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REVIEW

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Marine natural products

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Covering: 2012. Previous review: *Nat. Prod. Rep.*, 2013, **30**, 237–323.

This review covers the literature published in 2012 for marine natural products, with 1035 citations (673 for the period January to December 2012) 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 (1241 for 2012), 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.

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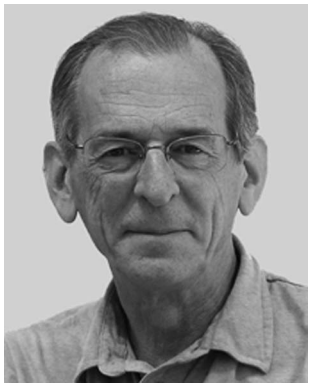
1 Introduction

This review is of the marine natural product (MNP) literature for 2012 and describes 1241 new MNPs from 382 articles, an 8% increase in the number of compounds reported for 2011.[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.

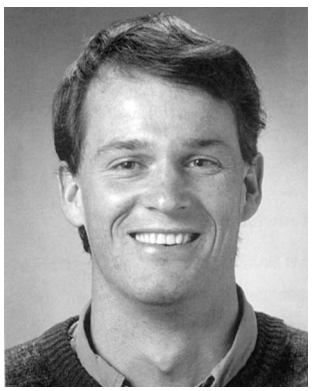
2 Reviews

A selection of the many reviews on various aspects of MNP studies is listed here. A comprehensive review of MNPs reported in 2010 has appeared,[2] as well as the highlights of compounds reported in 2011.[3] The two volume '*Handbook of Marine Natural Products*' has been published.[4] The continuing series on '*Marine Pharmaceuticals: The Preclinical Pipeline*' is now accessible from a web site.[5,6] A survey of new drugs derived from all natural products over the past 30 years has been presented.[7] Many classes or specific examples of marine-sourced compounds have been reviewed to varying extents, including conopeptides,[8,9] didemnins,[10] largazole,[11] peptides,[12–14] prenylated quinones and hydroquinones,[15] arsenolipids,[16] bryostatins,[17] multisulfide-containing metabolites,[18] fascaplysin,[19] tunichromes,[20] glycosides from sponges,[21] sea anemone toxins,[22] mycalamides and related compounds,[23,24] and polyhydroxysterols.[25] There were three

reviews of general classes of compounds that included reference to marine compounds – sesquiterpenoids,[26] cembrane diterpenes,[27] and diketopiperazines.[28] Reviews of natural products from various marine sources include those from cyanobacteria,[29,30] microalgae,[31,32] actinomycetes,[33] gorgonians,[34] ascidians,[35,36] sea cucumbers,[37] sponges,[38–40] seaweeds[41] and their endophytic fungi,[42] the marine flora and fauna of Fiji,[43] the sponges *Aplysina aerophoba*[44] and *Stylissa massa*,[45] and from the soft coral *Nephthea*.[46,47] Particular types of bioactivity have been reviewed in papers on marine anticancer drugs,[48] indoleamine 2,3-dioxygenase inhibitors,[49] kinase inhibitors,[50] protein tyrosine phosphatase inhibitors,[51] compounds with reversal effects on cancer multidrug resistance,[52] steroid nuclear receptor ligands from sponges,[53] mammalian DNA polymerisation inhibitors from microorganisms[54] and marine bioactives against inflammatory diseases.[55] Topics in chemical ecology of cyanobacteria[56] and sponges[57] have been covered, while marine bioprospecting has been reviewed.[41,58,59] The eighth in a companion series providing an overview of synthetic aspects of MNPs has appeared with coverage of publications from 2010.[60] There have been a number of papers which, while not necessarily being reviews, are useful to include here as they describe advances in techniques or approaches to discovery that are relevant to MNP studies. These include papers on configurational assignments,[61,62] marine proteomics,[63] guiding principles for natural product drug

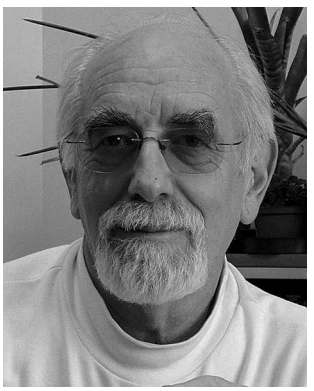


John Blunt obtained his BSc (Hons) and PhD degrees from the University of Canterbury, followed by postdoctoral appointments in Biochemistry at the University of Wisconsin-Madison, and with Sir Ewart Jones at Oxford University. He took up a lectureship at the University of Canterbury in 1970, from where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



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.

Rob Keyzers carried out his BSc(Hons) and PhD studies at Victoria University of Wellington. His thesis research, carried out under the guidance of Assoc. Prof. Peter Northcote, a former contributor to this review, focused on spectroscopy-guided isolation of sponge metabolites. He then carried out post-doctoral research with Mike Davies-Coleman (Rhodes University, South Africa) and Raymond Andersen (University of British Columbia, Canada) before a short role as a flavour and aroma chemist at CSIRO in Adelaide, Australia. He was appointed to the faculty at his alma mater in 2009 where he is currently a Senior Lecturer.



Murray Munro, Emeritus Professor in Chemistry at the University of Canterbury, has worked on natural products right through his career. This started with diterpenoids (PhD; Peter Grant, University of Otago), followed by alkaloids during a postdoctoral spell with Alan Battersby at Liverpool. A sabbatical with Ken Rinehart at the University of Illinois in 1973 led to an interest in marine natural products with a particular focus on bioactive compounds which has continued to this day. In recent years his research interests have widened to include terrestrial/marine fungi and actinomycetes.

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.

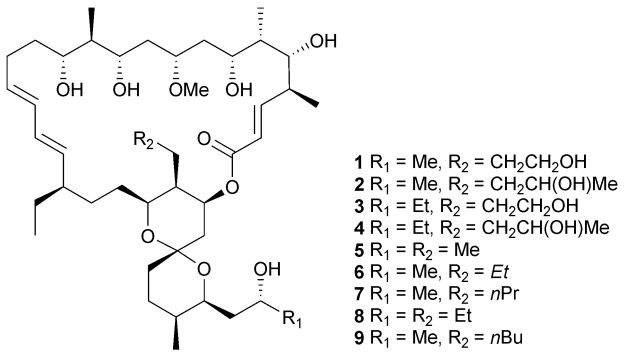
discovery,[64] mass spectometry-based metabolomics,[65] techniques for bioactives discovery from marine fungi[66] and a commentary on past and future aspects of MNP drug discovery.[67]

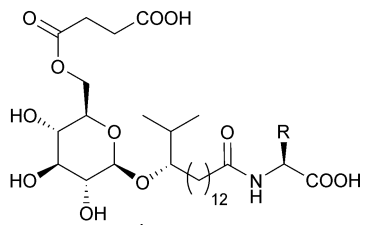
3 Marine microorganisms and phytoplankton

As a rich source of novel and bioactive marine microorganisms continue to be a major focus of many natural products research efforts, with a 10% increase in the number of compounds reported from the previous year following a 30% increase from 2010 to 2011. Unless otherwise stated, compounds described in this section were obtained from cultures of the named microorganisms.

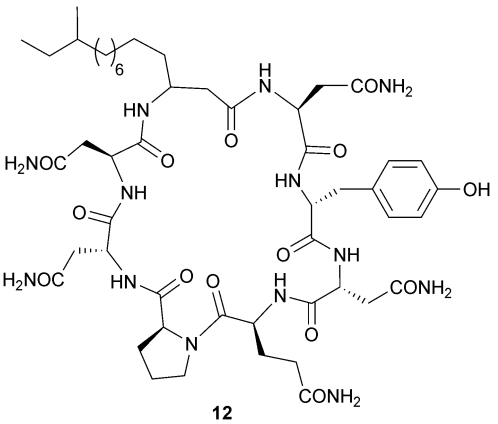
3.1 Marine-sourced bacteria (excluding from mangroves)

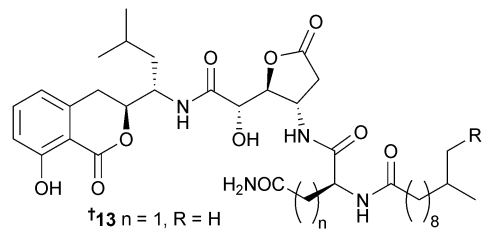
Actinoalloteichus sp. (sediment, Usa Bay, Kochi Prefecture, Japan) was the source of neomaclafungins A–I **1–9**, 26-membered macrolides of the oligomycin subfamily, which all displayed significant activity against *Trichophyton mentagrophytes* (*T. mentagrophytes*).[68] Glycolipopeptides eodoglucomide A **10** and B **11** were obtained from *Bacillus licheniformis* (sediment, Ieodo Reef, S. Korea) and are broad spectrum, moderately active antimicrobial agents, with ieodoglucomide B also cytotoxic to lung and stomach cancer cells.[69]

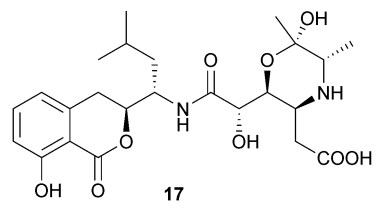




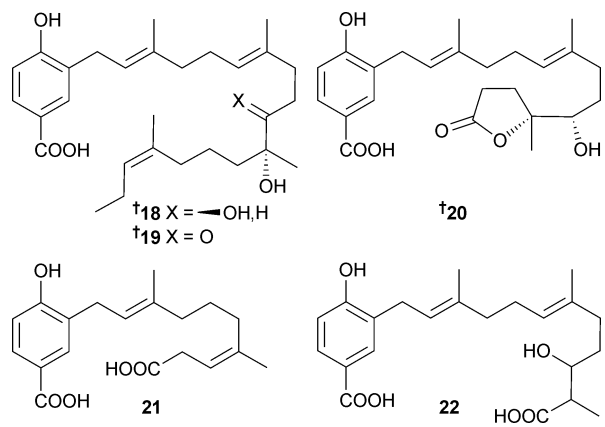
Bacillus mojavensis (pearl oyster *Pinctada martensii*, Weizhou Is., South China Sea) provided the antifungal iturinic lipopeptide mojavensin A **12**,[70] while the amicoumacin analogues lipoamicoumacin A–D **13–16** and a bacilosarcin analogue, bacisarcin C **17**, were isolated from *Bacillus subtilis* (*B. subtilis*) (sediment, Red Sea) together with several known amicoumacins. Bacilosarcin B[71] and amicoumacin A[72] were cytotoxic to HeLa cells and are strongly antibacterial.[73]



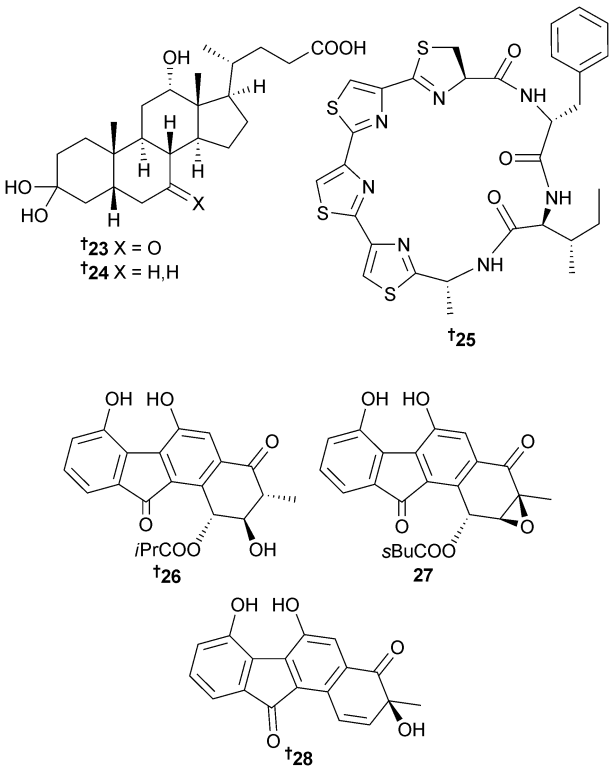




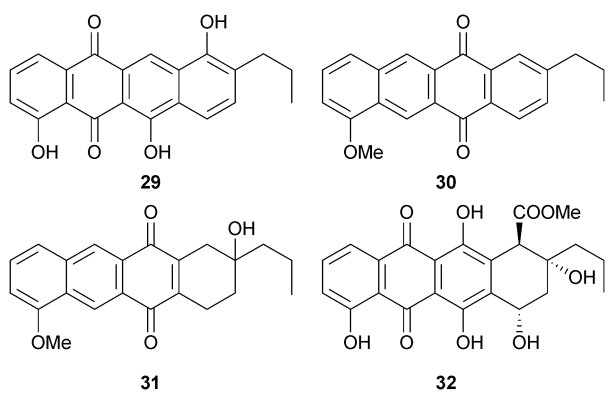
The known synthetic toluhydroquinone derivatives, 5-bromotoluhydroquinone[74] and 4-*O*-methyltoluhydroquinone[75] were obtained for the first time from a natural source from *Dothideomycete* sp. (red alga *Chondria crassicualis*, Yokiji Is., S. Korea). Both compounds were moderate 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavengers.[76] Of the erythrolic acids A–E **18–22**, meroterpenoids with a modified terpene sidechain isolated from *Erythrobacter* sp. (sediment, Trinity Bay, Galveston, Texas), only erythrolic acid D exhibited modest activity towards non-small cell lung cancer cells.[77]



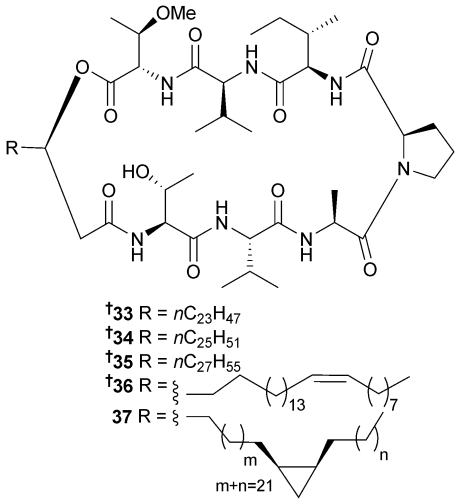
The cholic acid derivatives **23** and **24** were obtained from endophytic *Hasllibacter halocynthiae* (ascidian *Halocynthia roretzi*, Kyung-Po Beach, S. Korea)[78] and *Marinactinospora thermotolerans* (deep sea sediment, South China Sea) was the source of the sequential tristhiazole-thiazoline-containing cyclic peptide marthiapeptide A **25**, active against a panel of Gram-positive bacteria and strongly cytotoxic towards a panel of human tumour cell lines (HTCLs),[79] while from *M. rosaria* (sediment, South China Sea) three additional fluostatins I–K **26–28** were isolated.



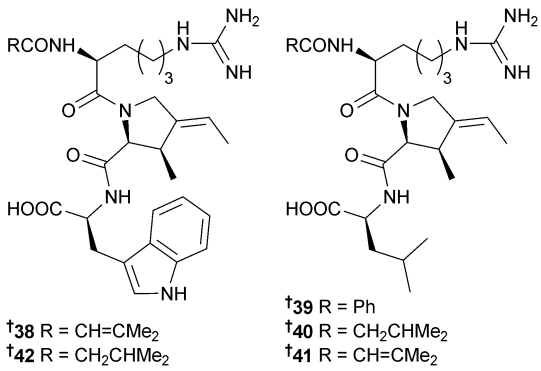
The antibiotic A201A, previously isolated from terrestrial *Streptomyces capreolus*,[80] was obtained from the marine environment for the first time from *M. thermotolerans* (deep sea sediment, South China Sea), and the gene cluster responsible for biosynthesis identified.[81] The known metabolites of terrestrial *Streptomyces* species, fluostatins C–F,[82,83] and phenanthroviridone,[84] were also obtained (first time from the marine environment).[85] The anthracyclinones **29–32** were obtained from a *Micromonospora* sp. (tunicate *Eudistoma vannamei*, Taíba Beach, Ceará, Brazil) – **29** and **32** were moderately cytotoxic to HCT-8 cells.[86]



Peptidolipins B–F **33–37** are lipopeptides obtained from *Nocardia* sp. (ascidian *Trididemnum orbiculatum*, Florida Keys), but the location of the cyclopropyl group in the sidechain of peptidolipin F was not determined. Peptidolipins B and E exhibited moderate activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA).[87]

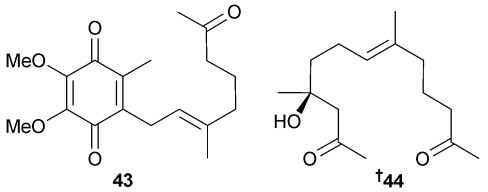


Upon assignment of the structure of the new lucentamycin analogue lucentamycin E **38** (*Nocardiopsis lucentensis*, sediment, Little San Salvador, Bahamas), the olefin geometries of the 3-methyl-4-ethylideneproline residues of lucentamycins A–D **39–42**, other tripeptides isolated from the same organism,[88] were reinvestigated and revised to (2*S*,3*R*,*E*)-3-methyl-4-ethylideneproline.[89] Total synthesis of lucentamycin A was accomplished *via* a novel strategy from Garner's aldehyde and corroborated the revised configurations.[90] Synthesis of the (*E*)-isomer of the proposed structure of lucentamycin A, *via* a stereoselective rhodium-catalysed reductive cyclisation process, and comparison of NMR data of synthetic with natural lucentamycin A indicated the need for the configurational revision.[91] *Phaeobacter* sp. (pulp mill effluent, coastal Southern USA) produces the known bacterial blue pigment indigoidine[92] which inhibited growth of *Vibrio fischeri* and was isolated from the "marine" environment for the first time.[93]



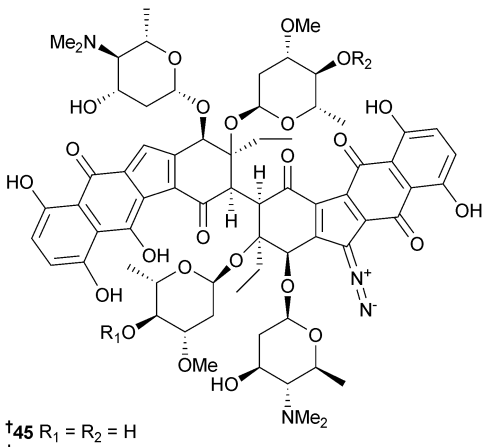
Pseudoalteromones A **43** and B **44** were obtained from *Pseudoalteromonas* sp. (cultured-type octocoral *Lobophytum crassum*,

Taiwan).[94,95] The ubiquinone derivative pseudoalteromone A possessed a 9C nor-monoterpenoid moiety, was cytotoxic to MOLT-4 (human acute lymphoblastic leukaemia) cells and inhibited release of elastase by human neutrophils.

