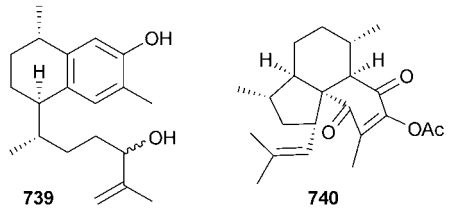

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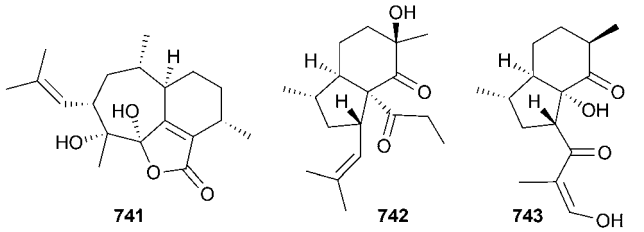

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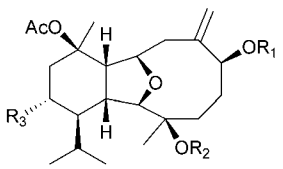
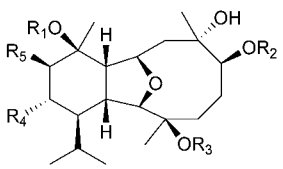
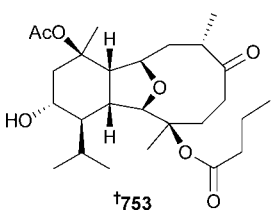


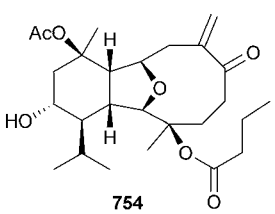
†**744** R_1 = H, R_2 = *n*-butanoyl, R_3 = H
†**755** R_1 = H, R_2 = *n*-butanoyl, R_3 = OH
756 R_1 = OH, R_2 = *n*-butanoyl, R_3 = OH
757 R_1 = H, R_2 = Ac, R_3 = OH



745 R_1 = Ac, R_2 = R_4 = R_5 = H, R_3 = *n*-butanoyl
746 R_1 = H, R_2 = Ac, R_3 = *n*-butanoyl, R_4 = O-*n*-butanoyl, R_5 = OAc
747 R_1 = H, R_2 = R_3 = *n*-butanoyl, R_4 = O-*n*-butanoyl, R_5 = OAc
748 R_1 = H, R_2 = propenoyl, R_3 = *n*-butanoyl, R_4 = O-*n*-butanoyl, R_5 = OAc
749 R_1 = H, R_2 =Ac, R_3 = *n*-butanoyl, R_4 = OH, R_5 = OAc
750 R_1 = R_2 = H, R_3 = *n*-butanoyl, R_4 = R_5 = OAc
751 R_1 = R_2 = Ac, R_3 = *n*-butanoyl, R_4 = OH, R_5 = H
752 R_1 = R_2 = R_3 = Ac, R_4 = OH, R_5 = H
758 R_1 = Ac, R_2 = R_5 = H, R_3 = *n*-butanoyl, R_4 = OH
759 R_1 = R_3 = Ac, R_2 = R_4 = R_5 = H



†**753**



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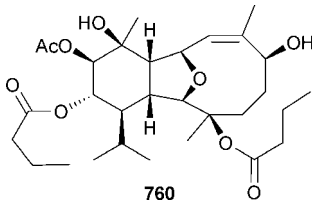
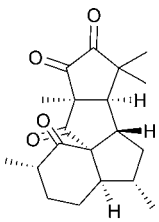


760

Modest cytotoxicity was observed for klysimplexins B and H. The structure of the unusual rearranged diterpene aberrarone **761** (*Pseudopterogorgia elisabethae*, San Andrés Is., Colombia) was secured.[632] Moderate antimalarial activity was observed for the metabolite. Investigation of hexane extracts of the same organism collected from the same locale led to the characterisation of elisapterosin F **762**.[633]

As with previous years, a large number of cembrane diterpenes have been reported from cnidarians. The monoexpoxide-containing cembranes knightol **763**, knightol acetate **764** and knightal **765** were isolated from the sea whip *Eunicea knighti* (Santa Marta Bay, Colombian Caribbean).[634] A library of natural product and semi-synthetic cembranes exhibited activity against a range of marine Gram-positive and -negative bacteria, while **763** and **765** were active in an anti-quorum-sensing bioassay.



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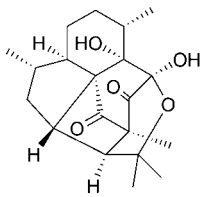

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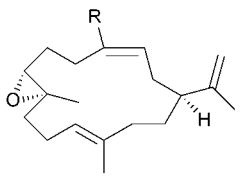
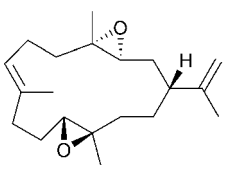


763 R = CH_2OH
764 R = CH_2OAc
765 R = CHO

A collection of *Sinularia* sp. (Lingshui Bay, Hainan Province, South China Sea) afforded diepoxycembrene A **766**,[635] while a collection of *Lobophytum* sp. from the same locale yielded 11,12-epoxy-sarcophytoxide **767**.[636]



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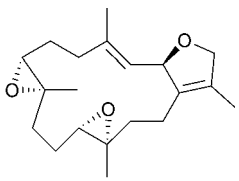
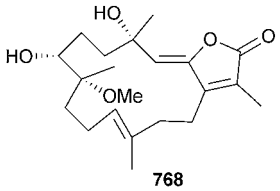


767

γ-Lactone-containing sarcophyolide A **768** was isolated from South China Sea specimens of *Sarcophyton* sp.[637] and the related diterpene **769** and ring-opened analogue secosarcophinolide **770** were also isolated from South China Sea collections of *Sarcophyton glaucum*.[638] The absolute configuration of **769**, which is enantiomeric to a cembrane previously reported as a semi-synthetic derivative of sarcophine[639] and as a natural product from *S. trocheliophorum*,[640] was confirmed by semi-synthesis from *ent*-sarcophine,[641,642] and an X-ray analysis.

trans-Fused α-methylene-γ-lactone-containing durumolides F–L **771–777** were isolated from an extract of *Lobophytum durum* (Dongsha Is., South China Sea).[643] The structure and relative



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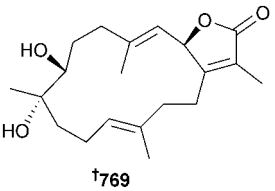
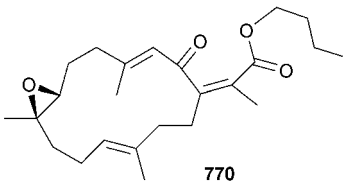
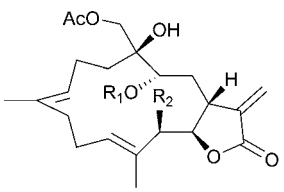


†769

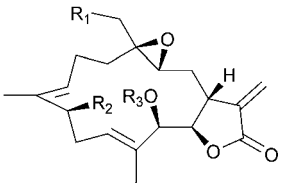


770

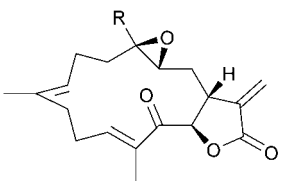
configuration of durumolide J **775** was the same as that reported for lobophytolide D (*Lobophytum* sp.),[644] though major differences in specific rotation and NMR chemical shifts were observed, especially at C-1 and C-13, suggesting that they are in fact diastereomers.



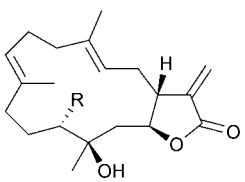
771 $R_1 = R_2 = H$
772 R_1 = Ac, R_2 = OH
773 R_1 = Ac, R_2 = OAc



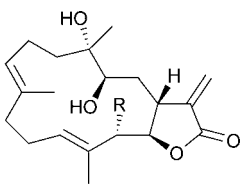
774 R_1 = OAc, R_2 = OH, R_3 = Ac
775 $R_1 = R_2 = R_3 = H$



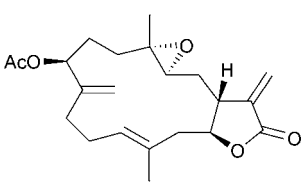
776 R = CH_2OH
777 R = CHO



†**778** R = OH
779 R = Cl



780 R = OAc
781 R = H



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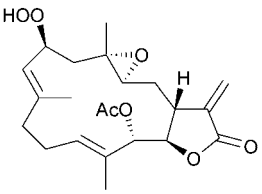

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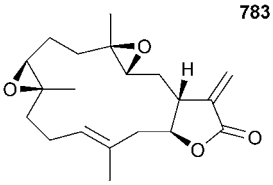
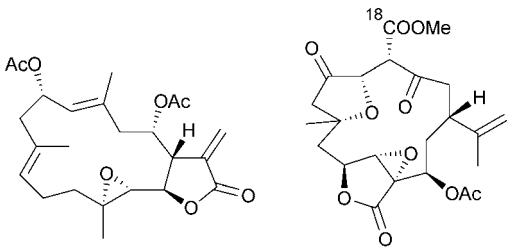


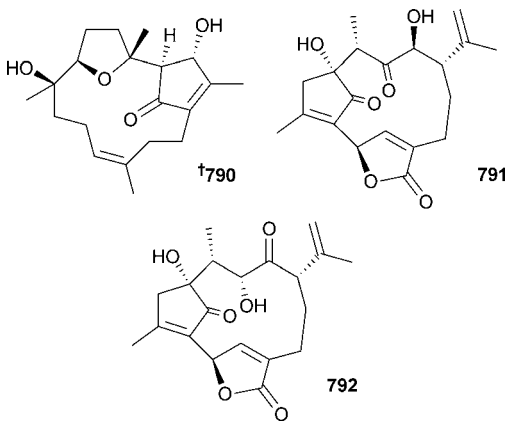
784

The structures of crassocolides G–M **778–784** (*Sarcophyton crassocaule*, Kenting, Taiwan) contain either an epoxide group or were derived from epoxide precursors.[645] Mild cytotoxicity was observed for most of the metabolites.

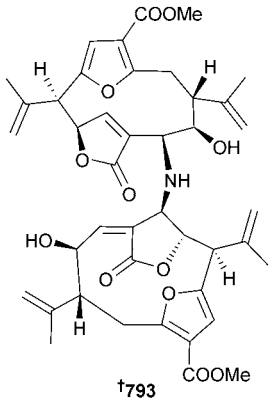
The erroneous *cis*-fused α-methylene γ-lactone structural depiction of lobomichaolide **785** (*Lobophytum michaelae*),[646] originally established by an X-ray analysis, has recently been corrected to the *trans*-fused lactone shown.[647] The 1,4-diketo-containing cembranoid leptogorgolide **786** and three related furanocembranolides, leptodiol **787**, leptodiol-7-acetate **788** and 8-*epi*-lopholide **789**, were isolated from *Leptogorgia* sp. (Jicarita, Panama).[648] The authors discussed the concept of genus-specific oxidation at C-18 as a taxonomic marker for octocorals, and in particular suggested that furanocembranolides such as **787–789** may be biosynthetic precursors to 1,4-diketo-cembranoids such as **786**.



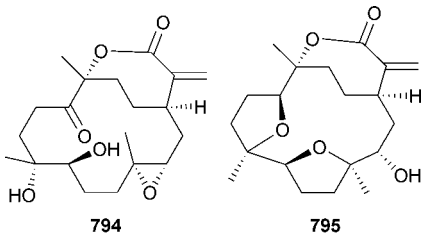
Lobocrasol **790** (*Lobophytum crassum*, Dongsha Is., Taiwan)[649] and corallolides A **791** and B **792** (*Pseudopterogorgia bipinnata*, Providencia Is., Colombia)[650] embody unusual carbon skeletons and exhibit mild biological activities.

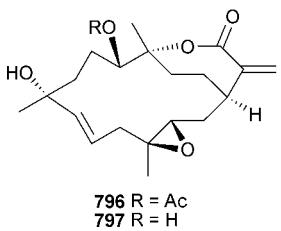


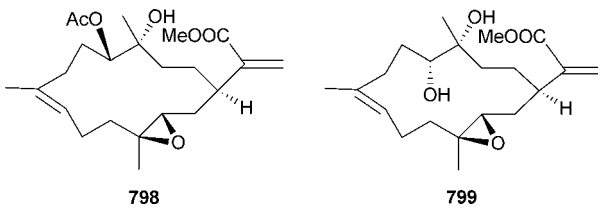
A Sweeting Cay (Bahamas) collection of *P. acerosa* gave the asymmetric dialkylamine bis(pseudopterane)amine **793**,[651] as well as the known symmetric analogue bis(gorgiacerol)amine[652] and the precursor cembrane pseudopterolide.[653] Both bis-diterpenoids were prepared by bubbling NH_3 through a solution of pseudopterolide. Mild cytotoxicity was exhibited by **793**.



The structures and relative configurations of the seven-membered lactone-containing diterpenes sinulaparvalide A **794** and B **795** (*Sinularia parva*, Lingshui Bay, Hainan Province, South China Sea) were established.[654] The structurally-related lactones flexibilisolide A **796** and ring-opened analogue flexibilisin A **797** were isolated from cultivated specimens of *Sinularia flexibilis*, while flexibilisolide B **798** and flexibilisin B **799** were isolated from wild specimens of the same species (Southern Pintung, Taiwan).[655] Base-catalysed hydrolysis of the co-metabolites 11-*epi*-sinulariolide acetate[656] and sinulariolide[657] yielded **797** and **799** respectively.