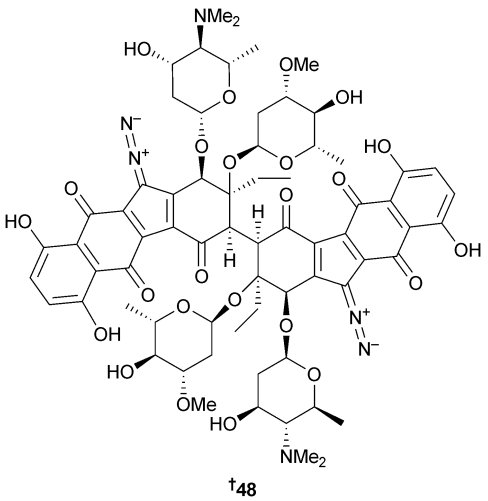


43 **†44**

2-Methyl-3-butyl-prodiginine has previously been identified as a metabolite of the marine bacteria *Hahella chejuensis*[96] and *Pseudoalteromonas rubra*[97] (by mass spectrometry) and now has been fully characterised as a metabolite of *Pseudoalteromonas* sp. (seawater, Cape Muroto, Japan).[98] Investigation of *Salinispora pacifica* (USDA Agricultural Research Service) resulted in the isolation of the complex metabolites (−)-lomaiviticin C–E **45–47** as growth inhibitors of several cancer cell lines. Lomaiviticin C was directly converted to the known (−)-lomaiviticin A,[99] allowing the absolute configuration of (−)-lomaiviticin A to be established as **48**.[100]

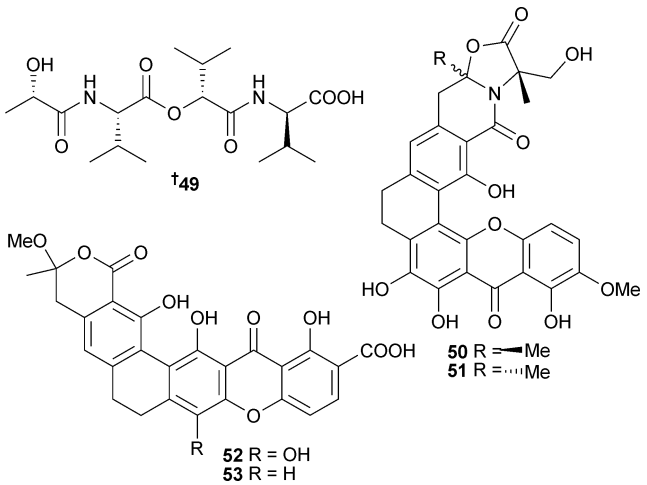


†45 $R_1 = R_2 = H$
†46 $R_1 = Me$, $R_2 = H$ and $R_1 = H$, $R_2 = Me$
†47 $R_1 = R_2 = Me$



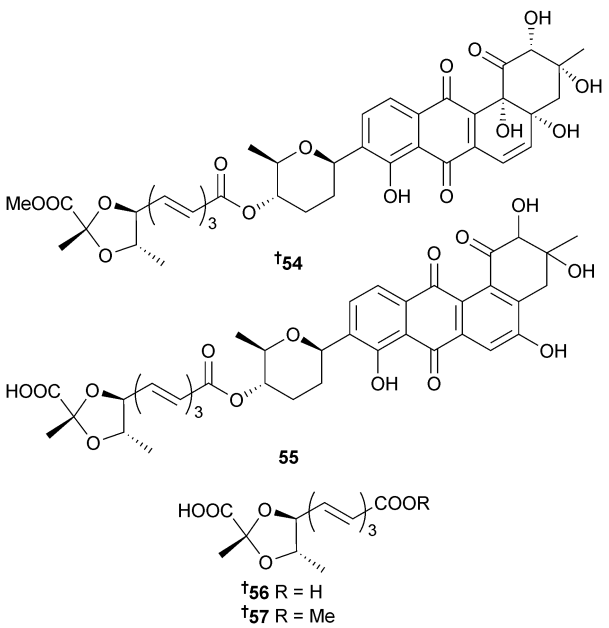
†48

The peptide **49** was obtained from *Streptomyces bacillaris* (sediment, Galveston Bay, Texas).[101] The polycyclic citreamicins A **50** and B **51**, citreaglycon A **52** and dehydrocitreaglycon A **53** were isolated from *S. caelestis* (seawater, Red Sea, Jeddah, Saudi Arabia). All displayed broad spectrum antibacterial activity. Citreamicins A and B and citreaglycon A also inhibited MRSA while citreamicins A and B were also significantly cytotoxic to HeLa cells.[102]



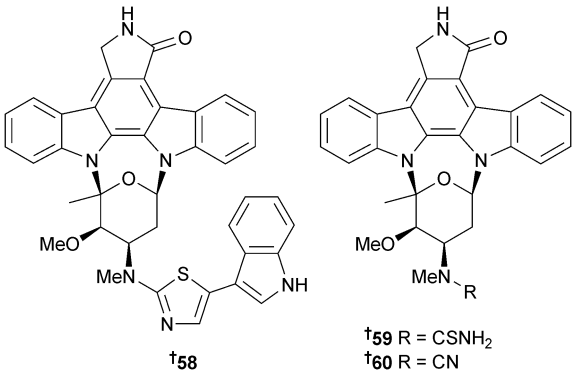
†49
50 R = Me
51 R = Me
52 R = OH
53 R = H

S. fradiae (sediment, source unspecified) yielded several capoamycin-type antibiotics, fradimycin A **54** and B **55** and fradic acid A **56** and B **57**, of which fradimycins A and B inhibited *Staphylococcus aureus* (*S. aureus*) growth and both, as well as the known anthraquinone MK844-mF10,[103] significantly inhibited growth of several cancer cell lines.[104]



†54
55
†56 R = H
†57 R = Me

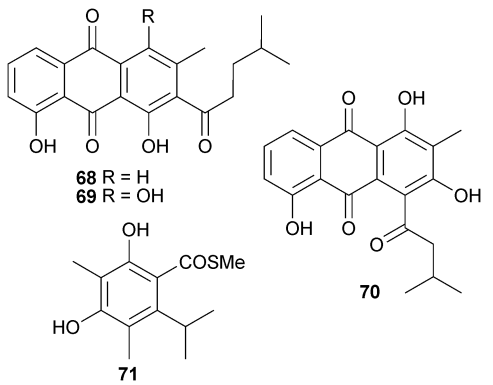
Fradcarbazoles A–C **58–60**, indolocarbazoles isolated from *Streptomyces fradiae* (sediment, Jiaozhou Bay, Shandong, China), possessed significant cytotoxicity against several HTCLs, in addition to inhibition of the kinase PKC-α.[105]



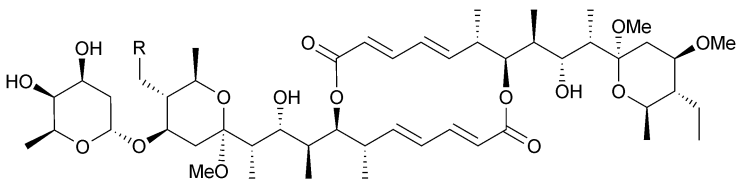
†58 †59 R = $CSNH_2$ †60 R = CN

Culture of *S. hygroscopicus* (fish *Halichoeres bleekeri*[106]) led to the isolation of macrolides halichoblelide B **61** and C **62**,[107] both significantly cytotoxic to a panel of HTCLs.[108] The *C*-glycoside angucyclines grincamycin B–F **63–67** were obtained from *Streptomyces lusitanus* (deep sea sediment, South China Sea). Of these, grincamycins B–E were moderately cytotoxic to several HTCLs and to B16 cells.[109]

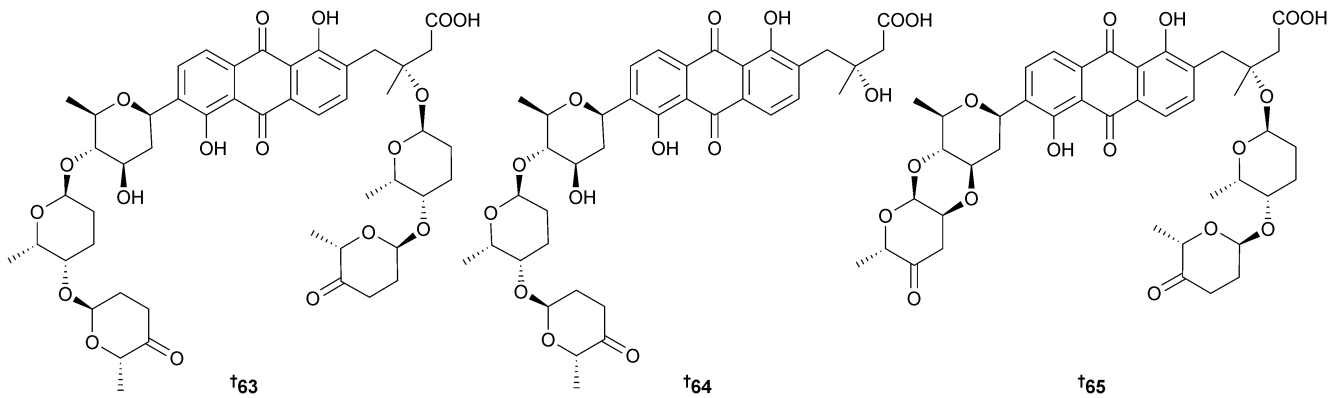
S. spinoverrucosus (sediment, Trinity Bay, Galveston, Texas) produced the anthraquinones galvaquinone A–C **68–70**. Galvaquinone B possessed epigenetic modulatory activity and moderate cytotoxicity against non-small-cell lung cancer (NSCLC) cells Calu-3 and H2887.[110] *S*-Methyl-2,4-dihydroxy-6-isopropyl-3,5-dimethylbenzothioate **71** was isolated from *Streptomyces* sp. (unidentified tunicate, Lyttelton Harbour, New Zealand) through use of an HPLC bioactivity profiling/microtitre plate technique in conjunction with microprobe NMR spectroscopy and was cytotoxic to P388 cells.[111]



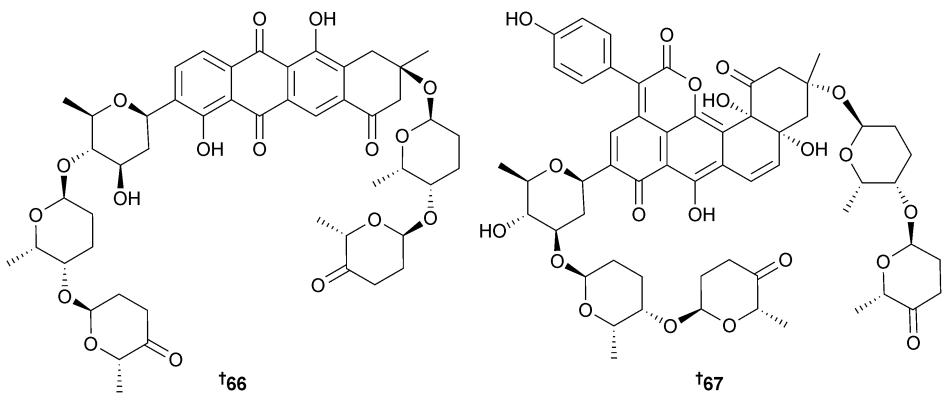
68 R = H
69 R = OH
70
71



†61 R = Me
†62 R = H

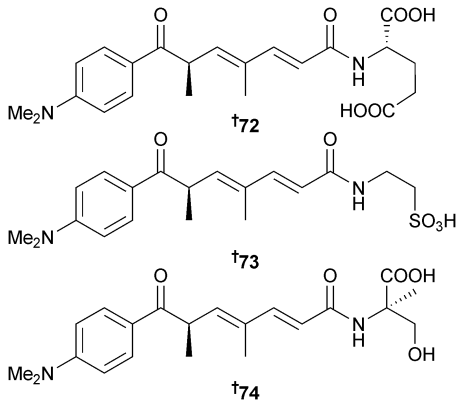


†63 †64 †65

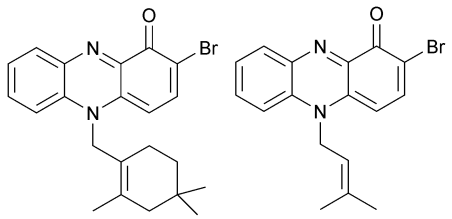


†66 †67

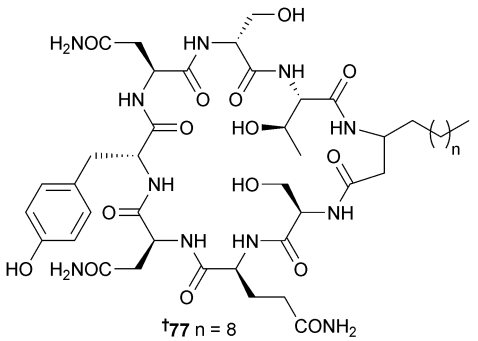
JBIR-109–111 **72–74** are trichostatin analogues isolated from a *Streptomyces* strain (unidentified sponge, Takara Is., Kagoshima, Japan).[112]

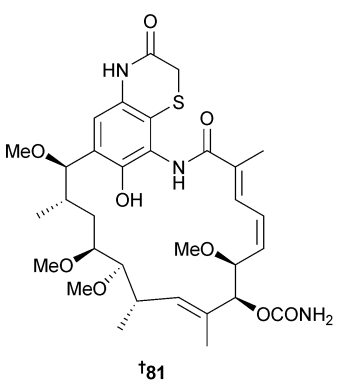


The phenazine derivatives **75** and **76** and lavanducyanin[113] were isolated from a marine-derived *Streptomyces* sp. (source unspecified). All three compounds inhibited TNF-α-induced NFκB activity and LPS-induced nitric oxide (NO) production.[114]

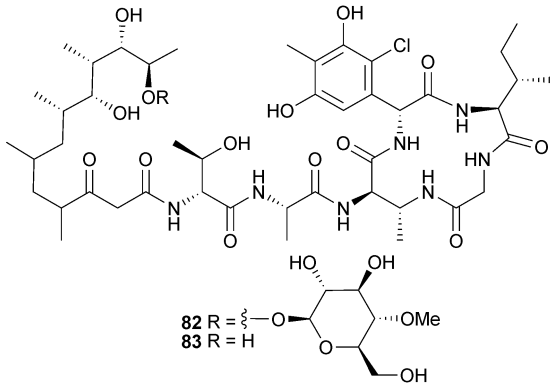


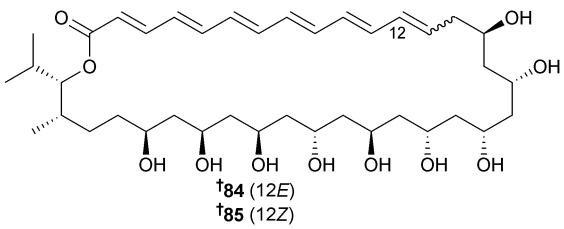
A *Streptomyces* strain (sponge *Dysidea tupha*, Rovinj, Croatia) produced the lipopeptides cyclodysidin A–D **77–80**[115] while another *Streptomyces* sp. (sediment, Heron Is., Queensland, Australia) yielded heronamycin A **81**, a benzothiazine ansamycin.[116]



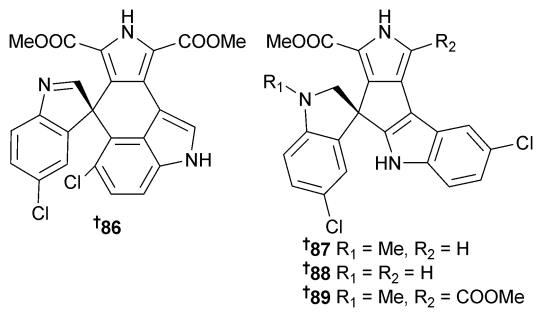


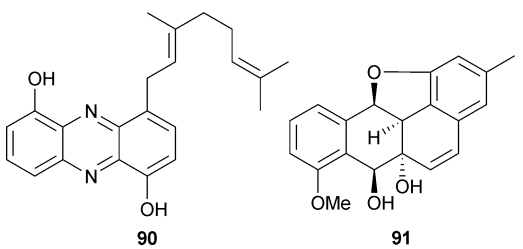
Noteworthy in the totopotensamide A **82** and the aglycone totopotensamide B **83** structures [*Streptomyces* sp. (gastropod mollusk *Lienardia totopotens*, Mactan Is., Cebu, Philippines)] are the previously undescribed 2,3-diaminobutyric acid-containing macrolactam and 4-chloro-5,7-dihydroxy-6-methylphenylglycine components.[117] Bahamaolide A **84**, a strong inhibitor of *Candida albicans* isocitrate lyase, and bahamaolide B **85** are macrocyclic lactones from a *Streptomyces* sp. (sediment, North Cat Cay, Bahamas).[118]



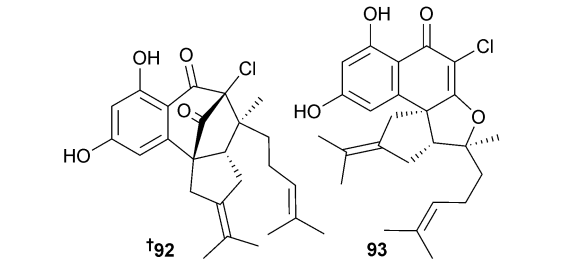


Spiroindimicins A–D **86–89** are *spiro*-bisindole alkaloids from a *Streptomyces* sp. (sediment, Bay of Bengal) obtained *via* a PCR-based screening approach. Spiroindimicins B–D displayed moderate cytotoxicity to a number of cancer cell lines.[119] The phenazine geranylphenazinediol **90** isolated from a *Streptomyces* sp. (sediment, Kiel Fjord, Baltic Sea) was an inhibitor of acetylcholinesterase,[120] while an angucyclinone derivative kiamycin **91** originating from a *Streptomyces* sp. (sediment, Qingdao, China) was an inhibitor of several HTCLs.[121]

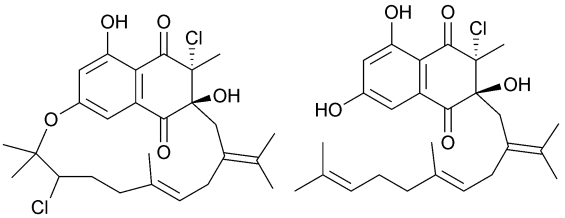




A *Streptomyces* sp. (sediment, Oceanside, California) was the source of the mixed polyketide-terpenoids merochlorin A–D **92–95**. Merochlorins A[122] and B[123] were both potent inhibitors of MRSA. *In vivo* studies determined the genetic basis for biosynthesis of the merochlorins and implicated the involvement of rare bacterial vanadium-dependent haloperoxidase genes.[122,123]

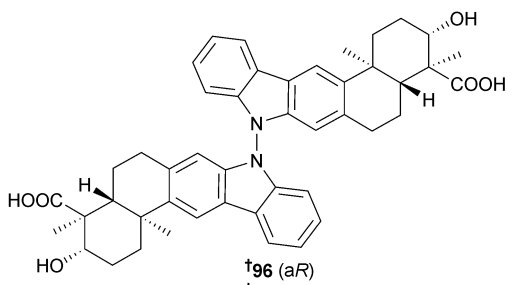


†92 93

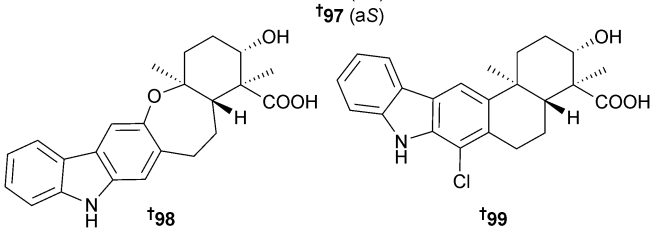


94 95

The antibacterial indolosesquiterpenes dixiamycin A **96** and B **97**, oxiamycin **98** and chloroxiamycin **99** were isolated from a *Streptomyces* sp. (sediment, South China Sea) along with the previously isolated xiamycin A.[124] Dixiamycins A and B are the first examples of naturally occurring *N*–*N*-coupled *atropo*-diastereomers.[125] The putative biosynthetic gene cluster for xiamycin A and oxiamycin was identified by a partial genome sequencing approach. Eighteen genes were proposed to be involved in the biosynthesis and indosespene was identified as a common precursor for the biosynthesis, which included an unusual oxidative cyclisation strategy.[126]

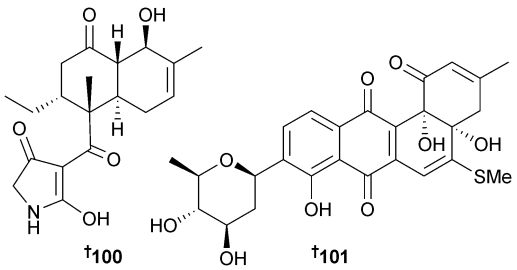


†96 (a*R*)
†97 (a*S*)



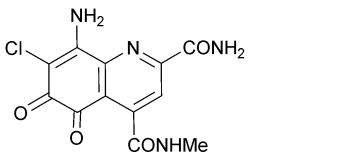
†98 †99

A histone deacetylase (HDAC)-based yeast assay employing a URA3 reporter gene was utilised in the isolation of streptosetin A **100** from a *Streptomyces* sp. (sediment, San Francisco Bay).[127] The *C*-glycosylated benz[α]anthraquinone derivatives, urdamycinone E,[128] urdamycinone G **101** and dehydroxyaquayamycin[129] were obtained from a *Streptomyces* sp. (sponge *Xestospongia* sp., Sichang Is., Chonburi, Thailand) and along with urdamycin E[128] were potent inhibitors of the *P. falciparum* K1 strain and inhibitors of *Mycobacterium tuberculosis*.[130] Urdamycinone E[128] and dehydroxyaquayamycin[129] were obtained for the first time as natural products.[130]

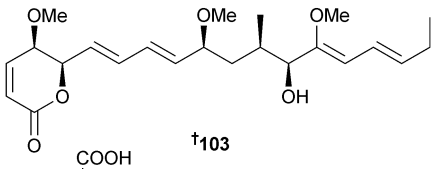


†100 †101

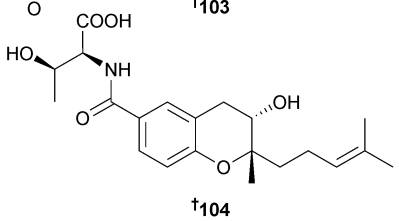
Streptomyces variabilis (sediment, Sweetings Cay, Bahamas) was the source of ammosamide D **102** (modest cytotoxicity to the MIA PaCa-2 pancreatic cancer cell line).[131] The cytotoxic linear polyketide pterocidin was originally obtained from endophytic *S. hygroscopicus* associated with the bracken *Pteridium aquilinum* but due to a lack of material the absolute configuration could not be determined.[132] The same authors have now isolated pterocidin from a marine *Streptomyces* strain (sediment, Otsuchi Bay, Japan) in sufficient quantities to determine the absolute configuration as **103**.[133] The absolute configuration of a threonine derivative obtained from *Streptomyces xiamenensis* (mangrove sediment, Fujian, China) as an inhibitor of the proliferation of WI26 (human lung fibroblast) cells was determined as **104**.[134] This threonine derivative had previously been reported in a Japanese patent as an inhibitor of asthma and rheumatoid arthritis.[135]



102

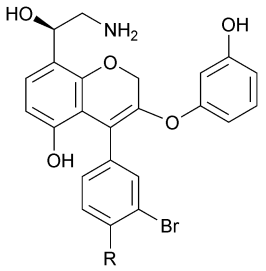


†103



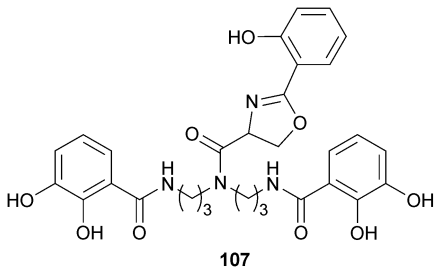
†104

The hydroxyethylamine chromene derivatives ammonificin C **105** and D **106** were obtained from *Thermovibrio ammonificans* (hydrothermal vent, East Pacific Rise) and induced apoptosis in a cell-based screen.[136]



†**105** R = OH
†**106** R = Br

Vibrio nigripulchritudo (global marine Galathea 3 expedition)[137] produced the siderophore nigribactin **107**, a modulator of *S. aureus* virulence gene expression,[138] while another *Vibrio* species (Gulf of Mexico) was the source of the amphiphilic siderophores ochrobactin-OH A–C, but only ochrobactin-OH B **108** was fully characterised.[139] A third *Vibrio* sp. (source unspecified, Okinawa, Japan) provided the cyclic acyldepsipeptide kailuin F **109**, as well as the known analogues kailuins B[140] and E[141] of which kailuin B displayed strong activity against the dinoflagellate *Prorocentrum micans*.[142]



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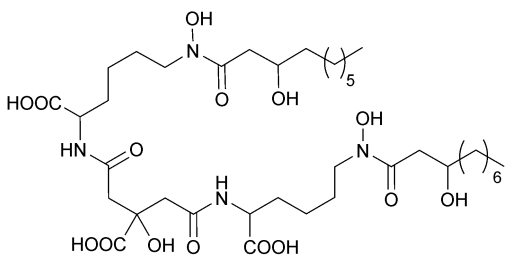
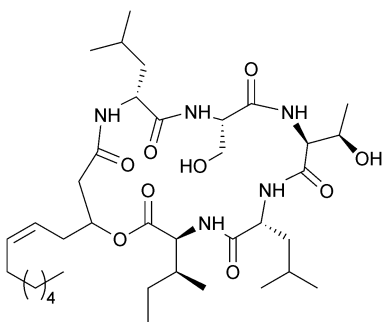


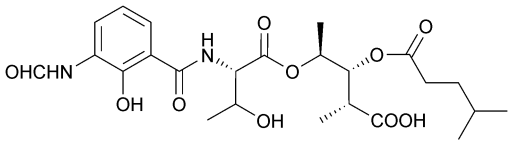
108



109

3.2 Bacteria from mangroves

Of the two antimycins, B1 **110** and B2 **111** from *Streptomyces lusitanus* (mangrove sediment, *Avicennia mariana*, Fujian, China), only antimycin B2 had moderate activity against *S. aureus* and *Laribacter hongkongensis*.[143] The indolocarbazoles streptocarbazole A **112** and B **113** were obtained from *Streptomyces* sp. (mangrove soil, species unspecified, Sanya, Hainan, China), but only streptocarbazole A was cytotoxic to HTCLs and arrested the cell cycle of HeLa cells at the G2/M phase.[144]



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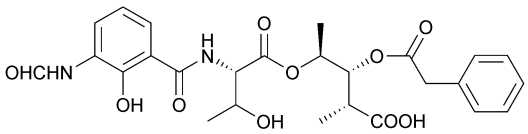
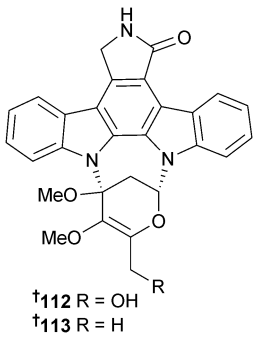
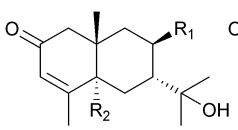


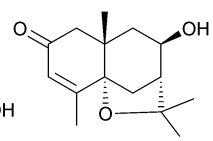
111



†**112** R = OH
†**113** R = H

The eudesmene-type sesquiterpenes kandenol A–E **114–118** were isolated from an endophytic *Streptomyces* sp. (mangrove stem *Kandelia candel*, Xiamen, Fujian, China) as weak to moderate inhibitors of *B. subtilis* and *Mycobacterium vaccae* growth.[145]





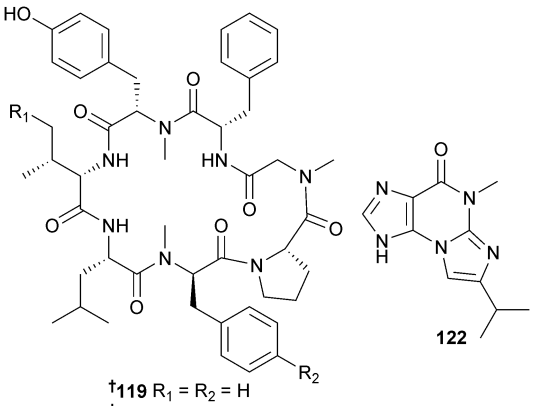
†**114** R_1 = OH, R_2 = H
†**115** R_1 = R_2 = OH
†**116** R_1 = OH, R_2 = OOH
†**117** R_1 = H, R_2 = OOH

†**118**

3.3 Marine-sourced fungi (excluding from mangroves)

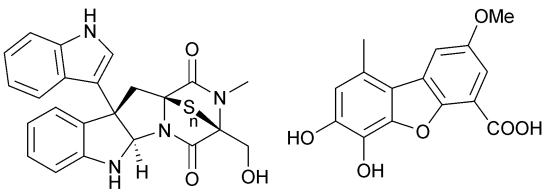
Cordyheptapeptides C–E **119–121** were isolated from *Acremonium persicinum* (sediment, South China Sea) with cytotoxicity against HTCLs noted for cordyheptapeptides C and E.[146] Acremolin was isolated from *Acremonium strictum* (unidentified Choristida sponge, S. Korea) with the original structure incorporating a 1*H*-aziridine moiety.[147] It was subsequently shown

that the reported NMR spectroscopic data were incompatible with the proposed antiaromatic heterocycle, which would have been an extremely unstable compound. A plausible alternative structure, an isomeric substituted N^2,3-ethenoguanine **122** has been suggested, which is consistent with all spectroscopic data.[148]



†**119** $R_1 = R_2 = H$
†**120** $R_1 = H$, $R_2 = OH$
†**121** $R_1 = Me$, $R_2 = OH$

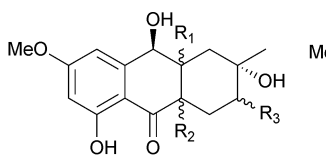
Indole diketopiperazines luteoalbusin A **123** and B **124**, isolated from *Acrostalagmus luteoalbus* (deep sea sediment, South China Sea), were potent cytotoxins against several HTCLs.[149] Porric acid D **125**, a dibenzofuran derivative from *Alternaria* sp. (Bohai Sea, Tianjin, China), was weakly inhibitory to *S. aureus*.[150]



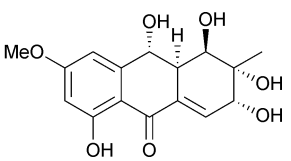
†**123** n =2
†**124** n =3

125

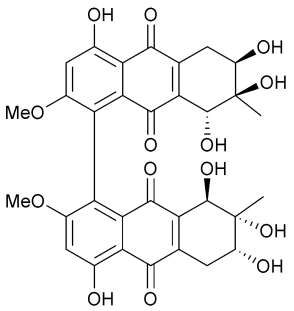
The hydroanthraquinone-derived tetrahydroaltersolanols C–F **126–129** and dihydroaltersolanol A **130**, in addition to the alterporriol-type anthranoid dimers alterporriols N–R **131–135**, were obtained from *Alternaria* sp. (soft coral *Sarcophyton* sp., Weizhou coral reef, South China Sea). Tetrahydroaltersolanol C and alterporriol Q were active against the porcine reproductive and respiratory syndrome virus while alterporriol P was cytotoxic to HTCLs.[151]



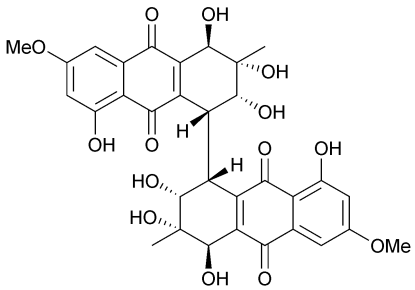
126 R_1 = ····H, R_2 = ▬H, R_3 = ····OH
127 R_1 = ▬H, R_2 = ····H, R_3 = ····OH
128 R_1 = ····H, R_2 = ▬H, R_3 = ▬OH
†**129** R_1 = ····H, R_2 = ▬H, R_3 = ····OAc



130



131



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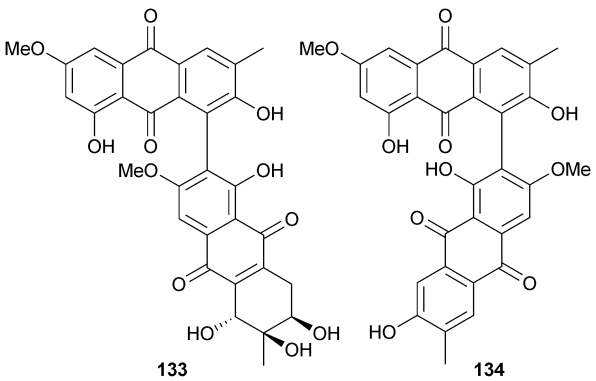
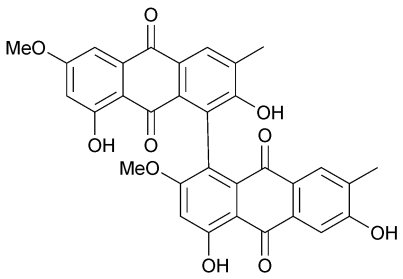
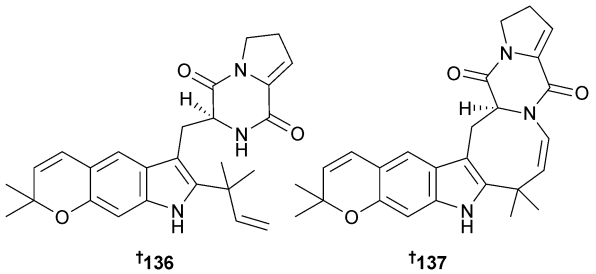


133 **134**

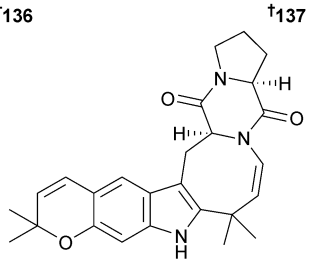


135

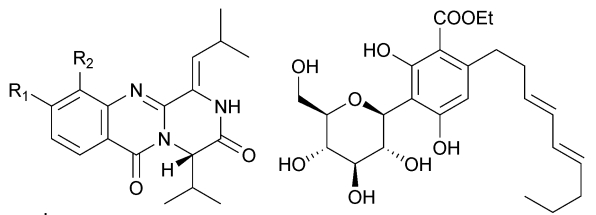
Aspergillus carneus (brown alga *Laminaria sachalinensis*, Kunachir Is., Russia) was the source of the prenylated indole alkaloids carneamide A–C **136–138**, the quinazolinone derivatives carnequinazoline B **139** and C **140**, the aryl *C*-glycoside carnemycin A **141** and a drimane sesquiterpenoid **142.** New to the marine area was a synthetic compound[152] (isolated as carnequinazoline A) and a known derivative of stromemycin[153,154] (isolated as carnemycin B).[155]



†136 †137

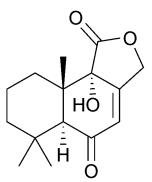


†138



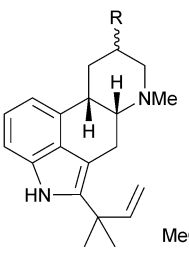
†139 R_1 = H, R_2 = OH
†140 R_1 = R_2 = OH

141

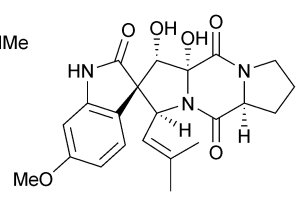


†142

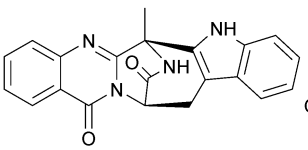
Two costaclavine alkaloids **143** and **144** were obtained from *Aspergillus fumigatus* (zoanthid *Zoanthus* sp., Amami Is., Kagoshima, Japan),[156] while *A. fumigatus* (soft coral *Sinularia* sp., Kunashir Is., Kuril Islands) produced the spirocyclic diketopiperazine alkaloid spirotryprostatin F **145** which had stimulatory phytoregulatory activity.[157] The same fungal strain was the source of the alkaloid fumiquinazoline K **146** and a nordammarane triterpenoid **147**.[158]