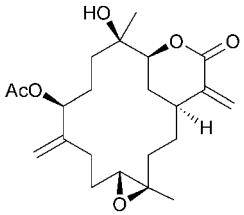






A Kenting (Taiwan) collection of *S. flexibilis* yielded a diverse array of cembranoids, including new examples named flexilarins A–J **800–809**.[658] The structure and relative configuration of flexilarin A **800** was determined, while acetylation of flexilarin I

808 yielded a product identical with querciformolide C.[659] Moderate cytotoxicity was observed for a number of the flexilarins, especially **803**, towards the Hep2 cell line.



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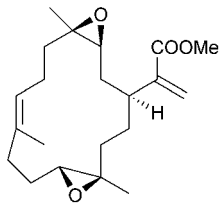

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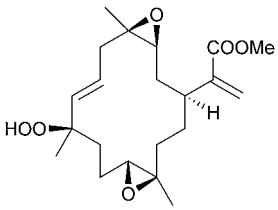

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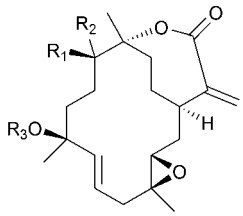
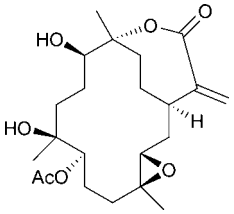


803 R_1,R_2 = O, R_3 = OH
804 R_1 = OAc, R_2 = R_3 = H
805 R_1 = R_3 = H, R_2 = OAc
806 R_1 = OH, R_2 = R_3 = H



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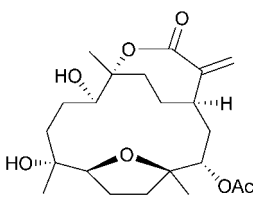

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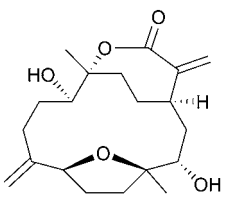

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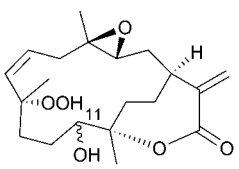
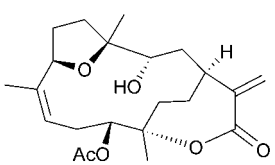


810 (11*R**)
811 (11*S**)



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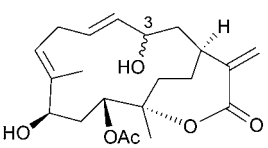
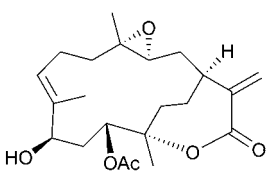


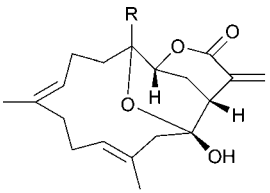
813 (3*R**)
815 (3*S**)

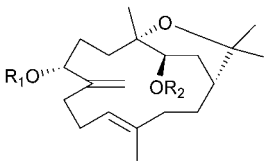


814

The structurally-related ε-lactones sinuladiterpene A–F **810–815** were reported from a Green Is. (Taiwan) collection of *S. flexibilis*.[660]

The unusual α-methylene *cis*-fused δ-lactone hemiketals durumhemiketalolide A–C **816–818**, isolated from *Lobophytum durum* (Dongsha Is., Taiwan), were potent inhibitors of iNOS expression in stimulated macrophage cells.[661] The structures and absolute configurations of new congeners of the decaryiol family of bicyclic diterpenes, decaryiol B–D **819–821** (*Lobophytum* sp., Siladen Is., North Sulawesi, Indonesia) have been reported.[662] A small library of decaryiol analogues was prepared, and *O*-methyl decaryiol identified with moderate levels of cytotoxicity towards a glioma cell line.

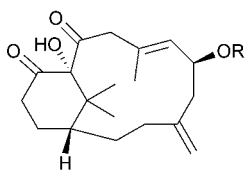




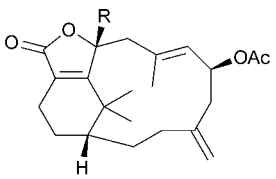
816 R = OH
817 R = OAc
818 R = OAc

†**819** R_1 = R_2 = H
†**820** R_1 = H, R_2 = Ac
†**821** R_1 = OH, R_2 = H

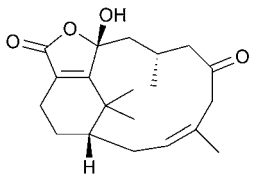
Norverticillanes cespihypotin W **822** and X **823**, and verticillane diterpenes cespihypotin Y **824** and Z **825** and cespihypotone **826** were sourced from *Cespitularia hypotentaculata* (Green Is., Taiwan).[663]



822 R = H
823 R = Ac

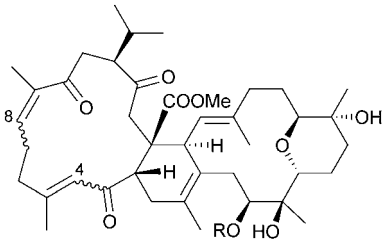


824 R = H
825 R = OH

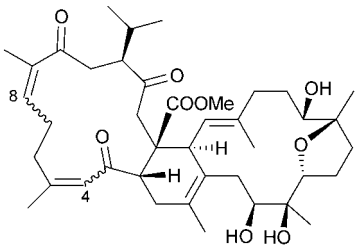


826

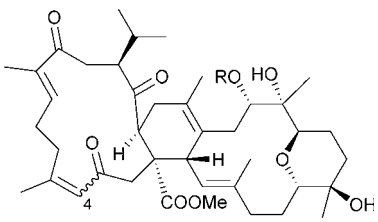
Eight new biscembranes have been reported from two studies of soft corals of the genus *Sarcophyton*. Seven mildly cytotoxic examples, bisglaucumlides E–K **827–833**, were isolated from *S. glaucum* (Amami Oshima, Kagoshima Prefecture, Japan).[664] The absolute configurations of **827** and **829–833** were determined by comparison of ECD data with those reported for congeners bisglaucumlides A and C.[665] The eighth biscembrane, methyl tortuoate D **834**, was isolated from *S. tortuosum* as a result of ESIMS screening, which indicated the presence of a molecular ion peak that did not correspond to any previously reported metabolites from this soft coral.[666] A full account of the total synthesis of related biscembrane methyl sarcophytoate[667] has been published.[668]



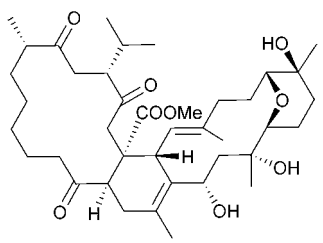
†**827** (4*Z*,8*E*) R = H
828 (4*E*,8*Z*) R = Ac



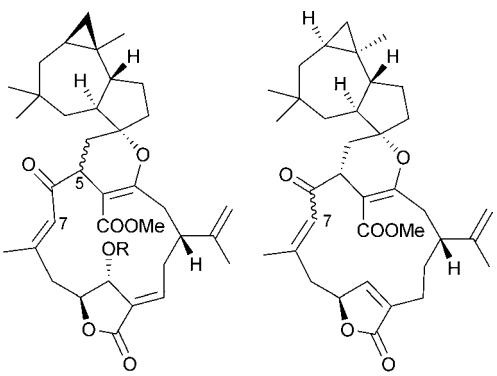
†**829** (4*E*,8*E*)
†**830** (4*Z*,8*Z*)



†**831** (4*Z*) R = H
†**832** (4*Z*) R = Ac
†**833** (4*E*) R = Ac



834

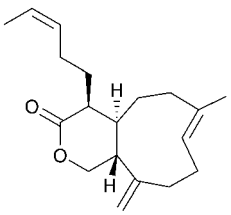


†**835** (5*R*) R = Ac
†**836** (5*S*) R = Ac
†**837** (5*S*) R = H

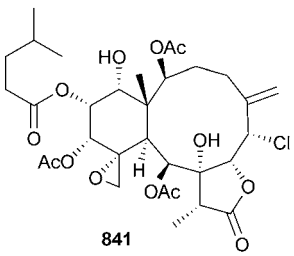
†**838** (7*Z*)
†**839** (7*E*)

Investigation of the chemistry of the hybrid soft coral *Sinularia maxima* × *S. polydactyla* yielded five new terpenoids bearing a cembrane–africanane skeleton.[669] The absolute configuration of (7*E*)-polymaxenolide **835** was established by a combination of Cu Kα radiation X-ray analysis and theoretical calculations of ECD spectra, while analysis of NOE and ECD data established the absolute configurations of the remaining new metabolites, (7*E*)-5-epipolymaxenolide **836** and polymaxenolides A–C **837–839**.[669]

A new norditerpene bearing a xenicane skeleton, isoacalycixeniolide A **840**, was isolated from *Acanthogorgia turgida* (Grandi Is., Goa, India).[670] Absolute configuration was assigned (ORD), with the same absolute configuration also being ascribed to co-metabolites acalycigorgin E[671] and acalycixeniolides B[672] and G.[673,674] In addition to a number of known briaranes, the new example juncin ZII **841** was reported from *Junceella juncea* (Sanya, Hainan Province, China).[675] Potent antifouling activity (*Balanus amphitrite*) was observed for both **841** and the structurally related briarane gemmacolide B.[676]

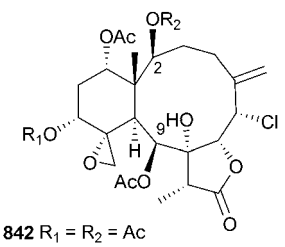


†**840**

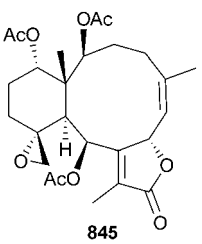


841

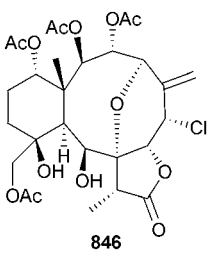
A Tai-Tong County (Taiwan) collection of *Junceella juncea* yielded juncenolides H–K **842–845**.[677]



842 $R_1 = R_2 = Ac$
843 $R_1 = Ac$, $R_2 = i$-butanoyl
844 R_1 = 3-methylbutanoyl, $R_2 = Ac$



845



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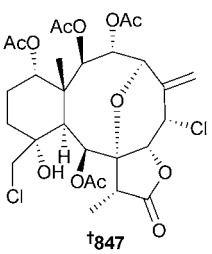
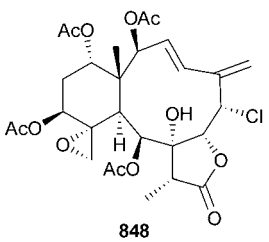


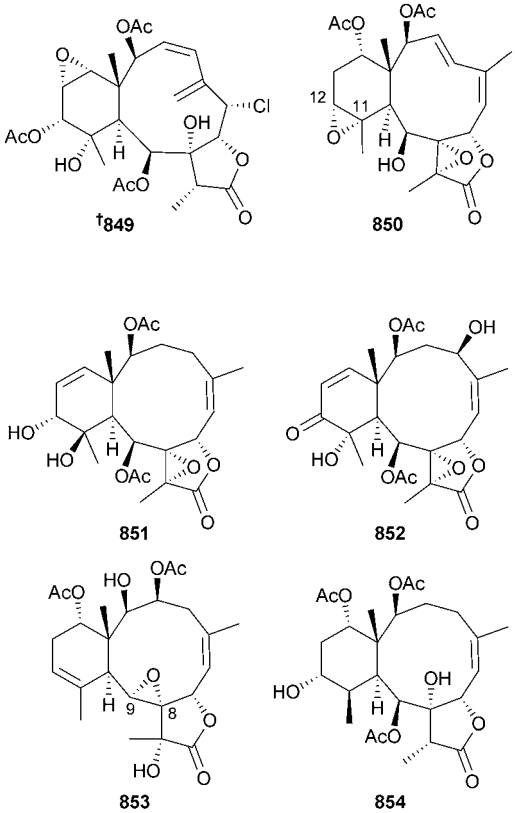
†**847**



848

Juncenolide H is a C-2,C-9 diastereomer of gemmacolide C.[676] Chlorinated briaranes fragilide E–G **846–848** were isolated from Southern Taiwan collections of *Junceella fragilis*.[678,679] The structure and absolute configuration of fragilide F, isolated from a male specimen of the gorgonian, was established. Fragilide G was isolated from a female specimen of the same organism. The study also questioned the assignments of ^{1}H NMR and MS data, but not the structure, for the previously reported briarane junceellonoid D.[680]

Briaexcavatins U–Z **849–854** were isolated from cultivated specimens of *Briareum excavatum* (Taiwan).[681,682] Briaexcavatin Y **853** contains an unusual 8,9-epoxide group; the same paper[682] also summarised the ^{13}C NMR chemical shifts associated with β-orientated 11,12-epoxide-containing briarane diterpenes.