†143 R = Me
†144 R = Me



†145



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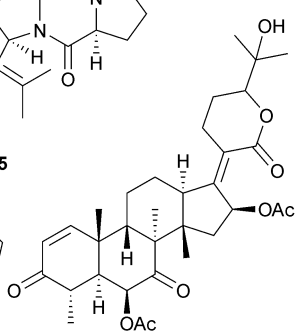
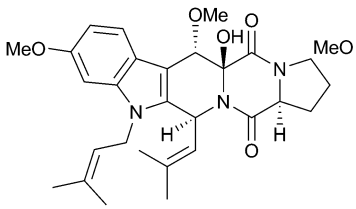
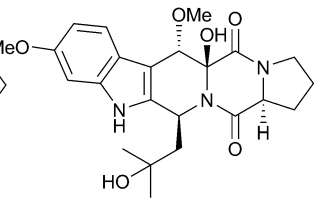


147

From *A. fumigatus* (intertidal mud, Yingkou, China) several diketopiperazines were isolated: prenylcyclotryprostatin B **148**, 20-hydroxycyclotryprostatin B **149**, 9-hydroxyfumitremorgin C **150**, 6-hydroxytryprostatin B **151** and spirogliotoxin **152**. Prenylcyclotryprostatin B and 9-hydroxyfumitremorgin C were moderate inhibitors of human leukaemic monocyte lymphoma (U937) cells.[159] 20-Hydroxycyclotryprostatin B was also reported from two other sources in 2012, firstly from *Aspergillus sydowii* (gorgonian coral *Verrucella umbraculum*, Sanya, Hainan province, China) as cyclotryprostatin E[160] and secondly, from a terrestrial *A. fumigatus* as 12β-hydroxy-13α-methoxyverruculogen TR-2.[161] The indole alkaloid **153** is also noted as a natural product in the first report but no other references to it are given or can be found in extensive literature searches.[160]



†148



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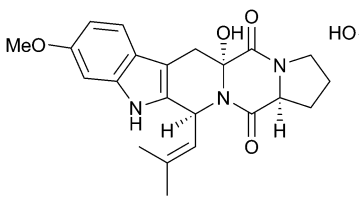

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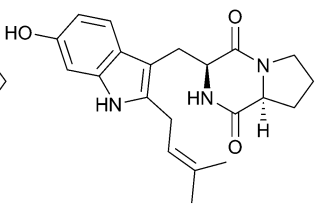

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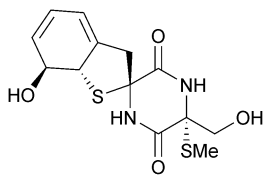
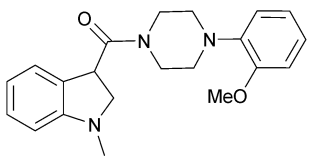
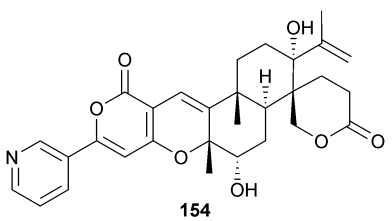


152

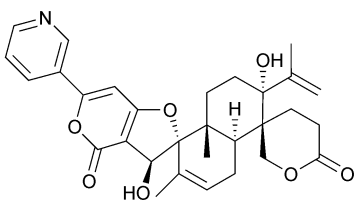


153

The sesquiterpene pileotin A **154** was isolated from *A. fumigatus* (sea urchin *Toxopneustes pileolus*, source unspecified) along with oxalicine B **155**, previously reported as a metabolite of *Penicillium oxalicum* in a PhD thesis[162] but now reported in the literature. Oxalicine B displayed moderate cytotoxicity to P388 cells.[163]

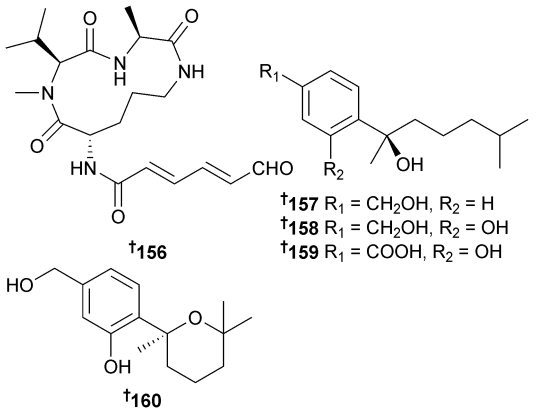


154

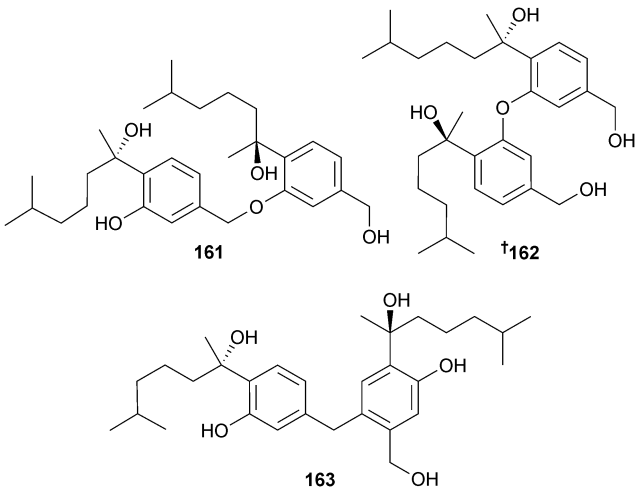


155

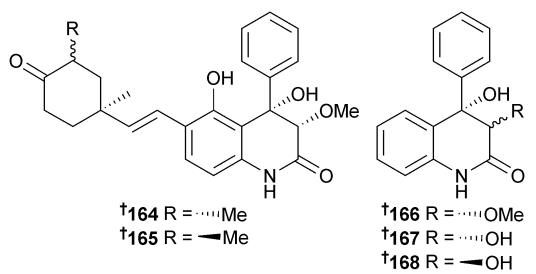
Aspergillus insulicola (sediment, Hawaii) produced the tripeptide pre-sclerotiotide F **156**[164] and *Aspergillus* sp. (sponge *Xestospongia testudinaria*, Weizhou coral reef, South China Sea) the four bisabolane-type sesquiterpenoids, aspergiterpenoid A **157**, (−)-sydonol **158**, (−)-sydonic acid **159** and **160**.[165] Also isolated for the first time from a marine environment was the related (*Z*)-5-(hydroxymethyl)-2-(6′-methylhept-2′-en-2′-yl) phenol, a known metabolite of a fungal endophyte.[166,167]



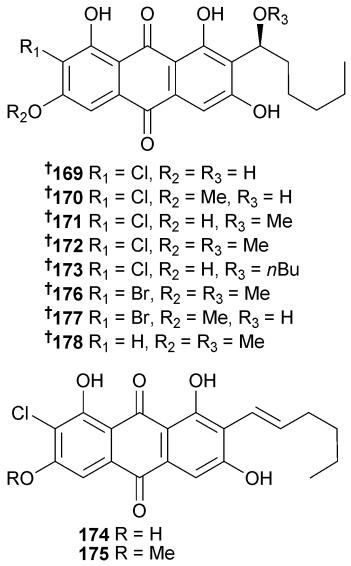
An endophytic *Aspergillus* sp. (sponge *Xestospongia testudinaria*, Weizho Is., South China Sea) produced the phenolic bisabolane sesquiterpenoid dimers disydonol A–C **161–163**. Only disydonols A and C were cytotoxic to HTCLs.[168]



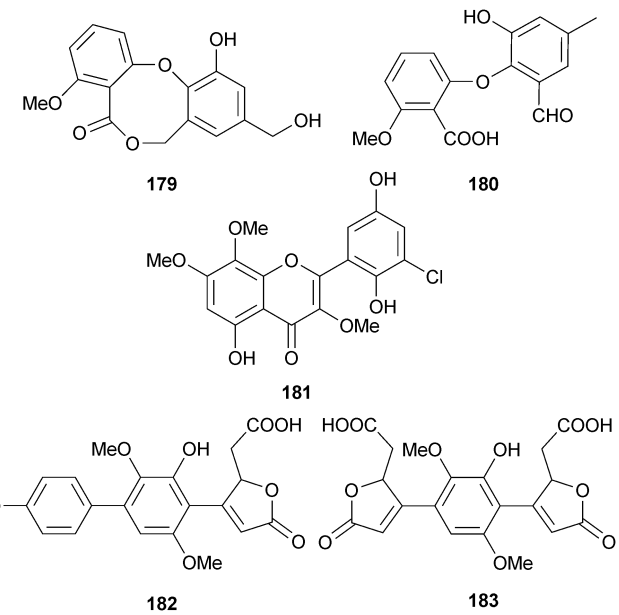
Aflaquinolones C–G **164–168** were obtained from an *Aspergillus* sp. (Dadaepo Beach, Busan, S. Korea); the same report also detailed the isolation of the related aflaquinolones A and B from a terrestrial *Aspergillus* sp.[169]



Investigation of *Aspergillus* sp. (sediment, South China Sea) resulted in the isolation of seven chlorinated anthraquinones **169–175**. On addition of sodium bromide to the fermentation media, three additional metabolites were obtained: two brominated anthraquinones **176** and **177** and a nonhalogenated anthraquinone **178**. 6-*O*-Methyl-7-chloroaveratin **170** inhibited growth of several HTCLs.[170]

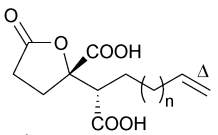


Aspergillus sp. (soil, Xiamen Beach, China) yielded barceloneic lactone B **179**, barceloneic acid C **180** and 5′-hydroxychlorflavonin **181**,[171] in addition to two *p*-terphenyl derivatives, terphyl acid **182** and terphyl diacid **183**.[172]

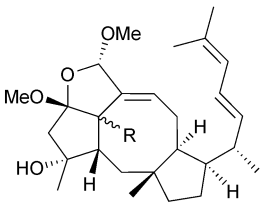


Three γ-butenolide derivatives spiculisporic acid B–D **184–186** were isolated from an endophytic *Aspergillus* sp. (sea urchin *Anthocidaris crassispina*, Qionghai, Hainan, China),[173] while the sesterterpenes ophiobolin O **187** and 6-*epi*-ophiobolin O **188**

were obtained from endophytic *Aspergillus* sp. (zoanthid *Zoanthus* sp., Ayamaru Cape, Amami Is., Japan) as moderate cytotoxins to P388 cells,[174] with ophiobolin O also inducing apoptosis and cell cycle arrest of MCF-7 cells through activation of MAPK signaling pathways.[175]

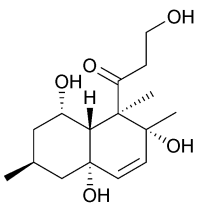


†**184** n = 7
†**185** n = 7, Δ saturated
†**186** n = 8, Δ saturated

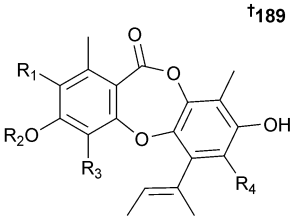


†**187** R = H
†**188** R = H

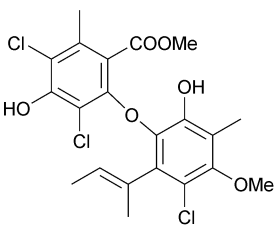
Decalin derivative decumbenone C **189** was isolated from *Aspergillus sulphureus* (sediment, location unspecified) as a potent cytotoxin against SK-MEL-5 human melanoma cells.[176] Coincidentally, decumbenone C was also isolated from the terrestrial basidiomycete *Craterellus odoratus* and named craterellone C.[177] *Aspergillus unguis* (unidentified sponge, Tub-La-Mu Bay, Pang-nga, Thailand) was the source of the depsidones aspergillusidone A–C **190–192**, a diaryl ether **193** and yielded the known synthetic intermediate 4-hydroxy-3-methyl-6-(1-methyl-1-propenyl)-2*H*-pyran-2-one[178] (first isolation from a natural source). The fungal metabolites, nidulin,[179] nornidulin[180] and 2-chlorounguinol[181] were also isolated, with nidulin and 2-chlorounguinol being first time MNP isolates. Aspergillusidones A–C, nidulin, nornidulin and 2-chlorounguinol all exhibited aromatase inhibition and aspergillusidones A and C showed radical scavenging activity in the xanthine/xanthine oxidase assay.[182]



†**189**

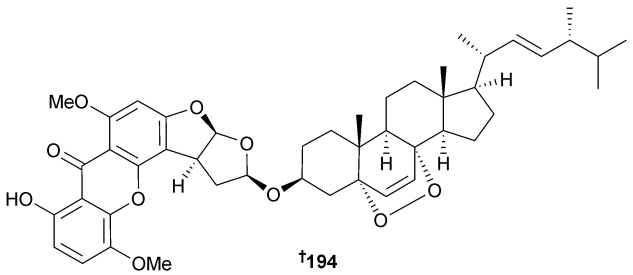


190 $R_1 = R_2 = R_3 = H$, $R_4 = COOH$
191 $R_1 = H$, $R_2 = Me$, $R_3 = R_4 = Cl$
192 $R_1 = R_4 = Cl$, $R_2 = R_3 = H$

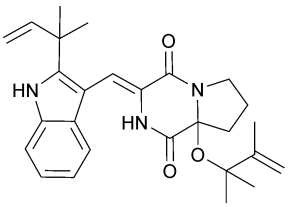


193

Asperversin A **194** and 9ξ-*O*-2(2,3-dimethylbut-3-enyl)brevianamide Q **195** were isolated from endophytic *Aspergillus versicolor* (brown alga *Sargassum thunbergii*, Pingtan Is., China), along with the known fungal metabolites brevianamide M,[183] 6,8-di-*O*-methylaverufin[184] and 6-*O*-methylaverufin.[185] Both brevianamide M[183] and 6-*O*-methylaverufin[185] were first time marine isolates.[186]

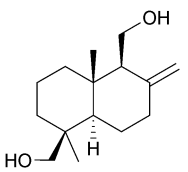


†**194**

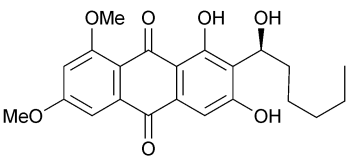


195

Endophytic *A. versicolor* (green alga *Codium fragile*, Dalian, China) produced the sesquiterpene albican-11,14-diol **196**, potently toxic to brine shrimp and a strong inhibitor of *E. coli* and *S. aureus.*[187] From another endophytic *A. versicolor* (brown alga *Sargassum thunbergii*, Qingdao, Shandong, China) the anthraquinone compound 6,8-di-*O*-methylaverantin **197** was obtained[188] together with the known anthraquinones 6,8-di-*O*-methylversiconol[189] and 6,8-di-*O*-methylnidurufin.[190]

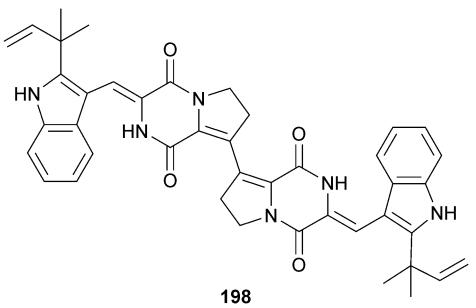


196

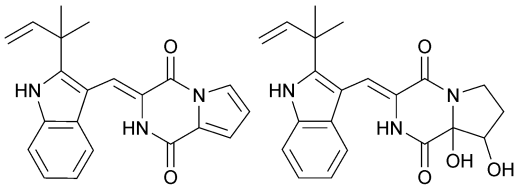


†**197**

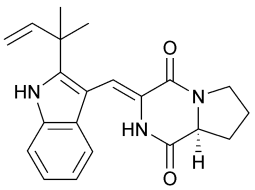
A. versicolor (sediment, Bohai Sea, China) was the source of the dimeric diketopiperazine brevianamide S **198** and the monomeric brevianamides T–V **199–201**. Brevianamide S showed selective activity against the Bacille Calmette-Guérin (BCG) strain of *Mycobacterium bovis* suggestive of a new mechanism of action with potential as an antitubercular drug lead.[191]



198

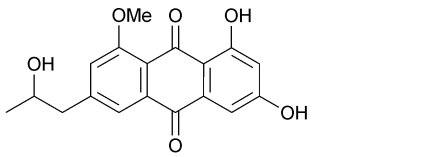


199 200



†201

The anthraquinone isorhodoptilometrin-1-methyl ether **202** was isolated from endophytic *A. versicolor* (green alga *Halimeda opuntia*, Rass Mohamed, south Sinai, Egypt) and displayed moderate activity against *B. subtilis*, *B. cereus* and *S. aureus*.[192] Examination of the endophytic *A. wentii* EN-48 (brown alga *Sargassum* sp., source unspecified) revealed three new tetranorlabdane diterpenoids asperolide A–C **203–205**[193] in addition to the terrestrial fungal metabolites, wentilactones A and B,[194] LL-Z1271-β,[195] and a known tetranorditerpenoid derivative.[196] All of these known metabolites were first time marine isolates.[193]



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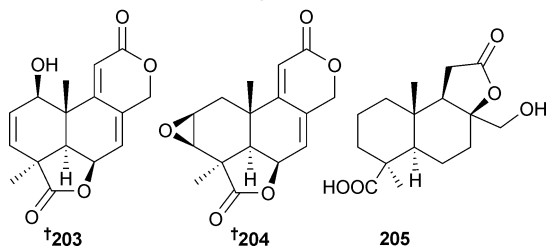
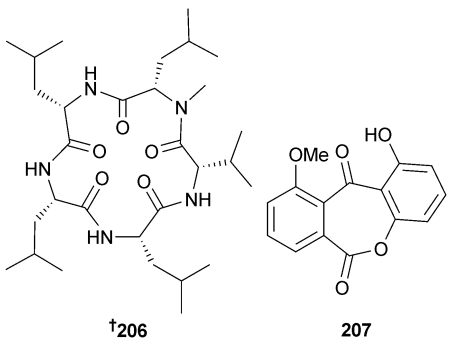


†203 †204 205

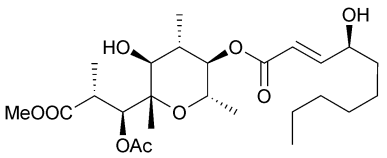
Application of OSMAC (one strain-many compounds) methodology to *Asteromyces cruciatus* (unidentified decaying green alga, La Jolla, USA) identified the pentapeptide lajollamide A **206** (absolute configuration determined by total synthesis).[197]



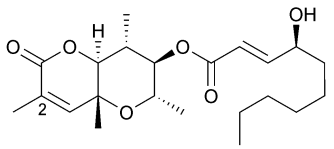
†206 207

Beauveria bassiana (unidentified sponge, Iriomote Is., Okinawa) produced 1-hydroxy-10-methoxy-dibenz[*b*,*e*]oxepin-6,11-dione **207**,[198] in addition to the known terrestrial metabolites chrysazin[199] and globosuxanthone A,[200] both first time marine isolates.