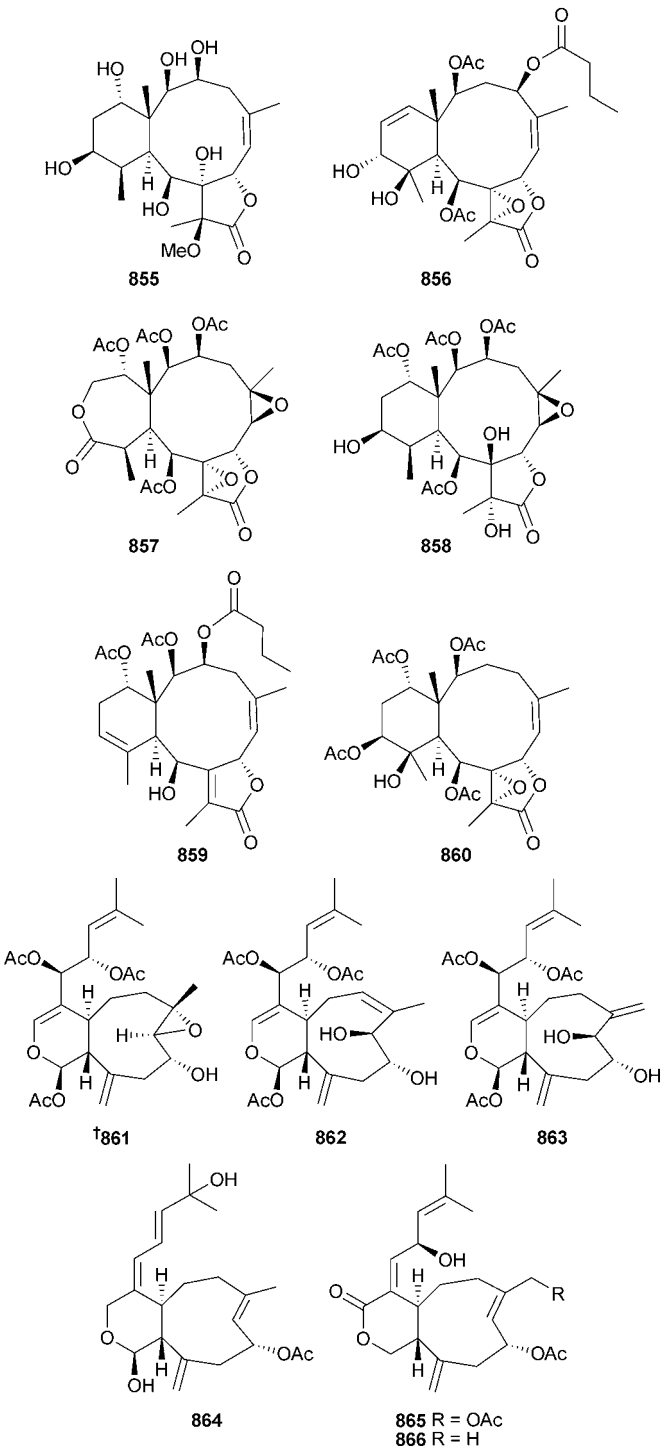


While excavatoids A **855** and B **856** were isolated from cultivated specimens of *B. excavatum*, wild-type specimens of the same organism (Southern Taiwan) yielded the 5,6-epoxy-briaranes excavatoids C **857** and D **858**.[683]

The structures and relative configurations of excavatoid A **855**, and cultivated gorgonian known co-metabolite briaexcavatin I,[684] were established. Excavatoid C **857** is unusual in that it bears a ε-lactone ring. A second publication reported the characterisation of excavatoids E **859** and F **860** from the same samples of cultivated *B. excavatum*.[685] Both metabolites were modest inhibitors of elastase release from human neutrophils.

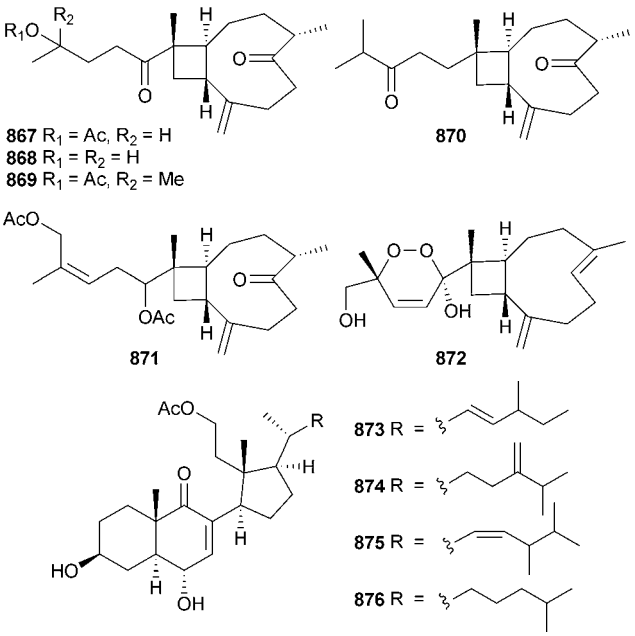
The xenicane diterpenes asterolaurin A–F **861–866** (*Asterospicularia laurae*, southern coast, Taiwan) generally inhibited elastase release and superoxide production by human neutrophils.[686]

In addition to the norhumulene metabolite presented earlier, xeniaphyllanes gibberosin O–S **867–871** and sinugibberoside

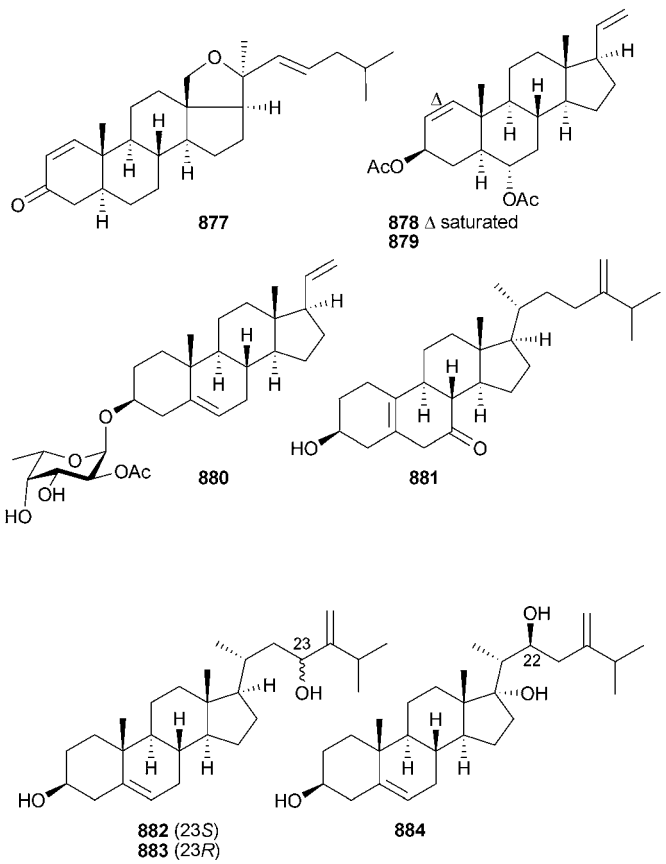


F **872** were isolated from *Sinularia gibberosa* (northeastern coast, Taiwan).[606] Two related congeners, 9,11-secosterols **873–876**, were isolated from *Eunicella cavolini* (Lichadonissia Is., Greece).[687] Moderate levels of *in vitro* cytotoxicity were observed towards human prostate and breast adenocarcinoma cell lines.

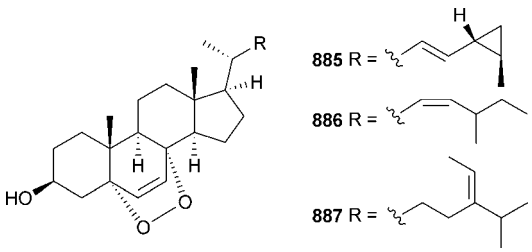
Of four new steroids (ximaosteroids A–D **877–880**) isolated from *Scleronephthya* sp. (Ximao Is., Hainan Province, China), ximaosteroid A was unusual in that it contained a fused tetrahydrofuran moiety.[688] Chabrosterol **881**, a 19-norergostane derivative, was reported from extracts of *Nephthea chabroli*



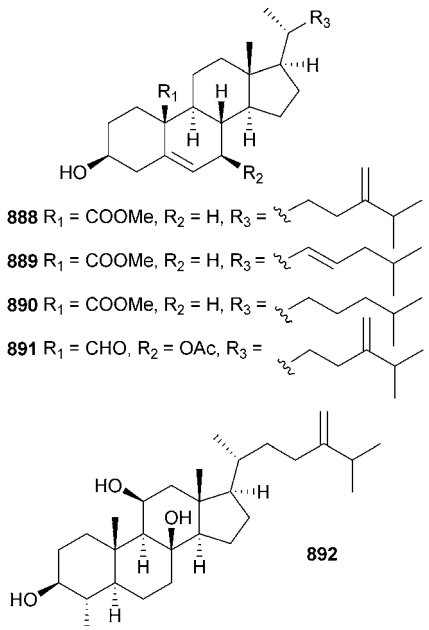
(Siaoliouciou Is., Taiwan)[610] and the related ergostanoids **882–884** came from *N. erecta* (Green Is., Taiwan).[611] The absolute configurations at C-23 in **882** and C-22 in **884** were determined (Mosher). Both **882** and **884** reduced the expression of iNOS and COX-2 proteins in LPS-stimulated murine macrophages.



Eunicella cavolini (Lichadonissia Is., Greece), the source of secosterols **873–876**, also harboured 5α,8α-epidioxysterols **885–887**.[689] Two of these sterols, **886** and **887**, were also isolated from an ascidian *Tridemnum inarmatum* (Achladi Bay, Maliakos Gulf, Greece).

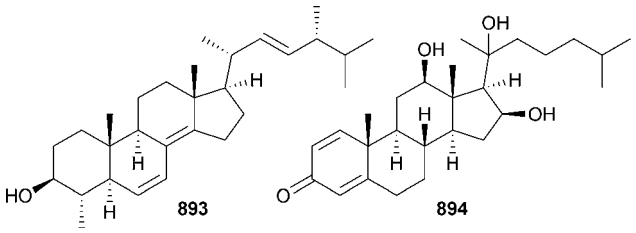


A number of the new and known epidioxysterols showed differential growth inhibition of MCF-7 cells depending upon the cell culture conditions and media used. A Tsau-Lou-Cho Is. (Taiwan) collection of *Nephthea chabroli* afforded the C-19-oxygenated sterols nebrosteroids I–L **888–891** and the 4α-methylated sterol nebrosteroid M **892**.[690] Of the five steroids, all but **890** reduced the levels of expression of iNOS and COX-2 proteins in stimulated murine macrophages.

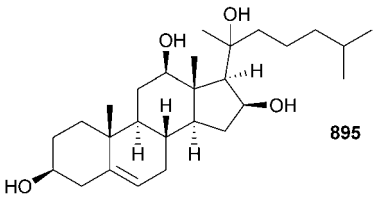


A second example of a 4α-methylated sterol, **893**, was reported from *Nephthea* sp. (Sepanggar Is., Sabah, Malaysia).[691] Ring A dienone-containing sterol **894** and regular sterol **895** were reported from *Chromonephthea* sp. (Naozhou Is., South China Sea),[692] while related dienone sterols **896** and **897** were isolated from a North Sulawesi (Indonesia) collection of *Minabea* sp.[693] Sterol **896** was previously reported as a microbial degradation product of cholesterol,[694] and the methyl ester derivative has been isolated from the Antarctic soft coral *Anthomastus bathyproctus*.[695] A (25*S*)-configuration was assigned to **897** after analysis of ^{1}H NMR shift differences observed between (*S*)- and (*R*)-phenylglycine methylester amide analogues.

Synthesis of hippuristanol (*Isis hippuris*)[696] has yielded a small library of related analogues. Biological evaluation of the library identified the importance of spiroketal stereochemistry and the presence/absence of methyl groups.[697] Further study of *Palythoa*



893 **894**



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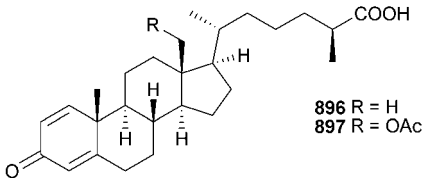
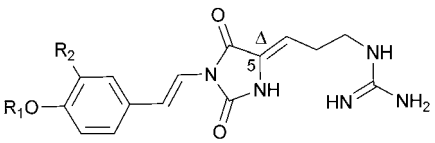


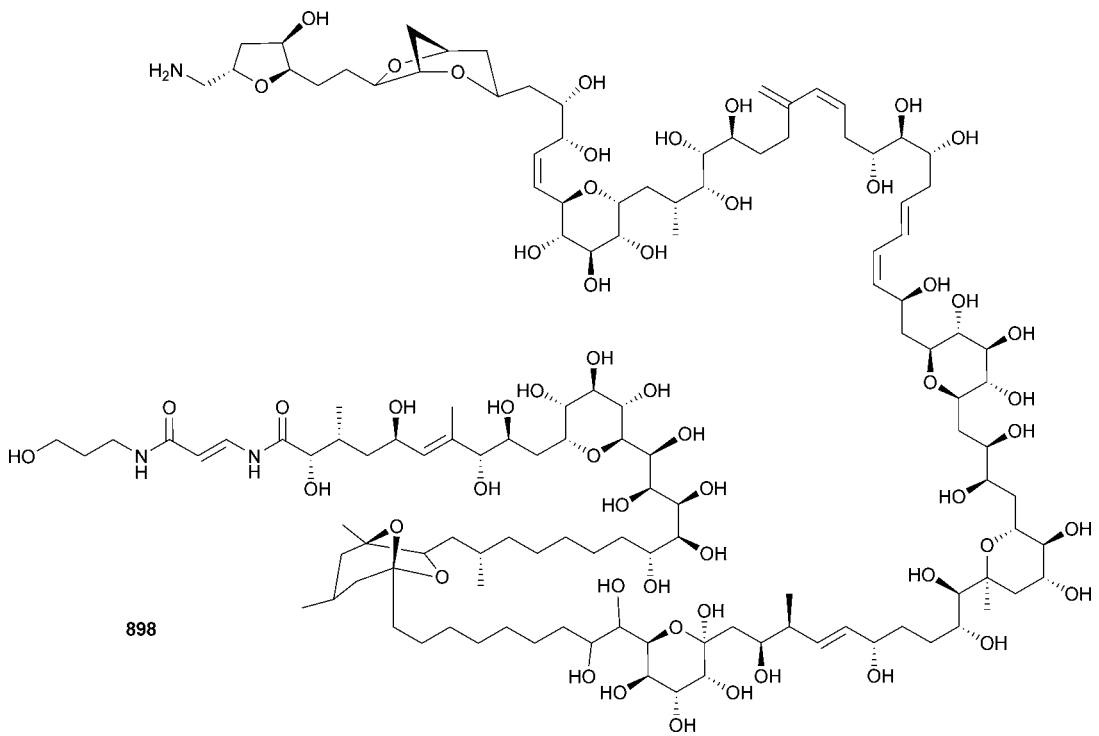
896 R = H
897 R = OAc

toxica obtained from the fabled tidepool on the island of Maui, the original source of palytoxin, has now revealed the presence of a second toxin, 42-hydroxypalytoxin **898**.[698] Comparative biological studies of the two toxins on skeletal muscle cells indicated that they have remarkably similar mechanisms of action. Preliminary data suggested the new toxin has an additional Na^+-dependent mechanism of action that was independent from the palytoxin target Na^+/K^+ pump.

Artificial predation of *Sinularia polydactyla* led to a statistically significant increase in production of 11β-acetoxypukalide[699] which correlated with upregulation of gene expression.[700] A study of light dependency on the growth, budding frequency and production of flexibilide[701] by cultivated *Sinularia flexibilis* found a curvilinear response, indicating that both low and high light intensity were detrimental to growth and metabolite production.[702] A comparative study of fatty acid content of soft corals that either harbour symbionts or are symbiont-free suggests that 18:3*n*−6, 18:4*n*−3 and 16:2*n*−7 acids are markers of the presence of zooxanthellae.[703] Concentrations of several fatty acids in zooxanthellae associated with jellyfish of the genus *Cassiopea* decrease with a decrease in light intensity, but the same acids increase in concentration in host tissue.[704] A Plane Is. (Marseilles) collection of the colonial sea anemone *Parazoanthus axinellae*, an epibiont on the sponge *Axinella damicornis*, afforded the 3,5-disubstituted hydantoins parazoanthine A–E **899**–**903**.[705] Absolute configuration at C-5 of **899**, and by analogy **902**,



†**899** $R_1 = R_2 = H$, Δ saturated, (5*S*)
900 $R_1 = R_2 = H$
901 $R_1 = Me$, $R_2 = H$
†**902** $R_1 = Me$, $R_2 = Br$, Δ saturated, (5*S*)
903 $R_1 = Me$, $R_2 = Br$



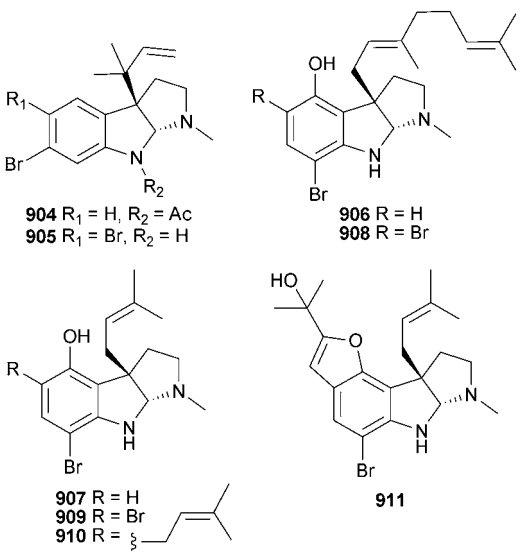
898

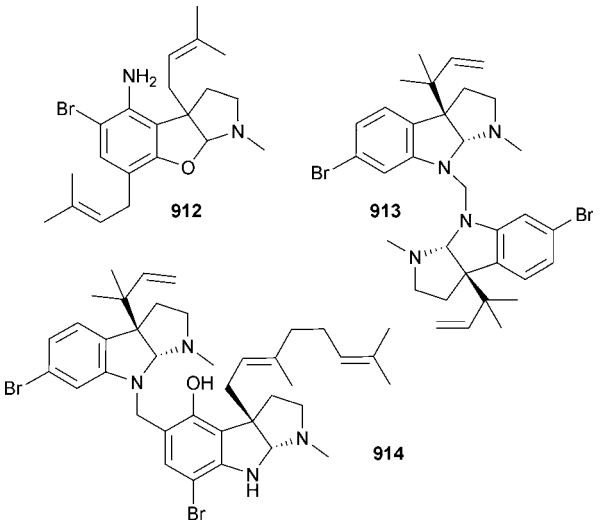
was determined by comparison of experimental ECD spectra with time-dependent DFT calculated spectra. Parazoanthine C was micromolar-active in the Microtox assay.

Dimethylsulfoniopropionate (DMSP) and the volatile decomposition product dimethylsulfide play important roles in global sulfur cycling: DMSP has been shown to be produced by the zooxanthellae in the symbiotic pairing of the anemone *Aiptasia pallida* and *Symbiodinium bermudense*.[706] Bandaporin, 20 kDa pore-forming actinoporin-family toxin, was isolated from the anemone *Anthopleura asiatica* (Banda, Tateyama, Japan).[707] The toxin exhibited lethal toxicity to crayfish and was potently haemolytic towards red blood cells, though the latter activity was inhibited specifically by sphingomyelin. UcI, a 30 kDa pore-forming cytolytic toxin, was isolated from the Northern red anemone *Urticina crassicornis*.[708] Model studies of haemolysis, using lipid vesicles, established that the presence of both sphingomyelin and cholesterol facilitates toxin binding to membranes. A further new actinoporin, fragaceatoxin C (20 kDa, *Actinia fragacea*, Northern Spain), was identified by a combination of fragment sequence, RT-PCR and cloning.[709] The power of solid-phase peptide synthesis and native chemical ligation has been demonstrated with the synthesis of APETx2,[710] a 42-residue toxin originally reported from *Anthopleura elegantissima*.[711]

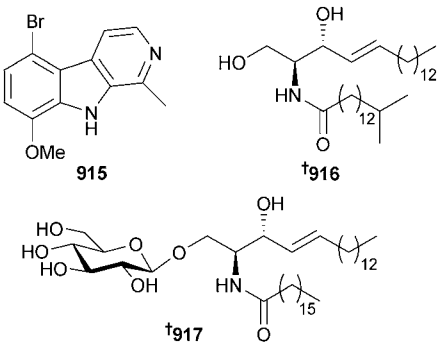
9 Bryozoans

Although there are still very few reports on bryozoan chemistry, there are several more this year than has been usual in past reviews. Chemical investigations of *Flustra foliacea* (Minas Basin, Bay of Fundy, Canada) resulted in 11 new flustramines F–P **904–914**. The dimers flustramine O **913** and flustramine P **914** may be artefacts of isolation. The metabolites possessed a different bromination pattern from that of previously reported flustramines[712–717] and some also possessed a new hydroxylation pattern on the aromatic ring. Flustramines F **904**, I **907** and L **910** had broad-spectrum antimicrobial activity.[718] Investigation of flustramines L **910** and N **912** after several years of storage indicated a slow interconversion. Examination of flustramine H **906** indicated that it also behaves in an analogous manner, but on a longer timescale.[718]

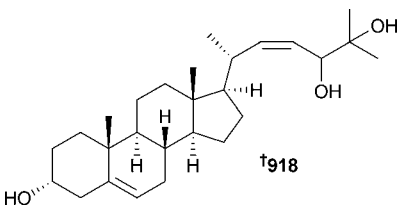




Pterocella vesiculosa (Alderman Is., New Zealand) was the source of a new alkaloid, 5-bromo-8-methoxy-1-methyl-β-carboline **915**, which displayed moderate inhibition of P388 murine leukaemia cells, in addition to growth inhibition of *B. subtilis*, *C. albicans* and *T. mentagrophytes*.[719] Investigations of *Bugula neritina* (Daya Bay, Shenzhen, China) resulted in isolation of a new ceramide **916** and cerebroside **917**, in addition to some known analogues.



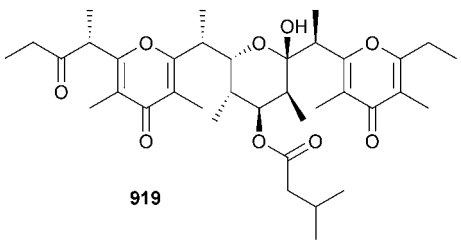
A cerebroside, *N*-[(1*S*,2*R*)-1-[(β-D-galactopyranosyloxy)-methyl]-2-hydroxyheptadecyl]hexadecanamide, was claimed as a new natural product but has been previously isolated from myelin;[720] however, the current report is the first isolation from the marine environment.[721] A new oxygenated sterol, (22*Z*)-3α,24ζ,25-trihydoxycholesta-5,22-diene **918**, was isolated from *Biflustra grandicella* (Huang Is., Shandong Province, China).[722]



Bryostatin 1[723] enhanced the efficacy of cytotoxic agents through modulation of the protein kinase C pathway, and was active in combination with vincristine for diffuse large B-cell lymphoma.[724]

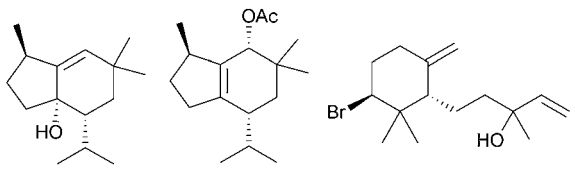
10 Molluscs

The last two years have seen a considerable decline in the number of new metabolites reported from molluscs. Mytilin-A, an antimicrobial peptide isolated from the mussel *Mytilus edulis*,[725] exhibited moderate levels of activity towards marine *Vibrio* species, yeasts and filamentous fungi that was not modulated by saline concentrations, suggesting a potential role in the control of marine pathogens in aquaculture settings.[726] Capillary electrophoresis–ESI-MS has been demonstrated as an analytical tool to detect the lipophilic marine toxins yessotoxin and pectenotoxins with limits of detection of 10 μg kg^{-1} and 130 μg kg^{-1} respectively.[727] The use of solid-phase extraction as an enrichment and clean-up procedure before LC–MS/MS analysis lowers the limit of quantification for okadaic acid, pectenotoxin 2, azaspiracid 1 and yessotoxin to 1 μg kg^{-1}.[728] Two new peptides of the D-superfamily (αD-Ms and αD-Cp) were reported from crude venom extract of *Conus mustelinus* and *C. capitaneus* (Olango Is., Sebu, Philippines).[729] The 11 kDa dimeric αD-conopeptides are potent nanomolar blockers of α7, α3β2 and α4β2 subtype neuronal nicotinic acetylcholine receptors.[729,730] Lt3a is a new M-family toxin purified from the venom of the worm-hunting cone snail *C. litteratus* (Yalong Bay, Hainan Province, South China Sea).[731] Automated sequence analysis indicated three residues were non-standard, with subsequent comparison with a cDNA sequence identifying carboxyglutamate and hydroxyproline post-translational modifications (PTMs). The peptide was found to enhance tetrodotoxin-sensitive sodium channel currents. An 86 amino acid-containing mature peptide, named con-ikot-ikot, purified from *C. striatus* (unknown location), inhibits the depolarisation of glutamate-gated ion channels, leading to neuronal death.[732] Two I-superfamily peptides, ca11a (38 residues) and ca11b (34 residues) of unknown function, were purified from the venom of South China Sea collections of *C. caracteristicus*.[733] A full-length cDNA of ca11a was generated, revealing the precursor peptide was comprised of a 20-residue signal peptide, a 22-residue pro-peptide and a 38-residue mature peptide. Using a cDNA probe of the signal peptide sequence, a number of new conotoxin peptide sequences were identified, including two O-superfamily toxins, suggesting a close evolutionary link between I- and O-superfamily toxins. Turritoxin pal9a, isolated from the turrid snail *Polystira albida*, contains 34 residues, including 6 cysteines, the pattern of which makes it a framework IX P-conotoxin peptide.[734] A Mexican Caribbean Sea collection of *Conus delessertii* yielded a 28 amino acid mature peptide, de7b, that included 6 cysteines, and exists as a mixture of different γ-carboxyglutamate and/or 4-hydroxyproline PTM isomorphs.[735] Mass spectrometry was used to investigate the distribution of PTM peptides related to Vc1.1 in the venom ducts of *Conus victoriae* (Broom, Western Australia): the finding of unmodified mature peptide in venom duct tissue indicated that some of the pre- and pro- region of the immature peptide was cleaved prior to PTM.[736] The study also noted that of 3 different disulfide isomers prepared, only the naturally occurring isomer exhibited nAChR activity and that some PTMs were detrimental to mammalian receptor activity. A homo-dimeric toxin, TxXIIIA, containing an odd number of cysteine residues in the monomer, has been identified in venom extracts of *C. textile*.[737] The use of synthetic oligomers to probe cDNA libraries generated from venom duct tissue continues to lead to identification of previously unreported conotoxins.[738–740] Given the potency of binding of conotoxins to their respective biological targets, it is of no surprise that they continue to act as highly specific molecular probes of receptors and ion channels. A number of studies have reported on structure–activity effects of modified α-conotoxins with nicotinic acetylcholine receptors (nAChRs),[741–743] including α-ImII binding to nAChRs on *Torpedo* membranes,[744] the use of fluorescent analogues,[745] and the preparation and biological evaluation of a hydrolytically stable dicarba-bridged (as opposed to disulfide-bridged) α-ImI analogue.[746] Structurally minimised analogues of the voltage-gated sodium channel-targeting μ-conotoxin KIIIA have been reported to retain biological activity,[747,748] and non-peptide mimics of analgesic ω-conotoxin GVIA have been reported.[749,750] A chimera of ω-conotoxins CVID and MVIIC, prepared using native chemical ligation methodology, was used to investigate the contributions of N- and C-terminal peptide segments to observed biological activity.[751] A study of the mucus and external body parts of a Hainan (South China Sea) collection of the pulmonate mollusc *Onchidium* sp. led to the characterisation of an intriguing bis-γ-pyrone polypropropionate, onchidione **919**.[752] Onchidione acted as a strong feeding deterrent, making treated food unpalatable to marine shrimps.