Botryotinia sp. (unidentified marine alga, Seongsan, Cheju, S. Korea) was the source of two botcinin derivatives **208** and **209**, which were assumed to be methanol reaction products rather than natural products.[201] The compound **209** was named botcinin G but this name had already been utilised for a metabolite of *Botrytis cinerea*[202] and again for a different metabolite of *B. cinerea*[203,204] which has a structure comparable to **209** but lacking the C-2–C-3 double bond. There is confusion in the chemical literature as one CAS Registry number appears to have been used for multiple structures.[201–204]

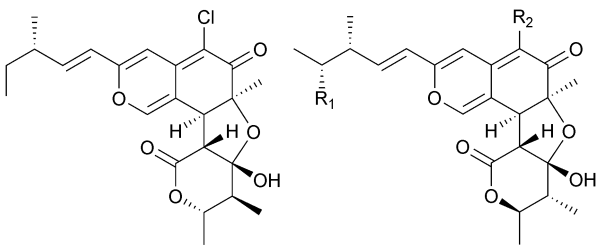


208



209

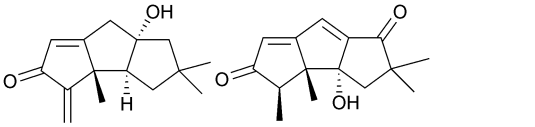
A strain of *Chaetomium globosum* (fish *Mugil cephalus*, Katsuura Bay, Japan), which has already yielded many chaetomugilin metabolites,[205–208] was the source of three further analogues: chaetomugilins S **210**, T **211** and U **212**. Chaetomugilin S was a moderate growth inhibitor of HTCLs and P388 cells.[209]



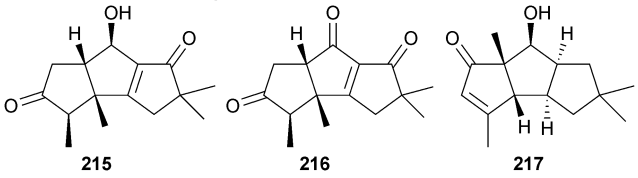
†210 †211 R_1 = OH, R_2 = H †212 R_1 = R_2 = H

Chondrostereum sp. (soft coral *Sarcophyton tortuosum*, Hainan, South China Sea) yielded triquinane-type sesquiterpenoids chondrosterin A–E **213–217**, of which chondrosterin A was cytotoxic to several cancer cell lines.[210,211] Endophytic *Coniothyrium cereale* (green alga *Enteromorpha* sp., Fehmarn, Baltic Sea) produced the isoindole pseudoalkaloid conioimide **218** and the polyketide cereoanhydride **219**. Conioimide exhibited selective inhibition of human leukocyte elastase. Biosynthetic feeding experiments with ^{13}C-labelled acetate proved that the major and

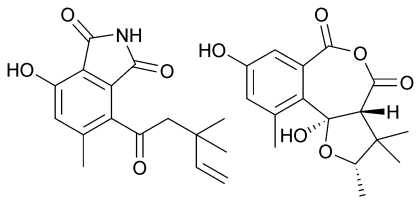
known *C. cereale* metabolite (−)-trypethelone[212] was polyketide-derived and it is proposed as the precursor of cereoanhydride.[213]



213 **214**

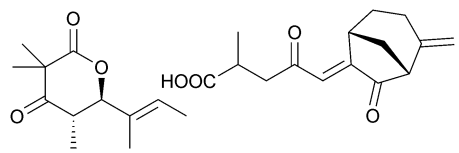


215 **216** **217**

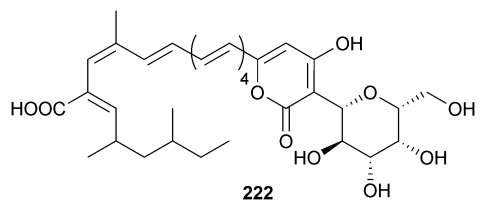


218 †**219**

The lactone helicascolide C **220** was isolated from endophytic *Daldinia eschscholzii* (red alga *Gracilaria* sp., South Sulawesi coast, Indonesia) and was fungistatic against the phytopathogenic fungus *Cladosporium cucumerinum*.[214] Both helicascolide C and helicascolide A,[215] previously isolated from the fungus *Helicascus kanaloanus*, have been synthesised by acid catalysed acetonide deprotection, followed by a one-pot intramolecular lactonisation as the key step.[216] The endophyte *Emericellopsis minima* (sponge *Hyrtios erecta*, Similan Islands, Thailand) was the source of the sesquiterpene **221**,[217] while an *Epicoccum* sp. (sponge *Callyspongia* sp., Sanya, China) provided the pyronepolyene *C*-glucoside *iso*-D8646-2-6 **222** along with the known isomer D8646-2-6.[218] Both pyrones significantly inhibited growth of the H1N1 virus along with weak NF-κB inhibition.[219]

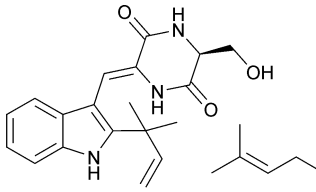


220 **221**

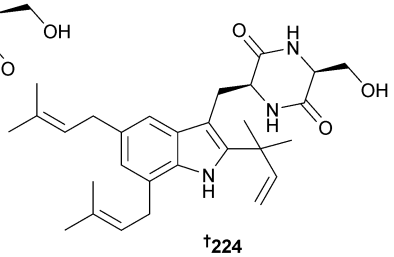


222

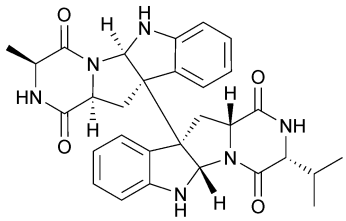
Endophytic *Eurotium cristatum* (brown alga *Sargassum thunbergii*, location unspecified) was the source of the indole alkaloids cristatumin A–D **223–226**, of which cristatumin A and the co-isolated known fungal metabolite tardioxopiperazine A[220] were active against *E. coli* and *S. aureus*, respectively, while cristatumin B and the co-isolated known fungal metabolite isoechinulin A[221] were moderately toxic to brine shrimp.[222]



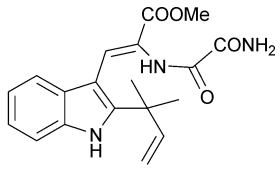
†**223**



†**224**

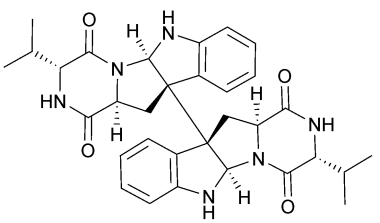


†**225**

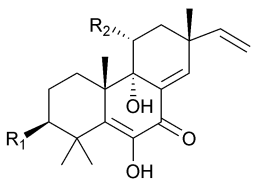


226

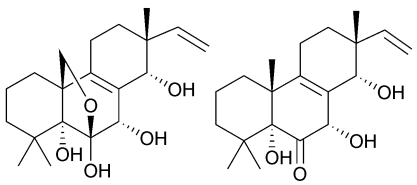
The diketopiperazine dimer eurocristatine **227** was isolated from endophytic *Eurotium cristatum* (sponge *Mycale* sp., Wonnapa Beach, Bangsaen, Thailand),[223,224] while scopararanes C–G **228–232** are oxygenated pimarane diterpenes obtained from *Eutypella scoparia* (sediment, South China Sea). Scopararane C was moderately cytotoxic to MCF-7 cells, while scopararane D was moderately cytotoxic to both SF-268 and MCF-7 cells[225] and was concurrently reported from another marine fungal species. This was *Epicoccum* sp. (sea cucumber *Apostichopus japonicus*, Yantai City, Shandong, China) and scopararane D was reported as a moderate cytotoxin, along with two further pimarane diterpenes, **233** and **234**, of which **233** was strongly cytotoxic to KB and KBv200 cells.[226]



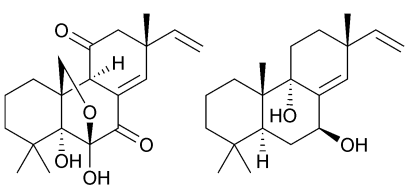
†**227**



†**228** $R_1 = R_2 = H$
†**229** $R_1 = OH$, $R_2 = H$
†**230** $R_1 = R_2 = OH$

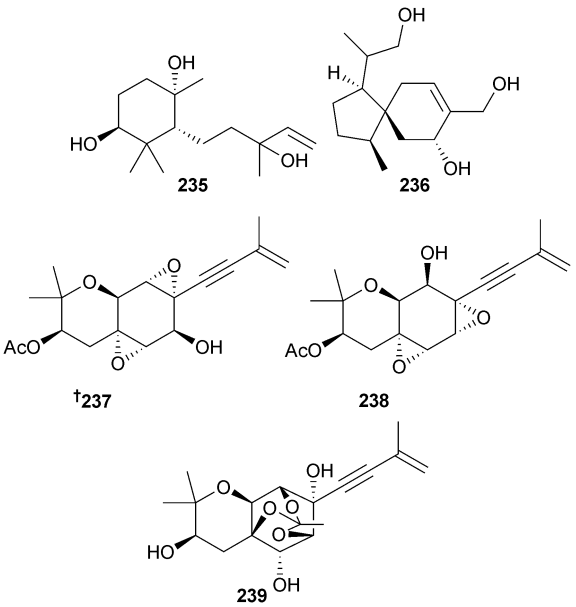


†**231** †**232**

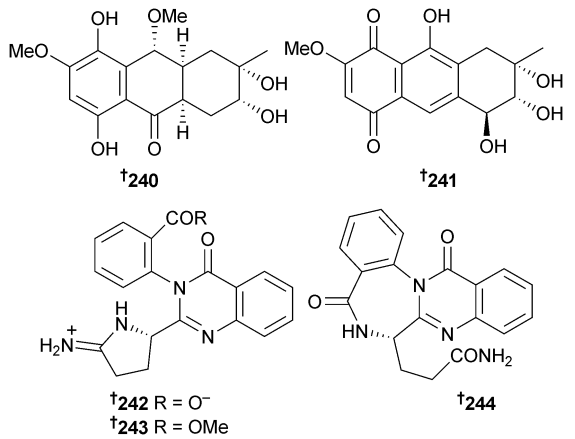


†**233** †**234**

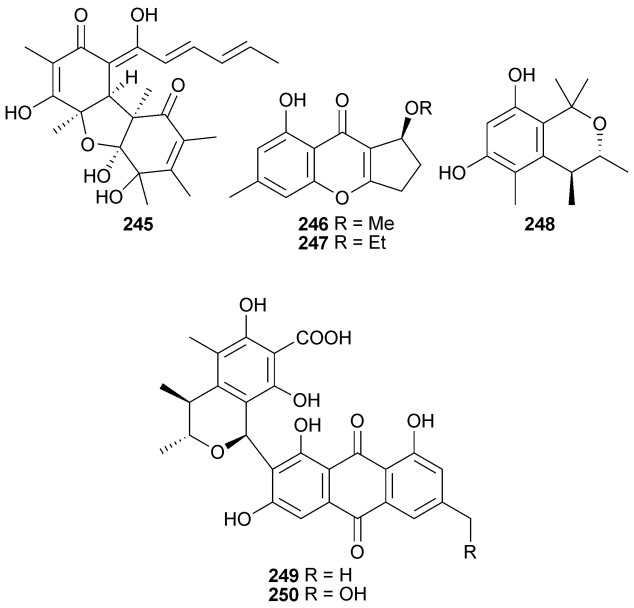
A monocyclofarnesane sesquiterpene **235** and an acorane sesquiterpene **236** were obtained from *Eutypella scoparia* (sediment, South China Sea),[227] while *Isaria felina* (sediment, South China Sea, Vietnam) was the source of the chromene derivatives oxirapentyn B–D **237–239**, in addition to oxirapentyn A, previously obtained from the terrestrial fungus *Beauveria felina.*[228] This is the first isolation from a marine source.[229]



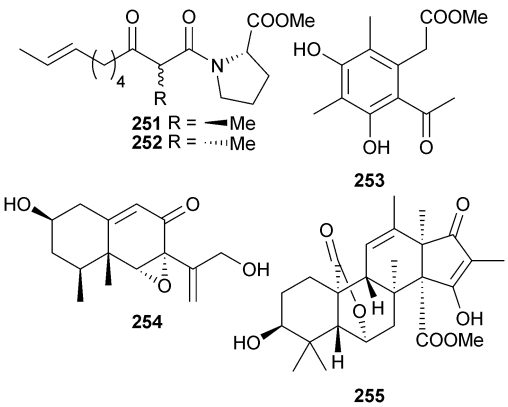
Two hydroanthraquinone analogues 4a-*epi*-9α-methoxydihydrodeoxybostrycin **240** and 10-deoxybostrycin **241** were isolated from endophytic *Nigrospora* sp. (unidentified sea anemone, Weizhou, South China Sea). 10-Deoxybostrycin was strongly active against *B. cereus* and A549 cells.[230] An OSMAC approach to cultivation of *Penicillium aurantiogriseum* (mud, Bohai Sea, China) resulted in production of the auranomides A–C **242–244**.[231]



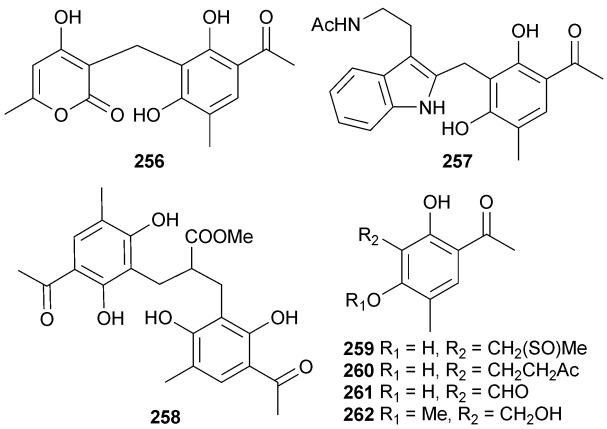
P. citrinum (unidentified sponge, Ishigaki Is., Okinawa, Japan) was the source of JBIR-124 **245**, a DPPH radical scavenger,[232] while *P. citrinum* (gorgonian sea fan *Annella* sp., Similan Islands, Thailand) yielded several polyketides including the benzopyranones coniochaetone C **246** and D **247**, an isochroman **248** and the anthraquinone-citrinin derivatives penicillanthranin A **249** and B **250**. Penicillanthranin A exhibited moderate activity against *S. aureus* and MRSA.[233]



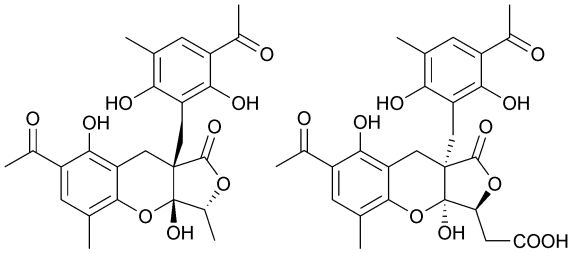
P. citrinum (sediment, Lanqi Is., Fujian, China) provided the epimeric tumonoic acids K **251** and L **252** along with methyl 2-(2-acetyl-3,5-dihydroxy-4,6-dimethylphenyl)acetate **253**,[234] while isophomenone **254** and 3-deacetylcitreohybridonol **255** were obtained from *P. commune* (sediment, South China Sea).[235]



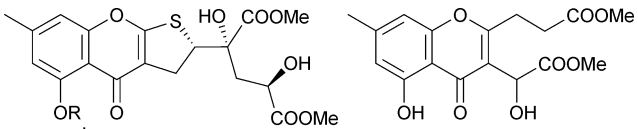
Communols A–G **256–262** are aromatic polyketides isolated from *P. commune* (gorgonian *Muricella abnormalis*, Danzhou, Hainan, China), of which communols A, F and G were moderately active against *E. coli* and *Enterobacter aerogenes* (*E. aerogenes*).[236,237]



Penilactones A **263** and B **264** are highly oxygenated polyketides from *P. crustosum* (deep sea sediment, Prydz Bay, Antarctica).[238] The dihydrothiophene-condensed chromones oxalicumone A **265** and B **266** and the chromone, oxalicumone C,[239] were isolated from *P. oxalicum* (gorgonian *Dichotella gemmacea*, Sanya, South China Sea, China). Oxalicumone C **267** has previously been reported as a reaction product of chloromonilicum, a metabolite of the cherry rot fungus *Monilinia fructicola*,[239] but this is the first notification as a natural product.[240]

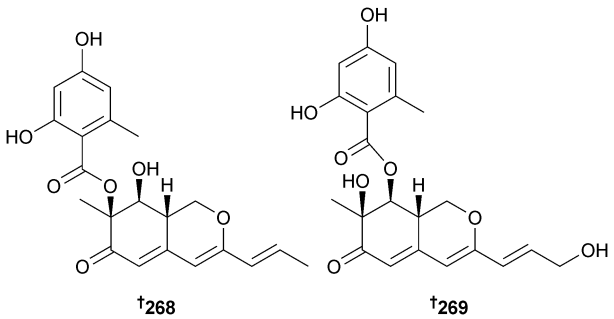


†**263** †**264**



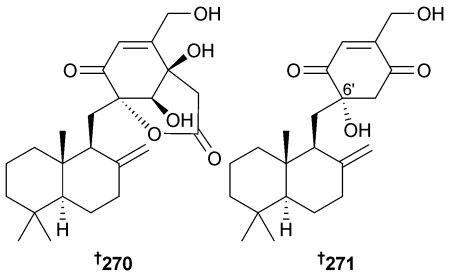
†**265** R= H
†**266** R= Me
267

Pinophilins A **268** and B **269**, hydrogenated azaphilones from *P. pinophilum* (seaweed *Ulva fasciata*, Kasai, Tokyo, Japan), along with the co-isolated metabolite Sch 725680,[241] selectively inhibited the activities of mammalian DNA polymerases (pols), A (pol γ), B (pols α, δ, and ε), and Y (pols η, ι, and κ) families and the growth and proliferation of several HTCLs.[242] Pinophilin A was simultaneously isolated as berkazophilone B from an extremophile *P. rubrum* (from an abandoned acidic, metal-sulfate contaminated open-pit copper mine) as a selective inhibitor of leukaemia cell lines.[243] The absolute configuration was determined by total synthesis.[244]