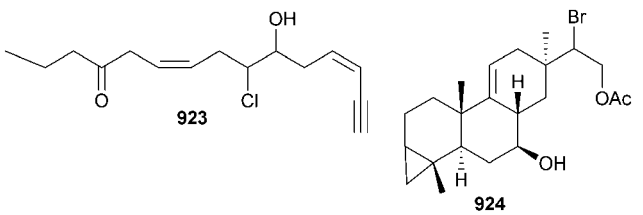


919

Sesquiterpenes **920–922**, acetogenin **923** and diterpene **924** were purified from extracts of the digestive and hermaphroditic glands of the sea hare *Aplysia fasciata* (Alfacs Bay, Spain).[753]



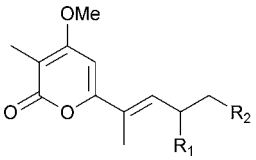
920 **921** **922**



923 **924**

Investigation of the chemistry of the herbivorous sacoglossan slug *Aplysiopsis formosa* (Azores) led to the isolation of α-pyrone polyketides aplysiopsene A–D **925–928**.[754] The structures represent shorter side chain variants of the more usual sacoglossan polyketide metabolites such as the placidenes.[755,756]

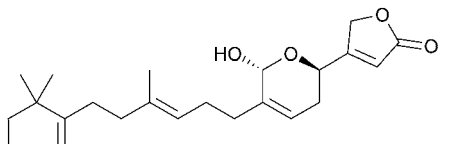
Stable isotope incorporation studies with *Placida dendritica* (Gulf of Naples) demonstrated a mixed acetate/propionate polyketide biosynthetic route to the placidenes.[757] Remarkably,



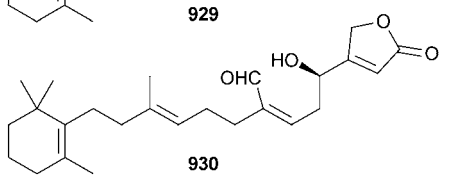
925 $R_1 = R_2 = H$
926 $R_1 = Me$, $R_2 = H$
927 $R_1 = H$, $R_2 = Me$
928 $R_1 = R_2 = Me$

the biogenesis of placidene A required only intact C_3 units, an ability previously demonstrated only by bacteria. The biosynthetic origin of Tyrian purple in *Dicathais orbita* has been traced to a number of tissue types by a combination of histochemistry and mass spectrometry.[758] An L-amino acid oxidase (escapin) present in the ink of the sea hare *Aplysia californica* oxidises L-lysine to yield hydrogen peroxide and a number of open-chain and cyclic piperidine products.[759] Malyngamides O and P (*Stylocheilus longicauda*)[251] structures have been confirmed by convergent synthesis.[253] Investigation of the chemistry of the nudibranch *Chromodoris willani*, found feeding on an unidentified sponge that contained manoalide[760] and secomanoalide,[761] yielded the deoxy analogues **929** and **930**.[762] Both **929** (previously reported as a synthetic intermediate[763]) and **930** exhibited moderate antimicrobial activity and were less potent inhibitors of PLA_2 than manoalide and secomanoalide.

The combined use of 1 mm and 1.7 mm NMR cryo-microprobes and MS has allowed structure elucidation on the



929



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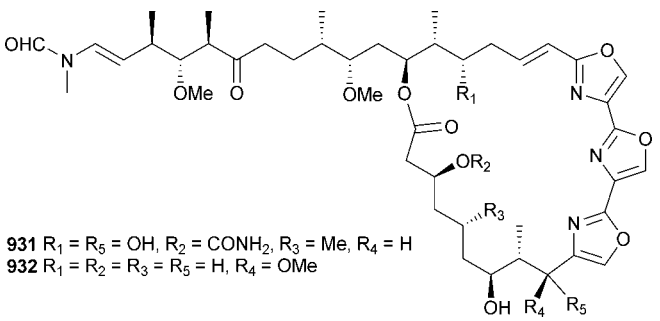
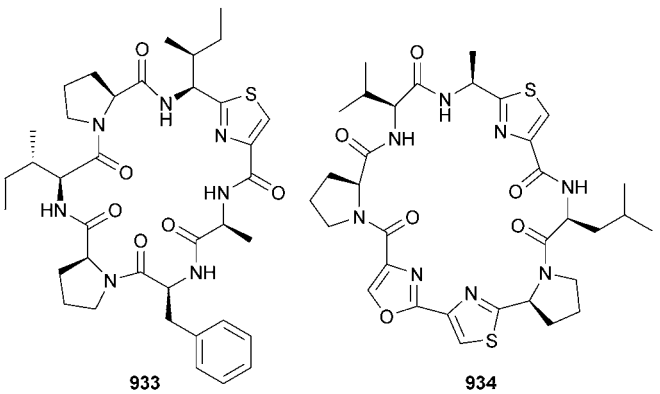


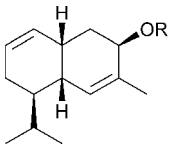
931 $R_1 = R_5 = OH$, $R_2 = CONH_2$, $R_3 = Me$, $R_4 = H$
932 $R_1 = R_2 = R_3 = R_5 = H$, $R_4 = OMe$



933 **934**

nanomolar scale of structures 9-*O*-desmethylkabiramide B **931**, 33-methyltetrahydrohalichondramide **932**, and sanguinamides A **933** and B **934**, from the extract of a single specimen of the Indo-Pacific nudibranch *Hexabranchus sanguineus*.[764] Kabiramide B,[765] isolated from the same species, had potent *in vitro* antifungal activity, while **932** was slightly less active and **931** the least inhibitory.

The aeolidean nudibranch *Phyllodesmium lizardensis*, endemic to Lizard Is., Great Barrier Reef, sequesters muurolene sesquiterpenes **935** and **936** from its preferred host coral *Heteroxenia* sp.[766]

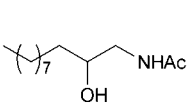


†**935** R = H
936 R = Ac

Further pharmacological investigations of zalypsis (PM00104), a synthetic human antitumour agent that is structurally related to the cytotoxic marine isoquinoline alkaloids ecteinascidin 743 (ascidian, *Ecteinascidia turbinata*)[767,768] and jorumycin (nudibranch, *Jorunna funebris*),[769] continue to identify new targets and information regarding the mechanism of action. The drug exhibited potent activity towards multiple myeloma *via* generation of DNA double-strand breaks,[770] formed DNA adducts, was particularly potent towards a gastric cancer cell line,[771] bound DNA in a different manner to ET-743,[772] and resistance to the drug could be conferred by the over-expression of zinc finger proteins.[773] A library of new nitrile-containing analogues of jorumycin, obtained by semi-synthesis of sponge-derived renieramycin M,[774] has expanded the structure–activity relationship of the ester side chain of these cytotoxic agents.[775]

11 Tunicates (ascidians)

With 35 new metabolites being the average reported from ascidians since 2007, the 52 natural products presented in this review indicates elevated productivity on the part of isolation chemists. The simple long-chain amino alcohols clavaminols G–N **937–942** were isolated as bioactive constituents of the ascidian *Clavelina phlegraea* (Bay of Naples, Italy).[776] Limited SAR analysis indicated that free amino and alcohol groups were required for cytotoxicity, while the presence of an additional hydroxyl group or lipid unsaturation were detrimental to activity.



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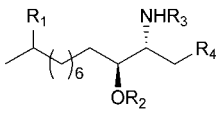
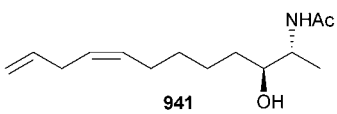
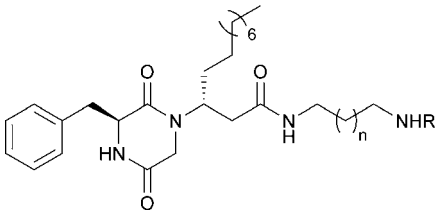


†**938** $R_1 = R_2 = H$, $R_3 = Ac$, $R_4 = OH$
939 $R_1 = R_4 = H$, $R_2 = R_3 = Ac$
940 $R_1 = R_4 = H$, $R_2 = Ac$, $R_3 = CHO$
942 $R_1 =$ Me, $R_2 = R_4 = H$, $R_3 = Ac$



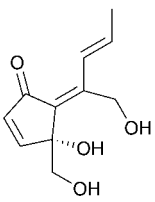
941

Two different species of *Didemnum* sp. (Bahia State, Brazil) yielded the antibacterial diketopiperazines rodriguesine A **943** and B **944** and the *N*-acetyl analogues **945** and **946**.[777]



†**943** n = 1, R = H
†**944** n = 2, R = H
†**945** n = 1, R = Ac
†**946** n = 2, R = Ac

The mildly cytotoxic didemnenone congeners **947–953** were isolated from two didemnid ascidians, *Lissoclinum* sp. and *Diplosoma* sp., collected respectively from Tarama Is. and Hateruma Is., Okinawa.[778] The metabolites were detected in extracts of *Prochloron* spp. separated from the two ascidians, suggesting the symbiont was the true producer of the polyketides.



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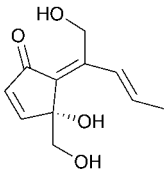

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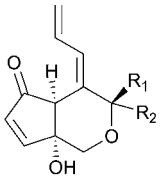
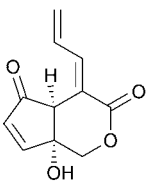


949 R_1 = OH, R_2 = H
950 R_1 = H, R_2 = OMe



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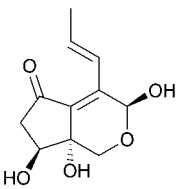

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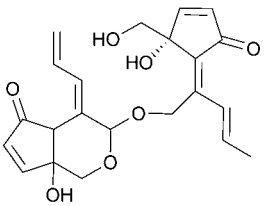
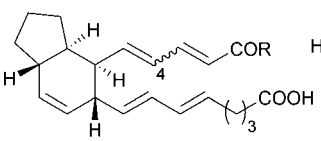
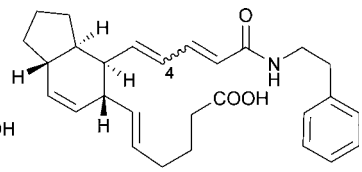


953

Bicyclic acids and amides **954–959**, isolated from a Jeju Is. (S. Korea) collection of an unidentified didemnid ascidian, exhibited mild cytotoxicity towards a panel of human tumour cell lines.[779] Notionally, the natural products could be derived from Diels–Alder cyclisation of long chain fatty diacids.

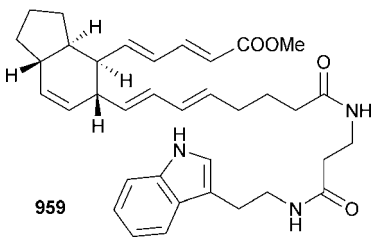


954 (4*Z*), R = OMe
955 (4*Z*), R = $NHCH_2CH_2Phe$
956 (4*E*), R = $NHCH_2CH_2Phe$

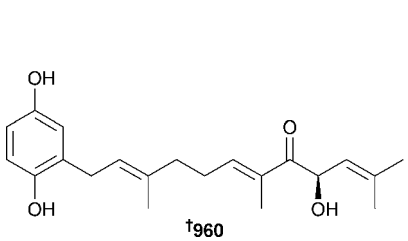


957 (4*Z*)
958 (4*E*)

Meroterpenoids rossinone A **960** and B **961** were isolated from Antarctic specimens of *Aplidium* sp. and exhibited a range of anti-inflammatory and antiproliferative biological properties.[780]

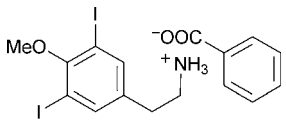


959



†**960** **961**

Didemnum rubeum (Chuuk Atoll) afforded iodotyramine derivatives **962–967**.[781] The occurrence of **962** as a benzoate salt and formamide **964**, examples of plant or microbial-derived natural products, suggested that **962–967** may be produced by an algal symbiont. ABCG2 is a human transporter protein linked to multidrug resistance where it appears to play a role, amongst others, in modulating the oral bioavailability of drugs.



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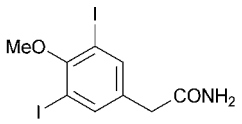

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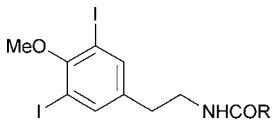
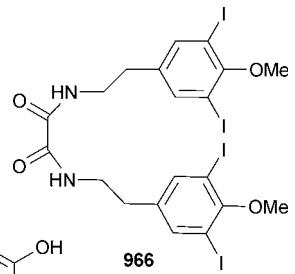


964 R = H
965 R = Phe



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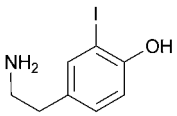
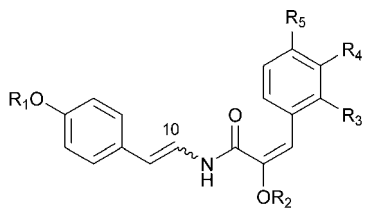


967

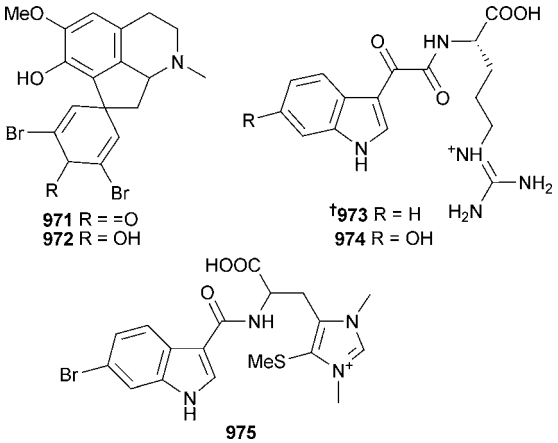
Screening for inhibitors of ABCG2 led to the isolation of a number of known alkaloids of the botryllamide family[782] as well as the characterisation of new congeners botryllamides I **968** and J **969** and revision of the structure of botryllamide H[783] **970** (*Botryllus tyreus*, Papua New Guinea).[784] Extensive mechanism-of-action investigations established botryllamide G to be the most potent and specific inhibitor of ABCG2.