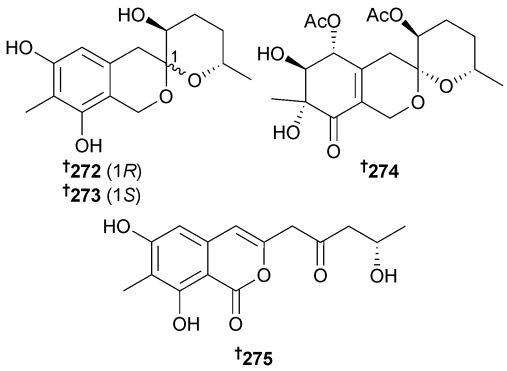
†**268** †**269**

Random diethyl sulfate mutagenesis of *P. purpurogenum* (sediment, Bohai Bay, Tianjin, China) gave a mutant producing the drimenyl cyclohexenone derivatives purpurogemutantin **270** and purpurogemutantidin **271**.[245] From another *Penicillium* strain (deep sea sediment, northern South China Sea) penicilliumin A was isolated and determined to have the same structure as purpurogemutantidin but no assignment of configuration at C-6′ was made. Differences in optical rotations between the two compounds suggest they may be diastereoisomers.[246]



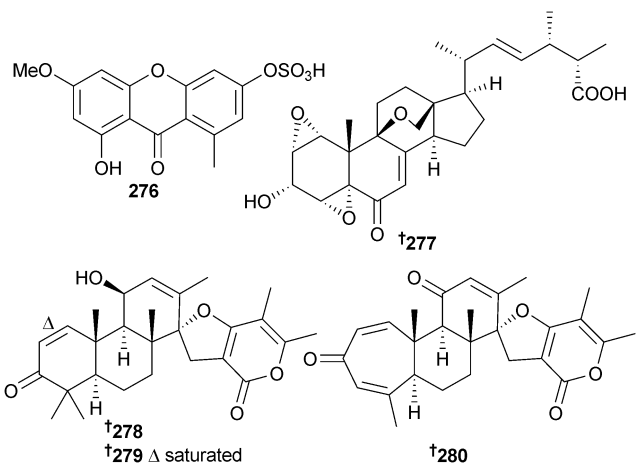
†**270** †**271**

Peneciraistins A–D **272–275** were isolated from *P. raistrickii* (saline soil, Bohai Bay, Shandong, China). Peneciraistin C was moderately cytotoxic to A549 and MCF-7 cells whilst peneciraistins A, B and D exhibited radical scavenging activities against DPPH.[247] Two further compounds were isolated and named peneciraistins E and F, with structures assigned as 3-indoleformic acid derivatives, however, these structures have subsequently been corrected to contain six-membered N-containing rings[248] both of which are known compounds.[249,250]



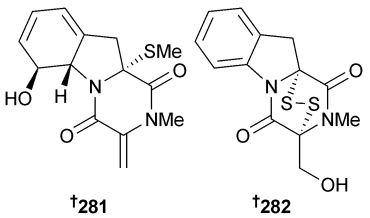
†**272** (1*R*)
†**273** (1*S*)
†**274**
†**275**

1-Hydroxy-3-methoxy-6-sulfo-8-methylxanthone **276** was isolated from *P. sacculum* (saltbush *Atriplex* sp., Dongying city, Shandong, China),[251] whilst *Penicillium* sp. (deep sea sediment, East Pacific Ocean) provided the polyoxygenated sterol, sterolic acid **277** and the spiroditerpenoids brevione I–K **278–280**. Brevione J and the known terrestrial fungal allelochemical brevione A[252] (obtained here for the first time from a marine source) were cytotoxic (MCF-7 cells).[253]



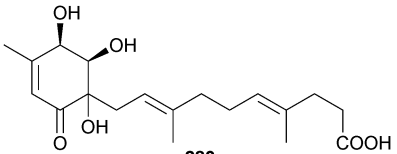
276
†**277**
†**278**
†**279** Δ saturated
†**280**

Penicillium sp. (deep sea sediment, Suruga Bay, Japan) yielded several gliotoxin-related compounds including **281** and **282**. Of the other known compounds, bisdethiobis(methylthio) gliotoxin,[254] 5a,6-didehydrogliotoxin,[255] gliotoxin[256] and gliotoxin G[257] inhibited histone methyltransferase (HMT), while **282** and gliotoxin G were cytotoxic to P388 cells.[258]

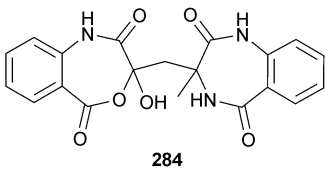


†**281** †**282**

Penicillone A **283** and penicillactam **284** were isolated from a marine *Penicillium* sp. (source not given).[259] A further compound, ethyl 2-(2,6-dihydroxybenzoyl)-3-hydroxy-5-(hydroxymethyl)benzoate,[260] was isolated and although commercially available this was the first reported isolation as a natural product.[259]

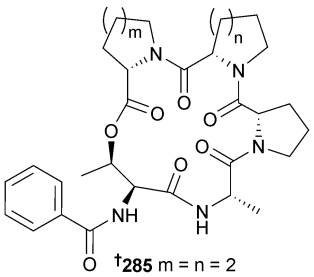


283

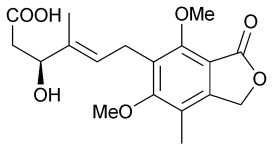


284

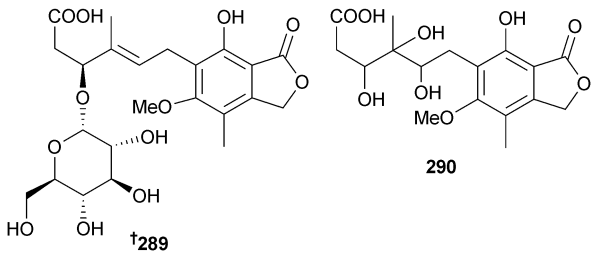
The depsipeptides JBIR-113, JBIR-114 and JBIR-115 **285–287** were obtained from *Penicillium* sp. (unidentified marine sponge, Takarajima Is., Kagoshima, Japan)[261] and another *Penicillium* sp. (sediment, South China Sea) was the source of the mycophenolic acid derivatives penicacid A–C **288–290** and the known terrestrial fungal metabolite 4′-hydroxy-mycophenolic acid,[262] obtained for the first time from a marine source. All of the isolated metabolites inhibited inosine-monophosphate dehydrogenase (IMPDH) to varying degrees and penicacid A and 4′-hydroxy-mycophenolic acid also displayed immunosuppressive activity.[263]



†**285** m = n = 2
†**286** m = 2, n = 1
†**287** m = 1, n = 2

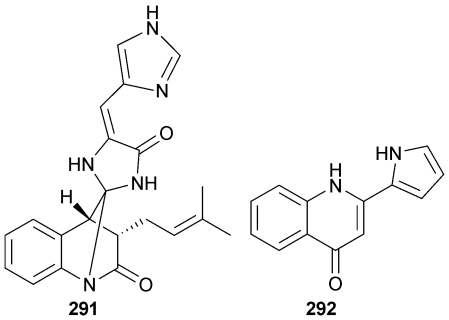


†**288**



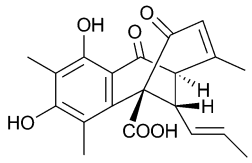
†**289** **290**

A halotolerant *Penicillium* sp. (source unspecified) yielded an alkaloid with a unique *spiro*-imidazolidinyl skeleton, penispirolloid A **291**, that exhibited antifouling activity toward *Bugula neritina* larvae[264] and *Penicillium* sp. (sediment, Jiaozhou Bay, China) was the source of the pyrrolyl 4-quinolinone alkaloid penicinoline E **292**.[265]

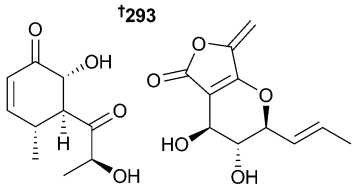


291 **292**

A sorbicillinoid derivative sorbiterrin A **293** with moderate acetylcholinesterase (AChE) inhibition, was obtained from *P. terrestre* (sediment, Jiaozhou Bay, China)[266] and arthropsadiol C **294** and massarilactone H **295** are polyketides obtained from *Phoma herbarum* (sediment, Yellow Sea, China). Massarilactone H and the co-isolated known fungal metabolites massarilactone G,[267] massarigenin C[268] and enalin A[269] displayed moderate neuraminidase inhibition. This was the first reported marine isolation of massarigenin C.[270]

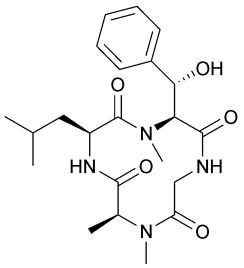


†**293**

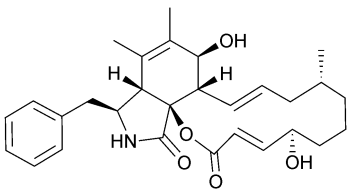


294 †**295**

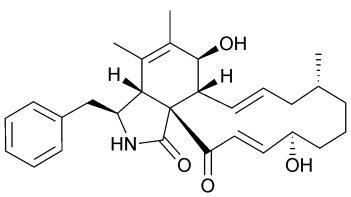
An endophytic *Phoma* sp. (giant jellyfish *Nemopilema nomurai*, southern coast, S. Korea) provided a cyclic tetrapeptide **296** which was a weak suppressor of NO production in RAW264.7 cells without notable cytotoxicity.[271] The same strain of fungus also provided four cytochalasin derivatives: cytochalasin B2 **297**, deoxaphomin B **298**, deoxaphomin C **299** and 20-deoxycytochalasin F **300**. Cytochalasin B2 and deoxaphomin C were cytotoxic to several HTCLs.[272,273]



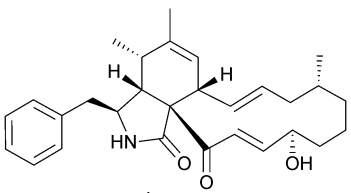
†296



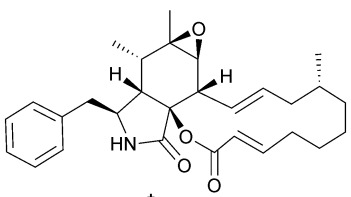
†297



†298

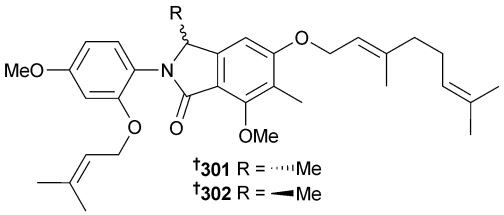


†299

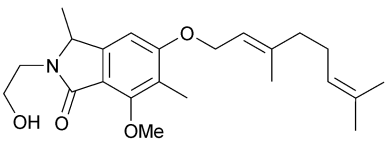


†300

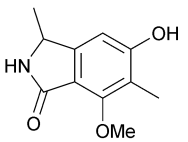
Stachylidium sp. (sponge *Callyspongia cf. flammea*, location unspecified) yielded phthalimidine derivatives, the enantiomeric marilines A1 **301** and A2 **302** and marilines B **303** and C **304**. The various marilines were active in a wide range of bioassays.[274]



†301 R = ····Me
†302 R = —Me

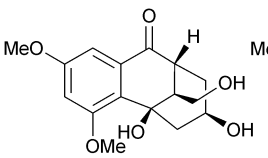


303

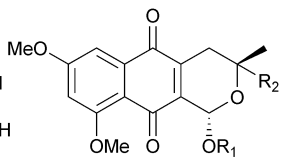


304

Torula herbarum (sea hare *Notarchus leachii*, Beihai, Guangxi, China) was the source of the heptaketide herbarone **305** and the *ent*-astropaquinones B **306** and C **307**. *O*-Methylherbarin, a metabolite previously reported from *T. herbarum*,[275] was also obtained and the absolute configuration determined as **308**.[276]

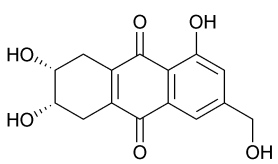


†305

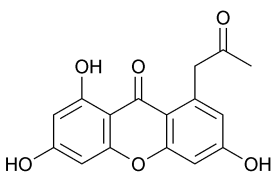


†306 R_1 = OMe, R_2 = H
†307 R_1 = OH, R_2 = H
†308 R_1 = OH, R_2 = OMe

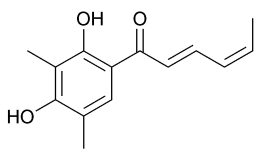
Trichoderma aureoviride (gorgonian sea fan *Annella* sp., Similan Islands, Thailand) provided trichodermaquinone **309** and trichodermaxanthone **310**.[277] An endophytic *Trichoderma* sp. (sea star *Acanthaster planci*, Hainan Sanya National Coral Reef Reserve, China) produced two sorbicillinoid



†309



310



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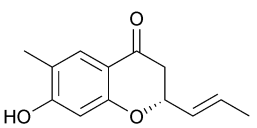
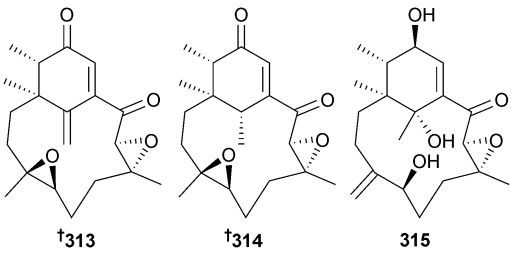


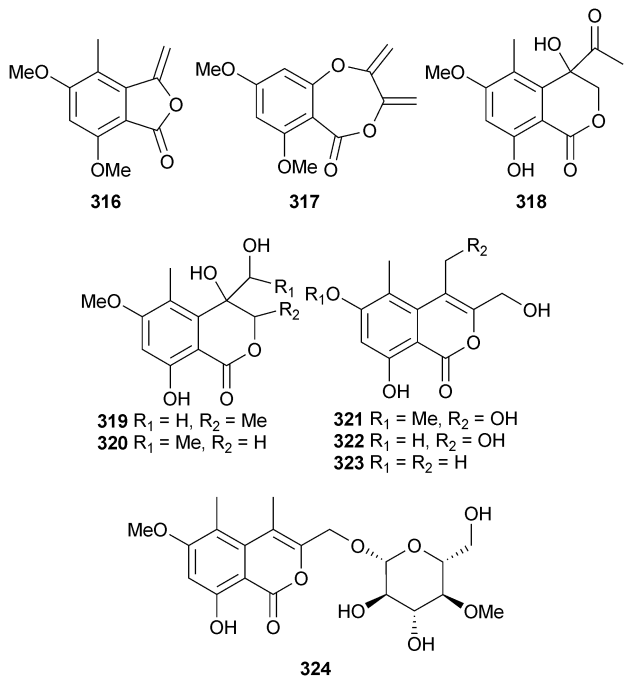
†312

analogues (4′*Z*)-sorbicillin **311** and **312** (moderately cytotoxic to several HTCLs),[278] while three diterpenes phomactin K–L **313–315** were obtained from an unidentified fungus (brown alga *Ishige okamurae*, Tateishi, Kanagawa, Japan).[279]

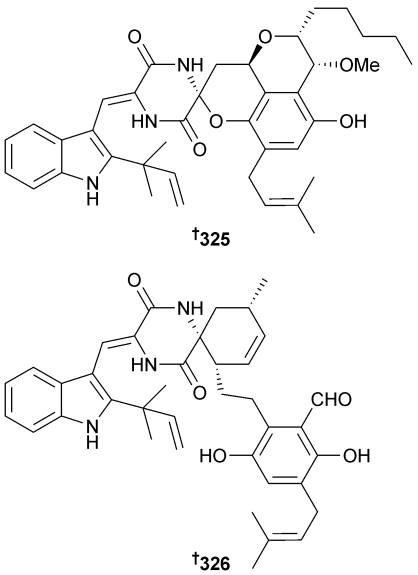


3.4 Fungi from mangroves

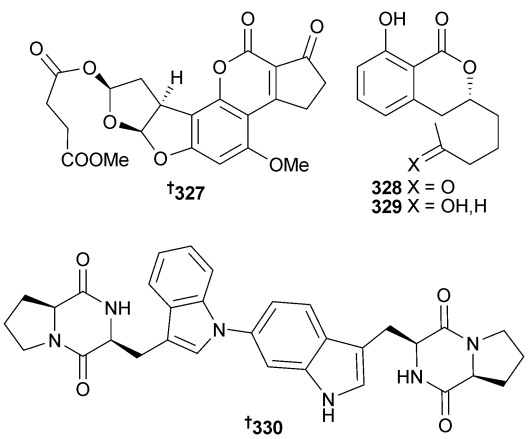
An endophytic *Acremonium* sp. (mangrove branch *Rhizophora apiculata*, Satun, Thailand) provided the phthalide derivative, acremonide **316** and the isocoumarin derivatives acremonone A–H **317–324**.[280]



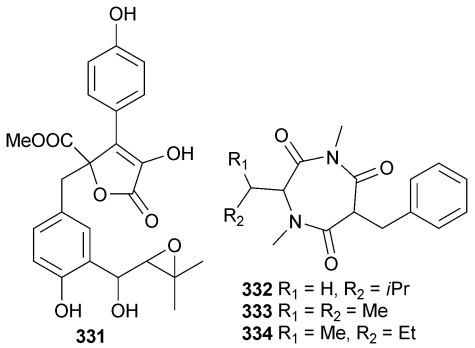
The racemic spiroalkaloids effusin A and dihydrocryptoechinulin D (shown here as one of the enantiomers **325** and **326**, respectively) were obtained from *Aspergillus effusus* (mangrove rhizosphere soil, Fujian, China). The racemates were subsequently each resolved and absolute configurations determined by solution time dependent density function theory (TDDFT) electronic CD (ECD) calculations. The racemate of dihydrocryptoechinulin D inhibited growth of P388 cells and the (12*R*,28*S*,31*S*)-enantiomer **326** showed selective, moderate inhibition of topoisomerase I.[281]