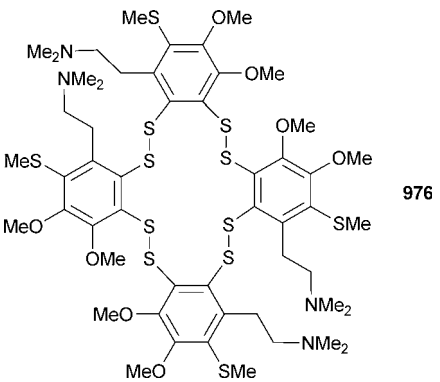
968 (10*E*), R_1 = R_2 = Me, R_3 = R_4 = H, R_5 = OH
969 (10*Z*), R_1 = R_2 = R_5 = H, R_3 = NC, R_4 = OH
970 (10*E*), R_1 = R_2 = R_5 = H, R_3 = NC, R_4 = OH

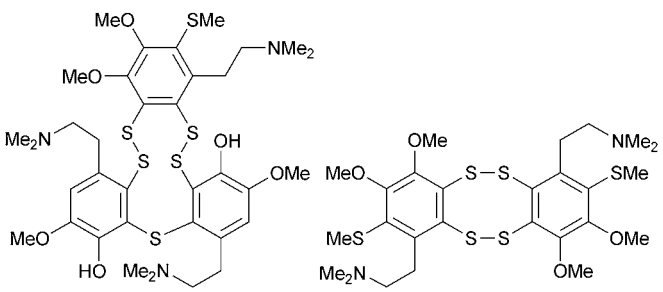
In what appears to be the first occurrence of proaporphine alkaloids from a marine source, saldedines A **971** and B **972** were isolated from an unidentified ascidian (Salary Bay, Madagascar).[785] Both alkaloids exhibited modest toxicity to brine shrimp. From a collection of *Leptoclinides durus* (Heron Is., Queensland, Australia) the indole alkaloids leptoclinidamines

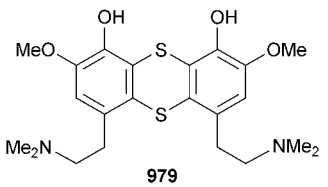
A–C **973–975** were isolated.[786] The absolute configuration of **973** was established by synthesis.

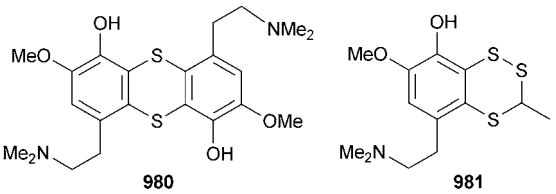


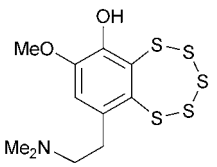
The polysulfide dopamine-derived alkaloids lissoclibadin 8–14 **976–982** were isolated as cytotoxic metabolites from *Lissoclinum cf. badium* (Manado, Indonesia).[787] Lissoclibadin 14 was recently reported from a Papua New Guinea collection of the same species and assigned the trivial name isolissoclinotoxin B.[788] The particular disulfide bonding arrangements presented in lissoclibadins 9 **977** and 10 **978**, as opposed to other isomeric possibilities, were selected solely on the basis that they were judged to be more thermodynamically stable by molecular mechanics calculations.

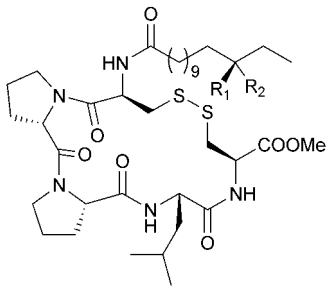






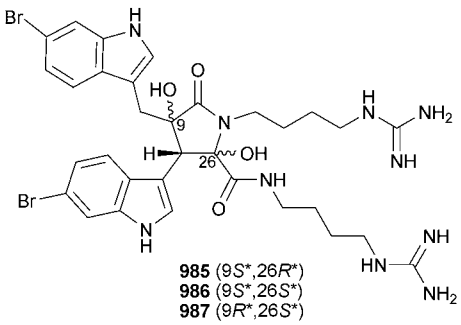




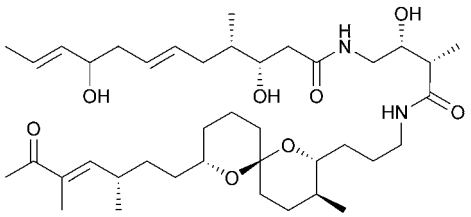


Specimens of *Eudistoma* sp. (Namena Is., Fiji) yielded disulfide-containing lipopeptides eudistomide A **983** and B **984**. The structures were confirmed by synthesis.[789]

Bioassay (neuronal nitric oxide synthase)-directed fractionation of a Great Barrier Reef collection of *Eusynstyela latericius* led to the isolation and characterisation of eusynstyelamides A–C **985–987**.[790] The spectroscopic data observed for **985** were essentially identical to those reported for eusynstyelamide, previously reported from a Fijian collection of *E. misakiensis*,[791] though the metabolites exhibited opposite specific rotations. It was concluded that the originally proposed structure of eusynstyelamide was in error and is better represented as the antipode of **985**.



The potently cytotoxic (A2780, IC_{50} 0.34 μM) lipopeptide 39-oxobistramide K **988** was isolated from *Trididemnum cyclops* (Madagascar).[792] The similarity of CD spectra with co-occurring bistramide A suggested the skeletal configuration shown.



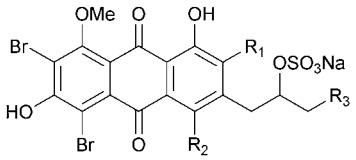
988

In addition to a number of known 5α,8α-epidioxysterols, two new examples, **886** and **887**, noted previously in the Cnidarian section of this review, were isolated from the ascidian *Trididemnum inarmatum* (Achladi Bay, Maliakos Gulf, Greece).[689] Bioassay screening led to the isolation of two antimicrobial peptides, halocyntin (26 aa residues) and papillosin (34 aa) from haemocytes of the solitary ascidian *Halocynthia papillosa*.[793] Botryllazine B (*Botryllus leachi*)[794] and analogues are mixed-type inhibitors of recombinant human aldose reductase.[795] An improved and more efficient microwave-assisted aldol condensation reaction was used to synthesise polyandrocarpamines A and B,[796] with the former compound subsequently shown to exhibit mild cytotoxicity towards the SF268 human tumour cell line.[797] The structures of eudistomins Y_1-Y_6 (*Eudistoma* sp.)[798] have been confirmed by synthesis.[799] Asymmetric synthesis of the reported structure of eudistomidin B (*Eudistoma* sp.)[800] indicates the structure of the natural product requires revision.[801] Racemic syntheses of aplicyanins A, B and E (*Aplidium cyaneum*)[802] and a library of analogues have been reported; biological evaluation against a panel of human tumour cell lines indicated the importance of bromine substitution and the presence of an acetyl group for activity.[803] The structure–cytotoxicity relationship of a number of natural and unnatural lamellarin alkaloids towards human tumour cell lines has been investigated.[804] Site-directed mutagenesis and metal-ion affinity chromatography has been used to investigate the binding affinity of two sites of the Vanabin2 vanadium-binding protein of *Ascidia sydneiensis samea*.[805] *Pyura chilensis*, a solitary ascidian eaten raw by coastal populations of Chile and Peru, has been shown to contain domoic acid, and so must now be considered a vector for Amnesic Shellfish Poisoning.[806]

12 Echinoderms

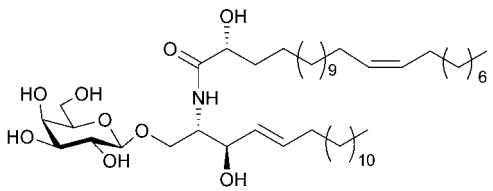
The number of new metabolites reported annually from echinoderms has remained relatively constant over the 2002–2008 period. Bioassay-directed (P388) fractionation of extracts of the inter-tidal ophiuroid *Ophiocoma scolopendrina* gave the mildly cytotoxic tetrameric phenylpropanoids ophiodilactones A **989** and B **990**.[807] The absolute configuration of **989** was determined (CD).

A deep-sea (Okinawa Trough, Japan) collection of the scarlet-coloured stalked crinoid *Proisocrinus ruberrimus* yielded the brominated anthraquinone pigments proisocrinin A–F **991**–**996**.[808] The ECD spectra of **991** and **992** were equal and opposite to those observed for **994** and **995**, implying an enantiomeric stereochemical relationship between the pairs of metabolites.

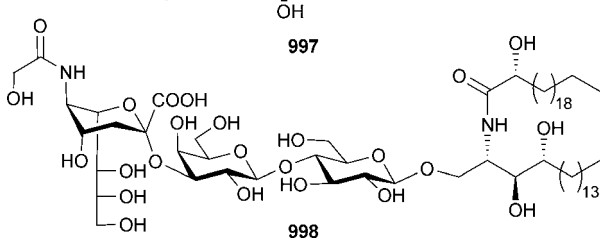


991 $R_1 = R_2 = Br$, $R_3 = Et$
992 $R_1 = H$, $R_2 = Br$, $R_3 = Et$
993 $R_1 = Br$, $R_2 = H$, $R_3 = Et$
994 $R_1 = R_2 = Br$, $R_3 = H$
995 $R_1 = R_3 = H$, $R_2 = Br$
996 $R_1 = Br$, $R_2 = R_3 = H$

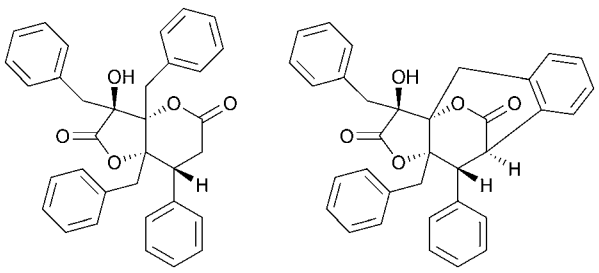
The structurally-related anthraquinones rhodoptilometrin[809] and 3-propyl-1,6,8-trihydroxy-9,10-anthraquinone[810] were re-isolated from the Australian crinoid *Colobometra perspinosa* (Family Is., Great Barrier Reef), and were modestly cytotoxic towards a panel of human tumour cell lines.[811] ^1H and ^{13}C NMR data observed for rhodoptilometrin were at variance with those data previously reported. The study also reported the first occurrences of 2-[(phenylacetyl)amino]ethanesulfonic acid and γ-hydroxybutyric acid from a marine source. Whilst galactocerebrosides have usually been reported from starfish, in what appears to be the first report of such a metabolite from a sea cucumber, **997** was isolated from *Bohadschia argus* (Zanpamisaki, Okinawa).[812] The starfish *Linckia laevigata* (Okinawa) yielded a number of ganglioside natural products, from which LLG-1 **998** was identified.[813]



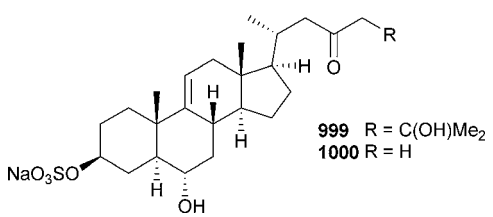
997



998



989 990



999 R = C(OH)Me_2
1000 R = H

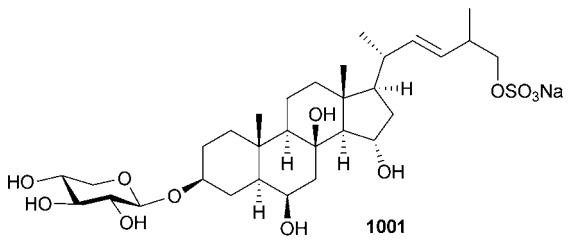
Sterol sulfates lysaketotriol **999** and lysaketodiol **1000**, isolated from the hollow tube feet (ambulakrums) of the starfish *Lysastrosoma anthosticta* (Sea of Japan), were found to increase reactive oxygen species formation by mouse macrophages.[814]

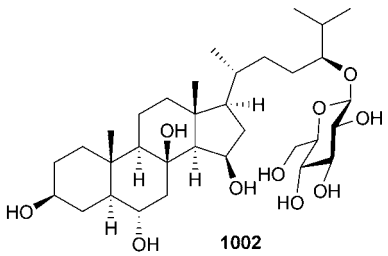
Evasterioside C **1001** is a 24-norsterol isolated from *Evasterias retifera* (Sea of Japan).[815] Given the occurrence of 24-norsterols in phytoplankton, a food chain link source of the metabolite was proposed. The same paper also reported the related glycosides evasteriosides D **1002** and E **1003** from *E. echinosoma* (Gulf of Shelichov, Sea of Okhotsk).

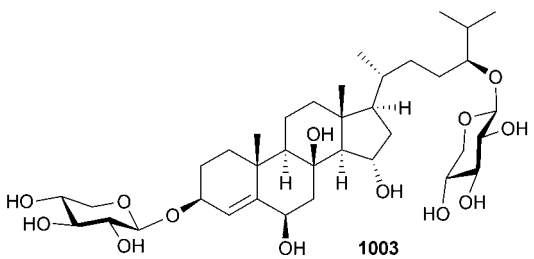
Of the five steroidal monoglycosides recently reported from *Hippasteria kurilensis* (deep-sea dredging, Kuril Is., Sea of Okhotsk), kurilensosides E–G **1004–1006** are unusual due to the lack of a 6-hydroxyl group.

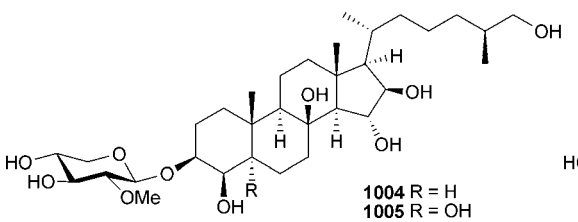
Kurilensoside H **1007** contained a 4,5-epoxy functionality, and **1008** was the 15-sulfate analogue of co-metabolite echinasteroside C.[816] The authors also reported on the analysis of the hydroxylation patterns of over 500 oxidised sterols from starfish species. They proposed a dominant sequence of oxidation processes starting at C-3 and progressing in turn from C-6, then C-15 to C-8 that could be used to explain the substitution patterns observed. Such a sequence highlights the unusual finding of **1004–1006**, which as noted earlier, lack a 6-hydroxyl group. More regular 6-hydroxy-steroidal glycosides kurilensosides I **1009** and J **1010** were subsequently reported from the same collection of *H. kurilensis*.[817]

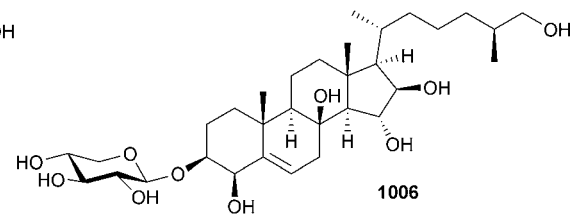
The 4-*O*-methyl-D-GalNAc-containing glycoside anthenoside A **1011** (*Anthenea chinensis*, Sanya Bay, South China Sea) was mildly cytotoxic towards a panel of three human tumour cell lines and also promoted tubulin polymerisation.[818] The same tubulin bioassay was used to direct the isolation of novaeguinosides A–D **1012–1015** from the starfish *Culcita novaeguineae*

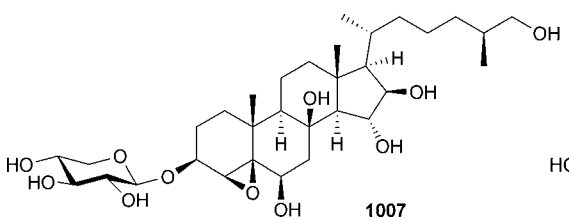


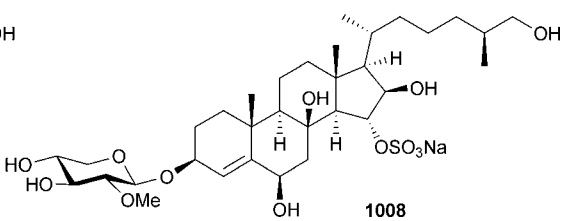




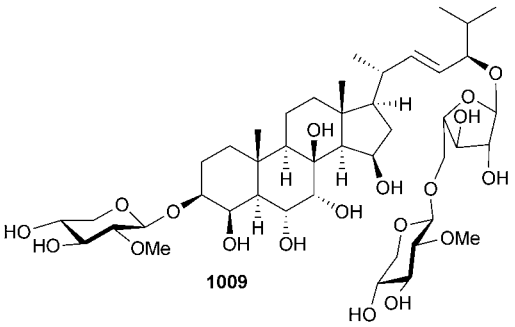




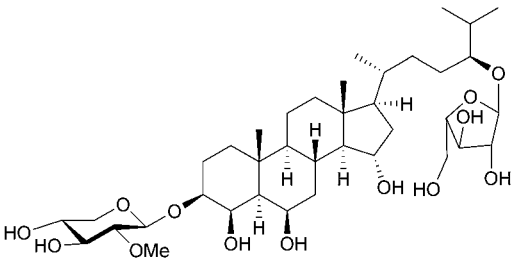




(Sanya Bay, South China Sea).[819] By comparing structures with other (inactive) saponins, the authors noted that the presence of $\Delta^{9(11)}$-3β,6α-dioxysteroids bearing a sulfate group at C-3 and an oligosaccharide at C-6 was a common structural motif for cytotoxicity in this series. The importance of the 24-sulfate group for the observed tubulin polymerisation promoting activities of these compounds was highlighted, with the finding that 24-desulfated analogues **1016** and **1017** (isolated from the



1009



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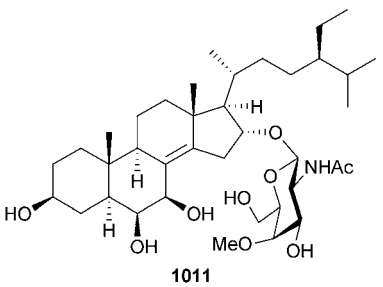
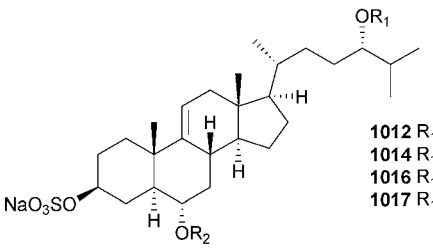
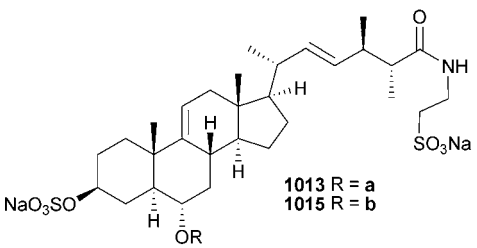


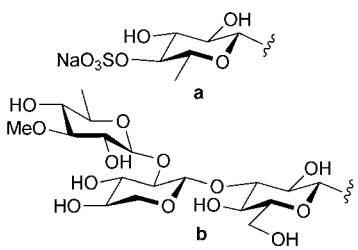
1011



1012 R_1 = SO_3Na, R_2 = **a**
1014 R_1 = SO_3Na, R_2 = **b**
1016 R_1 = H, R_2 = **a**
1017 R_1 = H, R_2 = **b**

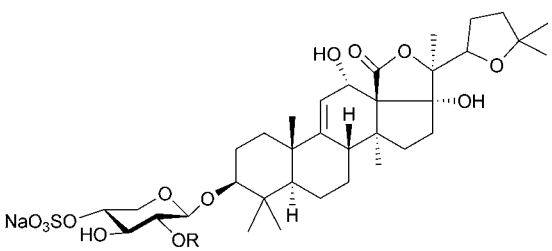


1013 R = **a**
1015 R = **b**

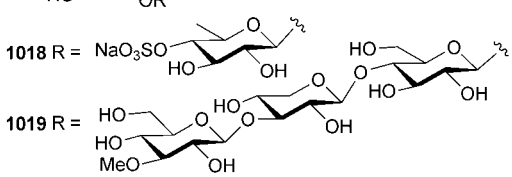


a

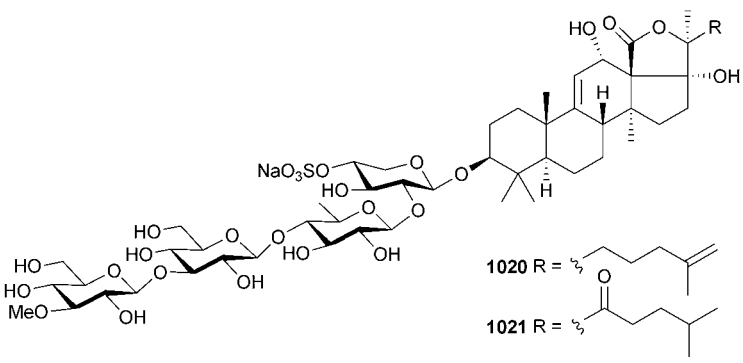
b



1018 R =



1019 R =



1020 R =

1021 R =

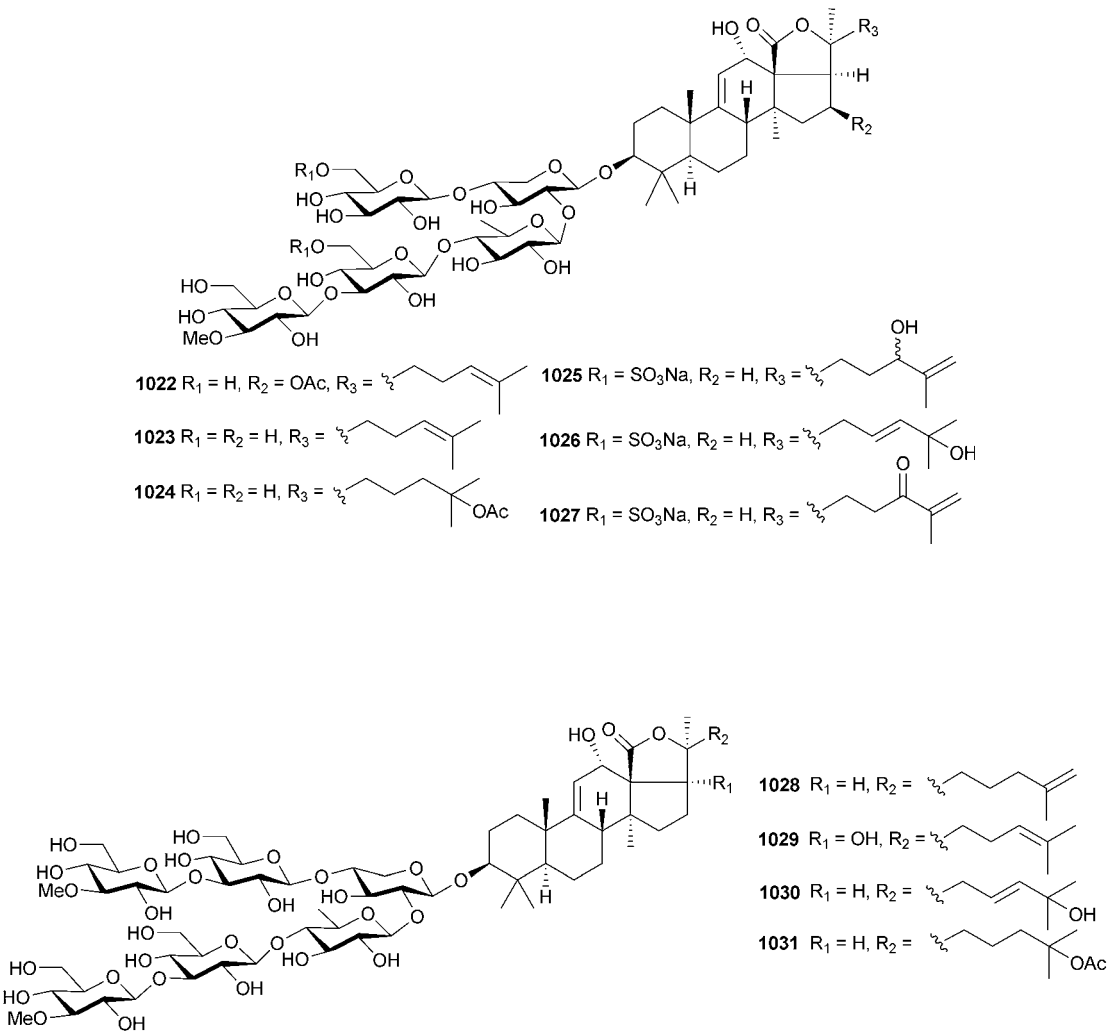
same organism) were inactive in the assay and less potent cytotoxins.[820]

A monosulfated analogue **1018** (*Actinopyga lecanora*, Hainan Is., South China Sea) of the well-known sea cucumber metabolite holothurin B[821] was unfortunately assigned a trivial name (lecanoroside A).[822] Lecanoroside B **1019** was also isolated from the extract. Bioactive triterpene glycosides **1020** and **1021** (*Holothuria scabra*, South China Sea) were assigned the trivial names scabrasides A and B,[823,824] which unfortunately was a duplication of the name for a secoiridoid isolated from the rhizomes and roots of the terrestrial plant *Gentiana scabra* var. *buergeri*.[825]

Holothuria (*Microthele*) *axiloga*, also collected from Hainan Is., South China Sea, yielded arguside F **1022**, impatienside B **1023** and pervicoside D **1024**, of which only impatienside B exhibited broad-spectrum antifungal activity.[826] The closely related sulfated triterpenes achlioniceosides A_1–A_3 **1025–1027** were reported from *Achlionice violaecuspidata* (= *Rhipidothuria racowitzai*) (Weddell Sea (epibenthic sledge), Antarctica).[827]

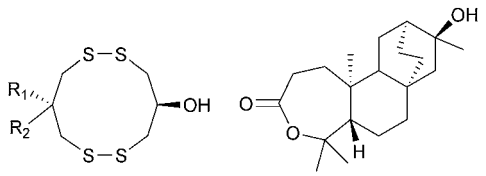
A Hainan Is. (South China Sea) collection of *Bohadschia marmorata* yielded the hexaosides marmoratoside A **1028**, 17α-hydroxyimpatienside A **1029**, marmoratoside B **1030** and 25-acetoxybivittoside D **1031**.[828] Moderate antifungal activities were observed for **1028** and **1029**.