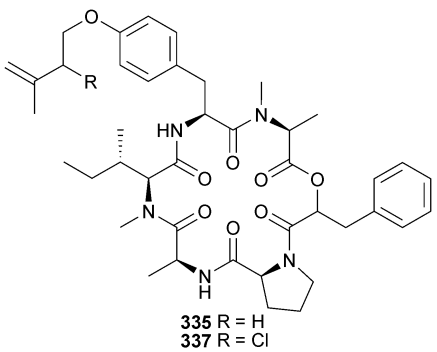


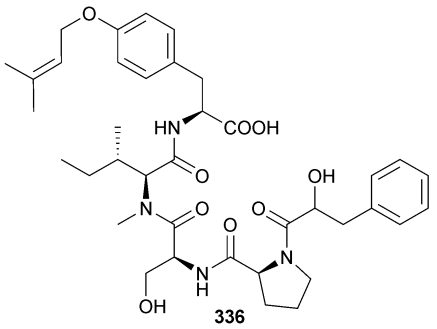
Aflatoxin B2b **327** was obtained from endogenous *A. flavus* (mangrove root *Hibiscus tiliaceus*, Wenchang, Hainan, China) and was moderately active against *E. coli*, *B. subtilis* and *E. aerogenes*.[282] The dihydroisocoumarin derivatives aspergillumarin A **328** and B **329** were isolated from *Aspergillus* sp. (mangrove leaf *Bruguiera gymnorrhiza*, South China Sea),[283] while aspergilazine A **330**, a diketopiperazine dimer consisting of two diketopiperazine units with a rare N-1 to C-6 linkage, was obtained from *A. taichungensis* (mangrove root soil, *Acrostichum aureum*, source not given).[284]



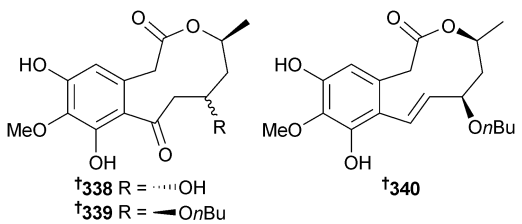
The butyrolactone 7″-hydroxybutyrolactone III **331** and terretriones A–C **332–334** were isolated from *A. terreus* (sediment, unnamed mangrove, Guangxi Zhuang, China).[285] Along with three known terrestrial fungal metabolites, verticillin D[286] and pullularins A and C[287] (isolated from a marine source for the first time), the endophytic *Bionectria ochroleuca* (mangrove leaf *Sonneratia caseolaris*, Hainan Is., China) produced the peptides pullularin E **335** and F **336**. Pullularin E was characterised as the chloro-derivative **337** that it had rapidly converted to.[288]

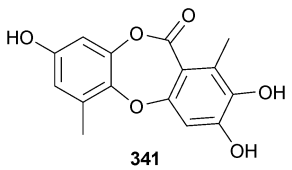




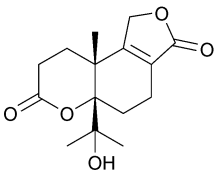


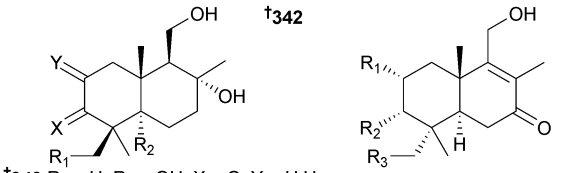
Corynespora cassiicola (mangrove leaf *Laguncularia racemosa*, Hainan Is., China) yielded xestodecalactones D–F **338–340** and corynesidone C **341** as well as the known terrestrial fungal metabolites corynesidone B[289] and 6-(3-hydroxybutyl)-7-*O*-methylspinochrome B,[290] both isolated for the first time as MNPs.[291]

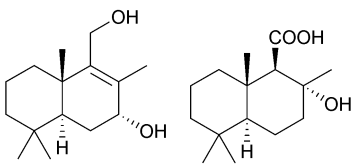




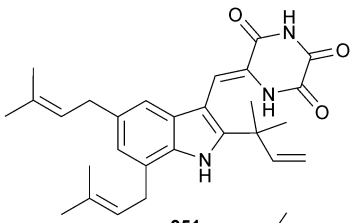
An endophytic *Diaporthe* sp. (mangrove leaves *Rhizophora stylosa*, Hainan Is., China) was the source of the sesquiterpenoid diaporol A **342** and drimane sesquiterpenoids diaporol B **343,** C **344** and F–H **345–347.**[292] Three synthetic sesquiterpenoids diaporol D **348,**[293] E **349**[294] and I **350**[295] were isolated for the first time as natural products.[292]

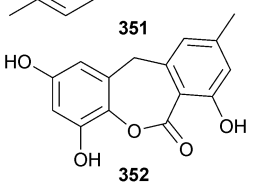




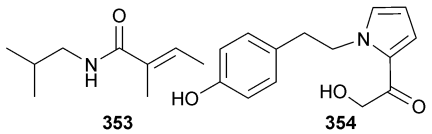


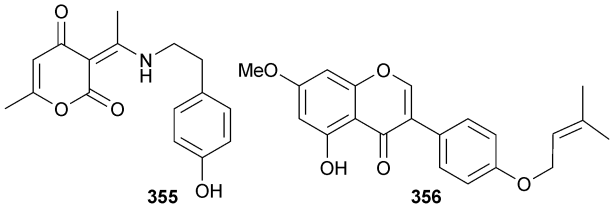
An endophytic strain of *Eurotium rubrum*, (semi-mangrove *Hibiscus tiliaceus*, Hainan Is., China) produced a diketopiperazine alkaloid 12-demethyl-12-oxo-eurotechinulin B **351** and an anthraquinone derivative 9-dehydroxyeurotinone **352,**[296] in addition to the known fungal metabolites variecolorin G[297] and alkaloid E-7.[297,298]



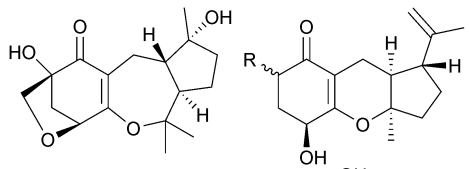


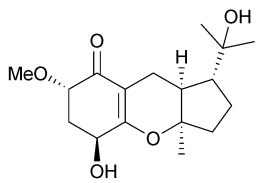
The alkaloids *N*-2-methylpropyl-2-methylbutenamide **353**, fusarine **354** and fusamine **355** were discovered from endophytic *Fusarium incarnatum* (mangrove fruit *Aegiceras corniculatum*, Xiamen, Fujian, China)[299] along with the known synthetic compounds, 2-acetyl-1,2,3,4-tetrahydro-β-carboline[300] and 3-(1-aminoethylidene)-6-methyl-2*H*-pyran-2,4(3*H*)-dione,[301] reported as first time MNPs. Fusarine was concurrently isolated from the Chinese plant *Alhagi sparsifolia*.[302] The isoflavone derivative **356** was obtained from an endophytic *Fusarium* sp. (mangrove leaves *Kandelia candel*, Dong Zai, Hainan, China).[303]





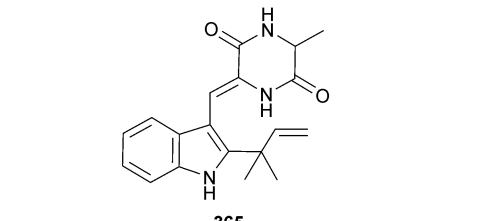
Endophytic *Guignardia* sp. (mangrove leaves *Scyphiphora hydrophyllacea*, Wenchang, Hainan, China) was the source of the meroterpenes guignardone F–I **357–360**.[304] It should be noted that the planar structure of guignardone G was the same as that of coibanol A, recently obtained from a plant endophyte, *Pycnoporus sanguineus* from Panama.[305] The co-isolated guignardone B[306] was obtained from a marine source for the first time.

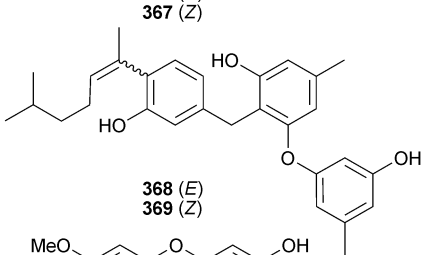


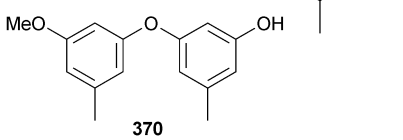


Use of epigenetic modifiers to activate secondary metabolite genes in *Leucostoma persoonii* (mangrove branch *Rhizopora mangle*, Florida Everglades) induced production of a new cytosporone analogue cytosporone R **361**, in addition to known cytosporones. Of the isolated compounds, cytosporone E,[307] a first time MNP, inhibited the malaria parasite *P. falciparum* and was moderately inhibitory towards MRSA.[308] Endophytic *Nigrospora* sp. (semi-mangrove stem *Pongamia pinnata*, Guangxi Zhuang, China) yielded griseofulvin derivatives **362** and **363**, 2,3-didehydro-19α-hydroxy-14-epicochlioquinone B **364**, in addition to griseophenone C[309] (obtained for the first time from a marine source).[310]

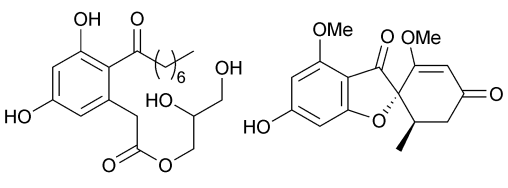
The diketopiperazine **365** (named chrysogenazine in an earlier patent application by the same authors),[311] was obtained from endophytic *Penicillium chrysogenum* (mangrove leaves *Porteresia coarctata*, Chorao Is., Goa, India) and displayed antibacterial activity comparable to that of streptomycin.[312] Endophytic *P. expansum* (mangrove *Excoecaria agallocha*, source unspecified) was the source of the polyphenols expansol C–F **366–369** and a new diphenyl ether derivative 3-*O*-methyl-diorcinol **370**.[313]

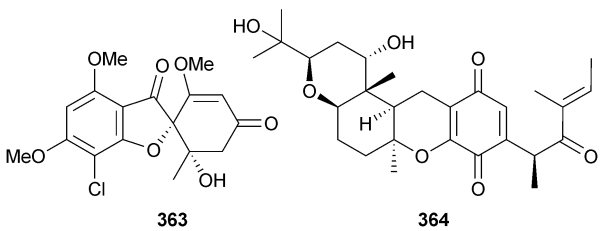


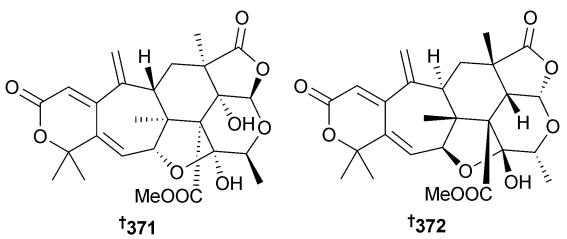


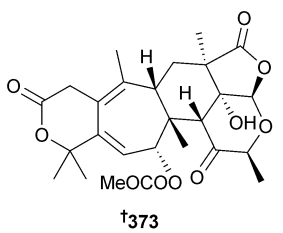


A *Penicillium* sp. (mangrove rhizospheric soil *Bruguiera gymnorrhiza*, Hainan Is., China) produced meroterpenoid derivatives 4,25-dehydrominiolutelide B **371**, 4,25-dehydro-22-

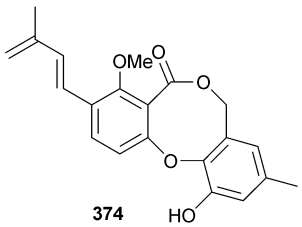








deoxyminiolutelide B **372** and isominiolutelide A **373** from static culture and diphenyl ether derivatives $\Delta^{1'3'}$-1′-dehydroxypenicillide **374**, 7-*O*-acetylsecopenicillide C **375** and hydroxytenellic acid B **376** from shaken culture.[314] A number of known compounds were also isolated from the shaken culture: penicillide,[315] secopenicillide C,[316] dehydroisopenicillide[317] and 3′-*O*-methyldehydroisopenicillide[318] (all obtained from a marine source for the first time).



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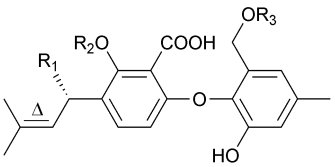
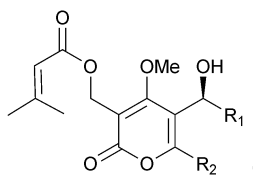
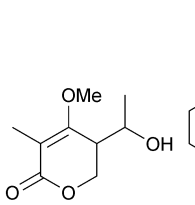


375 $R_1 = R_2 = H$, $R_3 = Ac$
†**376** $R_1 = OH$, $R_2 = Me$, $R_3 = H$, Δ saturated

The α-pyrones pestalotiopyrone A–C **377–379** were isolated from *Pestalotiopsis* sp. (mangrove twigs *Rhizophora apiculata*, Trang province, Thailand) and the seiricuprolides pestalotioprolide A **380** and B **381** (isolated as the diacetate) were obtained from *Pestalotiopsis* sp. (mangrove twigs *Rhizophora mucronata*, Satun province, Thailand).[319]



†**377** $R_1 = Me$, $R_2 = H$
†**378** $R_1 = H$, $R_2 = Me$



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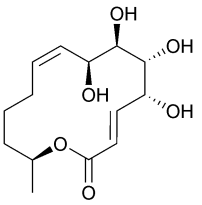
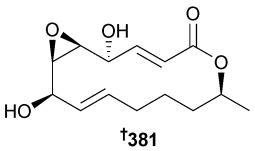
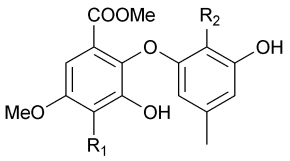


†**380**

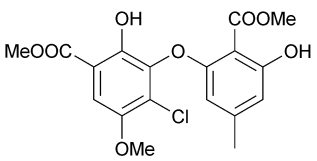


†**381**

An endophytic *Pestalotiopsis* sp. (mangrove branch *Rhizopora apiculata*, Satun, Thailand) provided the diphenyl ether derivatives pestalotether A–D **382–385**, the chromones pestalochromone A–C **386–388**, pestaloxanthone **389** and the butenolide pestalolide **390** (modestly active against *C. albicans* and *Cryptococcus neoformans*).[320]



382 $R_1 = Cl$, $R_2 = COOMe$
383 $R_1 = Cl$, $R_2 = H$
385 $R_1 = H$, $R_2 = COOMe$



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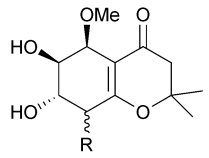
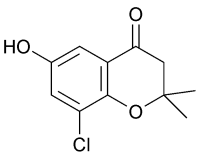


386 R = Cl
387 R = Cl



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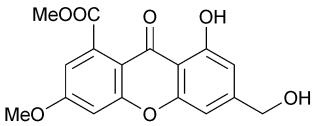

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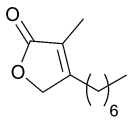
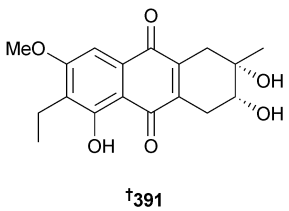
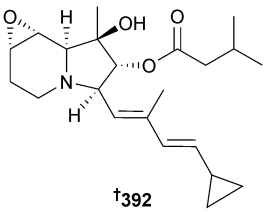


390

The tetrahydroanthraquinone derivative **391** was isolated from *Phomopsis* sp. (mangrove leaf *Rhizopora apiculata*, Songkhla, Thailand) and possessed weak cytotoxicity against MCF-7 cells in addition to antibacterial activity against *S. aureus* and MRSA.[321] *Saccharopolyspora* sp. (mangrove soil, Ishigaki Is., Japan) yielded the cyclizidine analogue JBIR-102 **392**, along with cyclizidine[322] itself (first time from a marine source). Both were cytotoxic to human malignant pleural mesothelioma (MPM) ACC-MESO-1 cells.[323]

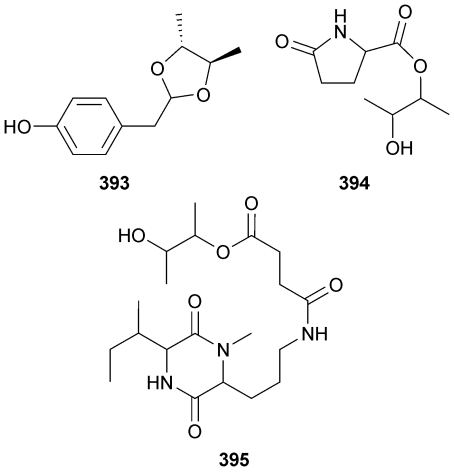


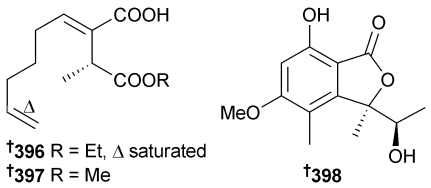
†**391**



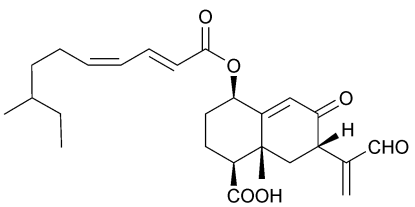
†**392**

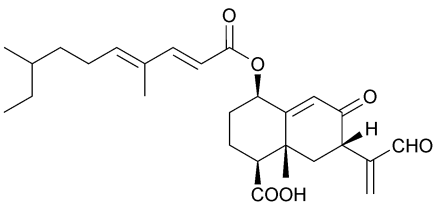
Trichoderma atroviride (mangrove root soil *Ceriops tagal*, South Sea, China) yielded three new metabolites **393**, **394** and atroviridetide **395**.[324] The succinic acid derivatives xylacinic acid A **396** and B **397** were isolated from *Xylaria cubensis* (mangrove branch *Bruguiera parviflora*, Suratthani, Thailand),[325] while *Xylaria* sp. (mangrove leaf *Acanthus ilicifolius*, Yangjiang, China) produced the lactone **398** in addition to (*S*)-8-hydroxy-6-methoxy-4,5-dimethyl-3-methyleneisochromen-1-one, which although claimed as new, was previously isolated from a terrestrial *Leptosphaeria* sp.[326] The current isolation is however the first from the marine environment.[327]