The freeze-dried liposomal encapsulation of nobiliside A[829] has been investigated,[830] while semi-synthetic acetoxy derivatives of nobiloside B retain antitumour effects with reduced haemolytic activity.[831] Patagonicoside A[832] and the desulfated analogue exhibited modest levels of antiproliferative activity towards human tumour cell lines, and promoted nuclear translocation of NF-κB and degradation of inhibitory protein IκBa.[833] Both triterpene pentaosides frondoside A[834] and cucumarioside A_2-2,[835] induced apoptosis in leukemic cells, but by differing mechanisms: cucumarioside A_2-2 was caspase-dependent, while frondoside A was caspase-independent.[836] MS/MS techniques were used to investigate the saponin chemistry of the body and Cuvierian tubules of a Mediterranean collection of *Holothuria forskali*.[837] The Cuvierian tubules, which act as a defensive organ, contained additional saponins not found in the organism body wall. Structures for a number of novel metabolites were proposed, but based solely on MS/MS data. Surface-associated fatty acids and sterols, including hexadecanoic acid, cholesterol, lathosterol and sitosterol of the starfish *Linckia laevigata*, *Fromia indica*, *Cryptasterina pentagona* and *Archaster typicus*, appear to reduce settlement of fouling diatoms, bryozoa and polychaete worms.[838]



13 Mangroves and the intertidal zone

In the previous review,[1] this section included compounds from microorganisms isolated from mangroves and other sources in the intertidal zone. For consistency, all reports for microorganisms from this region now appear in the marine microorganism and phytoplankton section of this review. The structures of macrocyclic polydisulfides **1032** and **1033**, isolated from the leaves and stems of the mangrove *Bruguiera gymnorrhiza*, were secured.[839] Extracts of the bark of *Excoecaria agallocha* (Hainan Province, China) afforded the atisane diterpene **1034**,[840] in addition to excoecarin V3, previously reported from the same species.[841] The latter natural product significantly inhibited adherence of the biofilm-forming bacterium *Pseudomonas pseudoalcaligenes*.

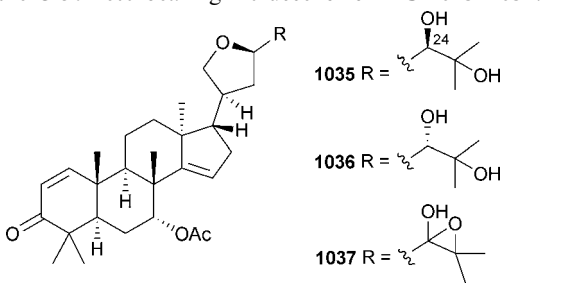


1032 R_1 = OH, R_2 = H
1033 R_1 = H, R_2 = OH

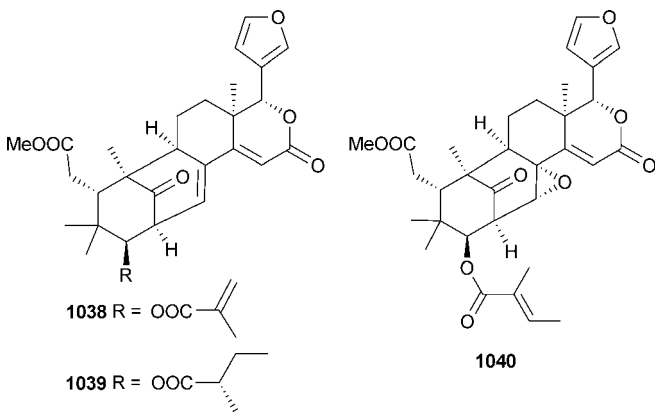
1034

Protoxylocarpins F–H **1035–1037** were isolated as non-cytotoxic constituents of the seed kernels of *Xylocarpus granatum* (Samutsongkram Province, Thailand).[842] The absolute configuration at C-24 of **1035** was determined, while all other stereogenic centres were assigned as relative only.

A collection of seeds of *X. granatum* (Krishna Estuary, Andhra Pradesh, India) yielded granatumins A–G **1038–1044**,[843] while seeds of *X. moluccensis*, collected in the same locale, contained the C-30 keto-bearing moluccensins A–G **1045–1051**.[844]

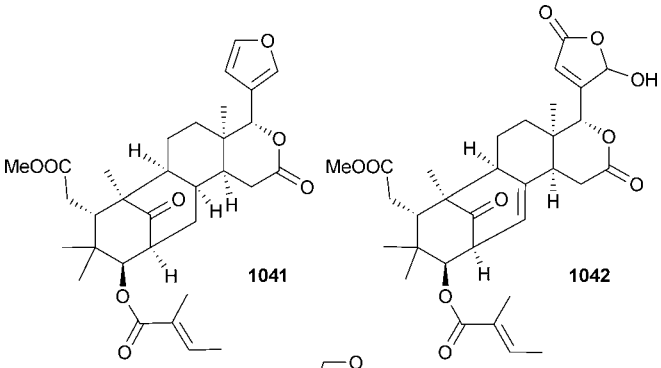


1035 R =
1036 R =
1037 R =



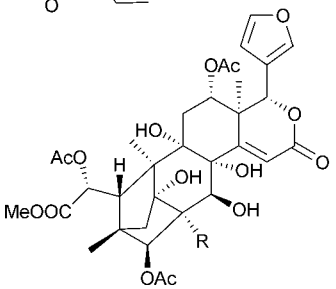
1038 R =
1039 R =

1040

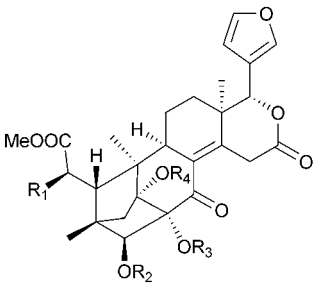


1041

1042



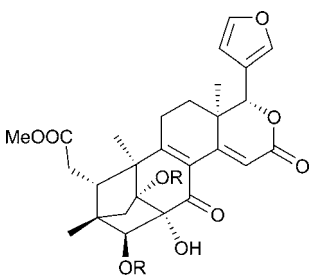
1043 R = H
1044 R = OH



1045 R_1 = R_3 = H, R_2 = R_4 = methylpropanoyl
1046 R_1 = R_3 = H, R_2 = (2*S*)-2-methylbutanoyl, R_4 = methylpropanoyl
1047 R_1 = R_3 = H, R_2 = methylpropanoyl, R_4 = (2*S*)-2-methylbutanoyl
1048 R_1 = OH, R_2 = (2*S*)-2-methylbutanoyl, R_3 = H, R_4 = methylpropanoyl
1049 R_1 = OH, R_2 = methylpropanoyl, R_3 = H, R_4 = (2*S*)-2-methylbutanoyl
1050 R_1 = R_4 = H, R_2 = R_3 = methylpropanoyl

14 Miscellaneous

The absolute configuration of (−)-complanine, isolated from the fireworm *Eurythoe complanata*,[845] was determined by stereoselective synthesis from (*R*)-malic acid.[846] Starting from D-



1051 R = methylpropanoyl

proline, tandem sequences of olefination and Suzuki coupling were used to confirm the structures and define absolute configurations of (+)-villatamines A and B,[847] mildly cytotoxic alkaloids isolated from the flatworm *Prostheceraeus villatus*.[848] A trace alkaloidal constituent of the hoplonemertine marine worm *Amphiporus angulatus*[849] was determined to be 3-methyl-2,3′-bipyridyl following synthesis of all eight possible isomers.[850] An 11.7 kDa glycine-rich cysteine-containing peptide isolated from the haemocytes of the spider crab *Hyas araneus* showed broad-spectrum antimicrobial properties.[851] The *N*-terminal region, devoid of cysteines, exhibited attenuated bioactivity.

15 Conclusion

The value of natural products as a source of drug leads has been well documented, with the majority of small-molecule pharmaceuticals across the disease spectrum being of natural product origin, or natural product derived/inspired.[852] Of the estimated 153,000 known natural products,[853] ~22,000 are of marine origin.[66] Currently very few marine natural products have been or are being developed into marketable drugs,[5] and this may be attributed in part to the fact that marine natural products have a much shorter history of discovery than their terrestrial and microbial counterparts. Furthermore, the major drug companies have invested little effort into the development of natural product leads over the past decade. However, it could be helpful to compare the potential "drug-likeness" of marine natural products with all other natural products, as measured by an examination of their Lipinski characteristics, to determine whether there are any features of marine compounds that might lead to them being inherently more or less suitable as drug candidates. In 2008 Quinn *et al.* analysed the "drug-likeness" of all the natural products, including those of marine origin, as listed in the Dictionary of Natural Products[853] (DNP) (April, 2005; ~126,140 unique compounds)[854] using the "rule of five" criterion described by Lipinski.[855] Briefly, this suggests that to be drug-like and orally-bioavailable a molecule must have a partition coefficient (log*P*) < 5, a molecular weight <500 Da, <5 hydrogen bond donors (HBD) and <10 hydrogen bond acceptors (HBA). By analyzing the derived Lipinski data from this set, it was found that the molecular weight plot peaked in the 300–400 Da range, clog*P* (calculated octanol–water log*P*) had a Gaussian distribution with a maximum at 2–2.5, HBA peaked at 3–5 and then fell off rapidly, while the HBD count rapidly fell from a maximum at 0. The Lipinski data for a marine natural product selection (20,174 compounds), calculated using ACD algorithms,[856] has now been compared to those reported for the DNP selection. This analysis shows great similarity between the two data sets. The most significant difference however was in the distribution of the clog*P* values for the marine compounds that had a maximum between 4 and 5, suggesting a greater average lipophilicity of the marine compounds. This skewing of the clog*P* distribution to higher values is not favourable in terms of bioavailability, but clog*P* values are not considered entirely reliable, especially with Br substituents.[854] When the Lipinski violations were compared for the marine *vs.* the DNP compound sets there was a marked change in distribution (see Fig. 1), with only 42% of all marine metabolites having zero Lipinski violations. However, the relative proportion of compounds having zero or one violations of

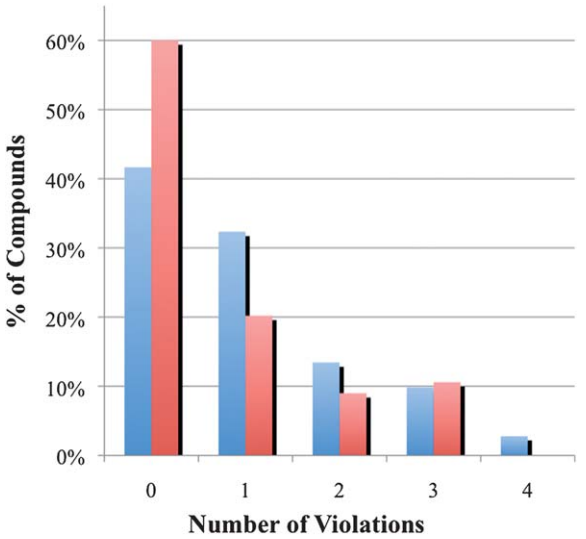


Fig. 1 Lipinski violations for marine natural products (blue) and all natural products (red).

Lipinski's "rule of five" was closer (74% *vs.* 80%). The broad conclusion that can be drawn from this very simple analysis of the general physico-chemical properties of marine natural products is that they too are "Lipinski-worthy", and in the future they should be a source of many more small-molecule pharmaceuticals.

An aim of the "rule of five" was to highlight bioavailability problems based on calculable physico-chemical parameters. In Fig. 2 the major marine phyla explored to date (each having >2% of all compounds isolated) are compared on the basis of zero or one Lipinski violation.

The analysis given in Fig. 2 highlights the lipophilicity of many of the compounds in the phyla examined, particularly for the Ochrophyta, Porifera, Mollusca and Cnidaria. Given the overall importance of log*P* to permeability and bioavailability, any conclusions that could be drawn from Fig. 2 about any particular phylum being a source of compounds with fewer Lipinski violations should be made with caution. More recently, simple rules that have been derived from an extensive analysis of ADMET (adsorption, distribution, metabolism, excretion and toxicity) parameters highlight the role of MW and clog*P*.[857] Increasing values in either MW or clog*P* are generally detrimental to more than one ADMET parameter. As a consequence it was suggested that a molecule has more desirable oral-bioavailability physico-chemical properties if MW < 400 and clog*P* < 4. An analysis of the marine natural products data based on these parameters is shown in Fig. 3, and suggests that the Actinobacteria and Ascomycota have a greater proportion of compounds that meet these criteria. These two phyla were also distinctive in the analysis shown in Fig. 2. Physico-chemical parameters can suggest the optimum combinations for potential pharmaceuticals, but the real test is placing purified compounds into biological testing, or implementing a bioassay-guided approach to selection. Ultimately, however, the potential of a marine natural product as a drug candidate will be determined by the biological evaluation results, not the calculated physico-chemical parameters.

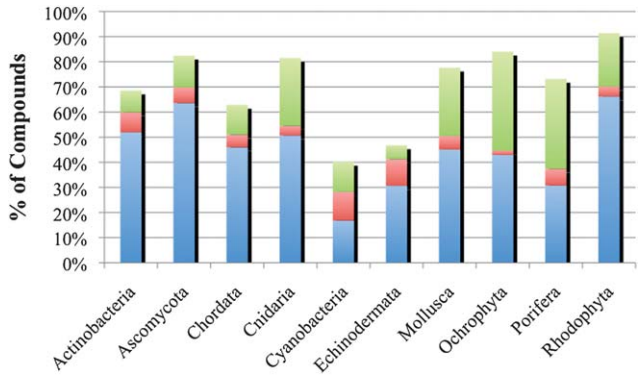


Fig. 2 Lipinski violations as a function of phylum: the total height of each bar is the sum of zero and one violations for that phylum. The % contributions are shown for zero violations (blue), one violation (but not clog*P*) (red) and the contribution from a clog*P* violation (green).

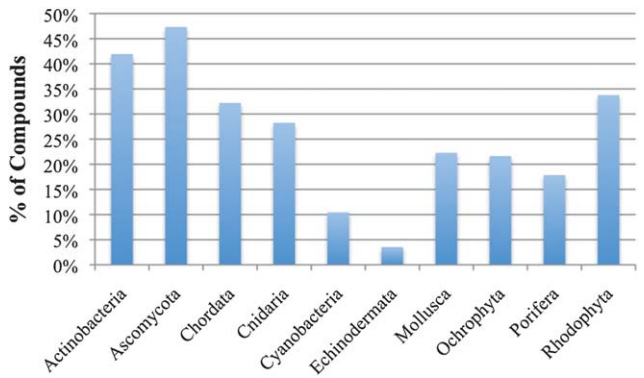


Fig. 3 Analysis of marine natural products having MW < 400 and clog*P* < 4.

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