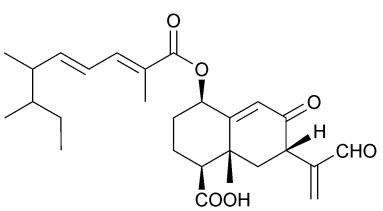


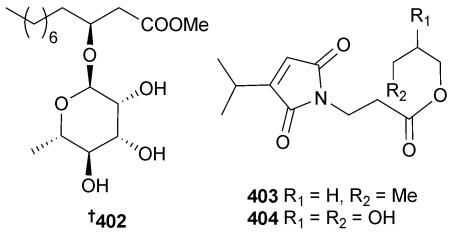


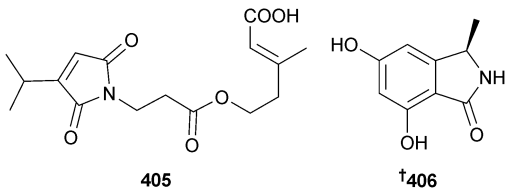
An endophytic *Xylaria* sp. (unidentified mangrove, South China Sea coast) was the source of the eremophilane sesquiterpenes **399–401**[328] and the known fungal metabolite 07H239-A.[329] A fatty acid glucoside **402** with moderate inhibitory properties against *S. aureus* and MRSA was obtained from an unidentified endophytic fungus (mangrove leaves *Scyphiphora hydrophyllacea*, Wenchang, Hainan, China),[330] while investigation of an unidentified endophytic fungus (mangrove leaves *Avicennia marina*, Oman) yielded farinomaleins C–E **403–405** and an isoindoline congener **406**,[331] in addition to the known farinomalein B.[332]





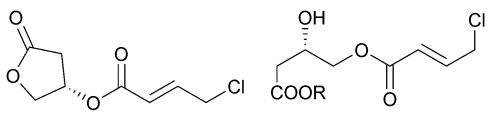






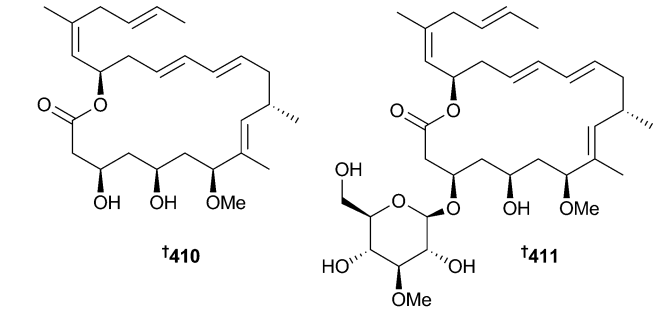
3.5 Cyanobacteria

Cyanobacteria continue to be a valuable source of new compounds, although the number of new metabolites isolated in the past year is somewhat less than in 2011. *Leptolyngbya crossbyana* (Hōnaunau reef, Hawaii) was the source of honaucins A–C **407–409**, chlorinated metabolites that were potent inhibitors of bacterial quorum-sensing (inhibited bioluminescence in *Vibrio harveyi*) and inhibited NO production and expression of several pro-inflammatory cytokines in RAW264.7 cells. Honaucin A was synthesised, along with some analogues, to determine the structural features required for activity and some of the analogues had improved potency in the assays.[333]

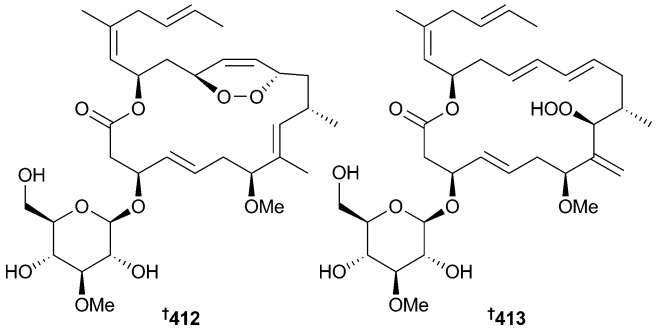


Investigation of *Lyngbya* sp., (Tokunoshima Is., Japan) identified the macrolide biselyngbyolide A **410**, which had potent apoptosis-inducing activity against HeLa S3 and HL-60 cells,[334] while biselyngbyasides B–D **411–413**, analogues of biselyngbyaside[335] and biselyngbyolide A[334] were obtained from another *Lyngbya* sp. (Tokunoshima Is., Japan). Biselyngbyaside B inhibited growth and induced apoptosis in HeLa S_3 and HL-60 cells with increased cytosolic Ca^{2+} concentration in the HeLa S_3 cells.[336]

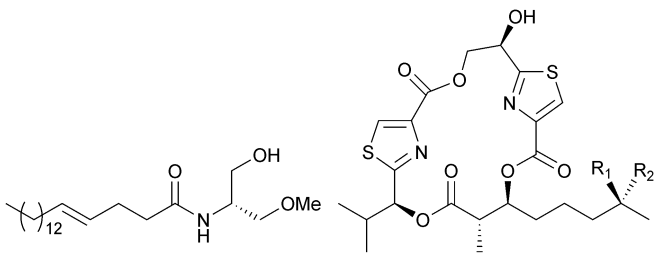
Serinolamide B **414**, a fatty acid amide obtained from a *Lyngbya* sp. (Piti Bomb Holes, Guam) along with malyngamide B[337] are cannabinomimetics, decreasing forskolin-induced cAMP accumulation.[338] The lipopeptides lyngbyabellin K **415** and L **416**, 7-*epi*-lyngbyabellin L **417** and lyngbyabellin M **418** and N **419** were isolated from *Moorea bouillonii* (Strawn Is., Palmyra Atoll, Central Pacific Ocean). The possibility that the linear lyngbyabellin M was an artefact of isolation could not be discounted. Lyngbyabellin N, which contains the unusual *N*,*N*-dimethylvaline terminus, was strongly cytotoxic to HCT116 cells.[339]



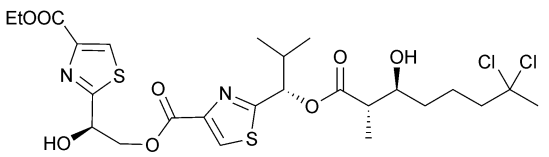
†410 †411



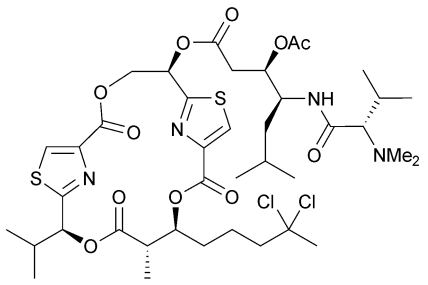
†412 †413



†414 †415 $R_1 = R_2 = Cl$ †416 $R_1 = H, R_2 = Cl$ †417 $R_1 = Cl, R_2 = H$

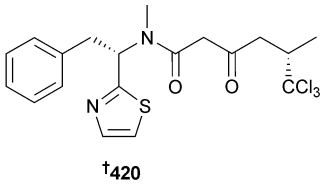


†418

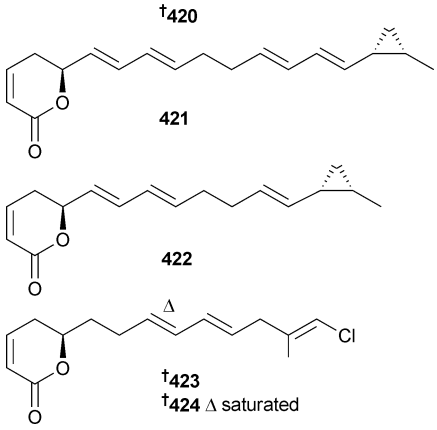


†419

The biosynthetic gene cluster for the chlorinated molluscicide barbamide,[340] obtained from the marine species *Moorea producens*, was heterologously expressed in the terrestrial actinobacterium *Streptomyces venezuelae* and resulted in the production of a new barbamide analogue 4-*O*-demethylbarbamide **420**, which also functioned as a potent molluscicide against the marine snail *Biomphalaria glabrata*.[341] An *Oscillatoria* sp. (Coiba National Park, Panama) was the source of the unsaturated polyketide lactone derivatives coibacin A–D **421–424** which had selective antileishmanial activity and potent anti-inflammatory activity.[342]

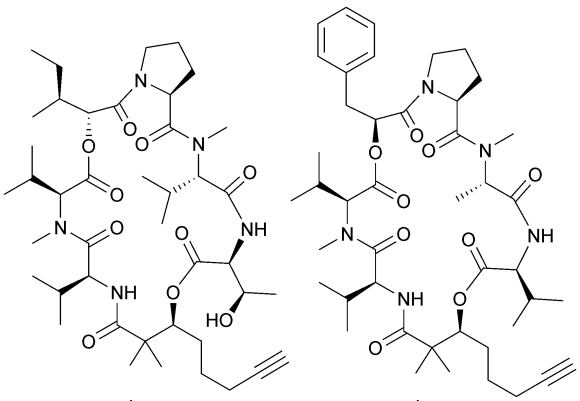


†420

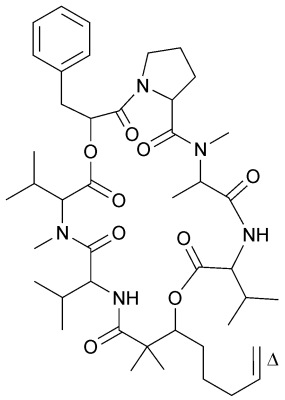


421 422 †423 †424 Δ saturated

The viequeamides, 2,2-dimethyl-3-hydroxy-7-octynoic acid (Dhoya)-containing cyclic depsipeptides, were obtained from the "button" cyanobacterium *Rivularia* sp. (Playa de la Chiva, Vieques Is., Puerto Rico). Of these, viequeamide A **425** was highly toxic to



†425 †426

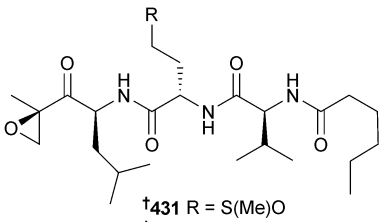


427 428 Δ saturated

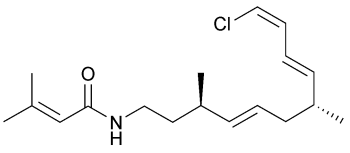
H460 human lung cancer cells. Viequeamides B–F could not be separated but the absolute configuration of the major component of the mixture, viequeamide B **426** was determined, along with planar structures for viequeamides C **427** and D **428**.[343]

Hoiamide D **429**, with two consecutive thiazolines and a thiazole as well as a modified isoleucine residue, was obtained independently in both its carboxylic and conjugate base forms from two *Symploca* sp. (Kolaio Is., Papua New Guinea; Kape Point, Papua New Guinea), respectively. The carboxylate anion inhibited p53/MDM2 protein binding.[344] Symplocin A **430**, an *N*,*N*-dimethyl-terminated peptide, was isolated from *Symploca* sp. (San Salvador Is., Bahamas) as a potent inhibitor of the protease enzyme cathepsin E. Determination of the absolute configuration of the terminal *N*,*N*-dimethylisoleucine and valic acid residues employed a new methodology; chiral-phase HPLC assignment of the corresponding 2-naphthacyl esters, a procedure that may be generally applicable to other N-terminal blocked peptides.[345]

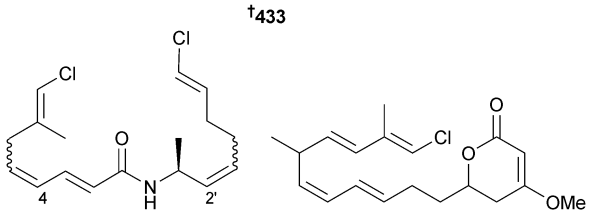
A collection of *Symploca* sp. (CARMABI, Curaçao) was the source of carmaphycins A **431** and B **432**, peptidic proteasome inhibitors containing a leucine-derived α,β-epoxyketone connected respectively to methionine sulfoxide or methionine sulfone. Covergent and flexible total syntheses of each were achieved. Both carmaphycins A and B strongly inhibited the β5 subunit (chymotrypsin-like activity) of the *S. cerevisiae* 20S proteasome and displayed strong cytotoxicity to lung and colon cancer cells, as well as potent antiproliferative effects to HTCLs.[346] Collections of cyanobacteria from Curaçao and Papua New Guinea each yielded metabolites containing a chlorovinyl group. The lipoamide janthielamide A **433** was obtained from "tropical marine *Symploca*" (Jan Thiel Bay, Curaçao) whilst further lipoamides kimbeamide A–C **434–436** and a ketide-extended pyranone kimbelactone A **437** were isolated from a consortium of "tropical marine *Symploca*" and *Moorea producens* (Kime Bay, New Britain, Papua New Guinea). Of these compounds, janthielamide A and kimbeamide A displayed moderate sodium channel blocking activity in murine Neuro-2a cells and janthielamide A was also an antagonist of veratridine-induced sodium influx in murine cerebrocortical neurons.[347]



†**431** R = S(Me)O
†**432** R = S(Me)O_2



†**433**



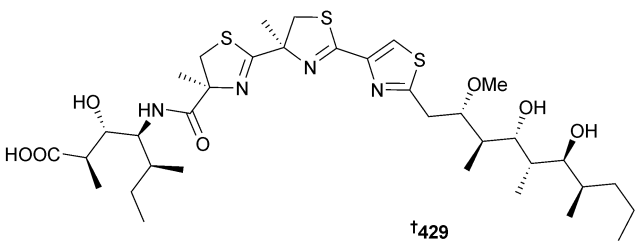
†**434** (4*E*, 2'*Z*)
†**435** (4*Z*, 2'*Z*)
†**436** (4*Z*, 2'*E*)

437

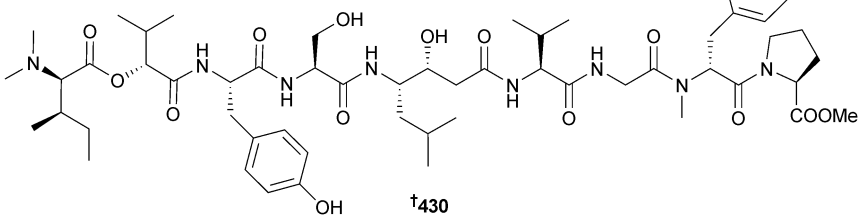
3.6 Dinoflagellates

Amphidinium sp. (red alga *Digenea simplex*, Okinawa, Japan) was the source of the polyol amdigenol A **438**,[348] while the polyether brevisulcenal F **439** was obtained from *Karenia brevisulcata* (Wellington, New Zealand)[349] and exhibited mouse lethality and toxicity to P388 cells.[350]

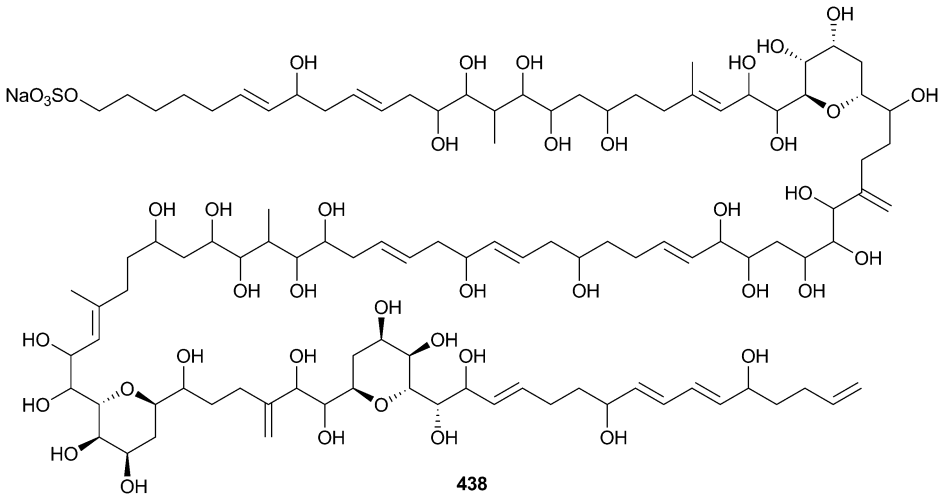
The structure of ovatoxin-a **440**, the major toxin of benthic *Ostreopsis ovata* (seawater, Adriatic and Tyrrhenian coasts, Italy), reported in a preliminary communication,[351] has now been fully characterised using NMR-based analysis.[352] Preliminary *in vivo* assessment of the activity of ovatoxin-a in mice indicated that it was lethal over a very short time period and also caused limb paralysis.[353] A new palytoxin congener,



†**429**



†**430**



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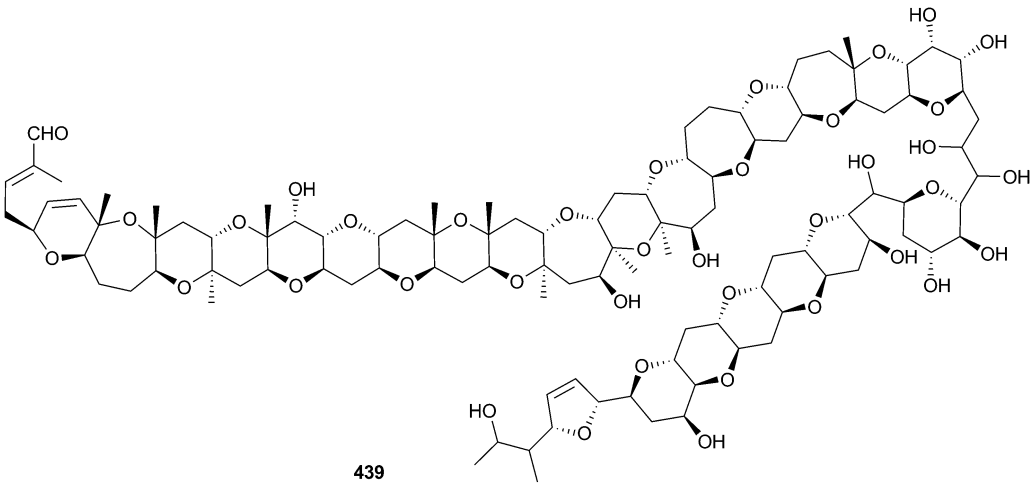

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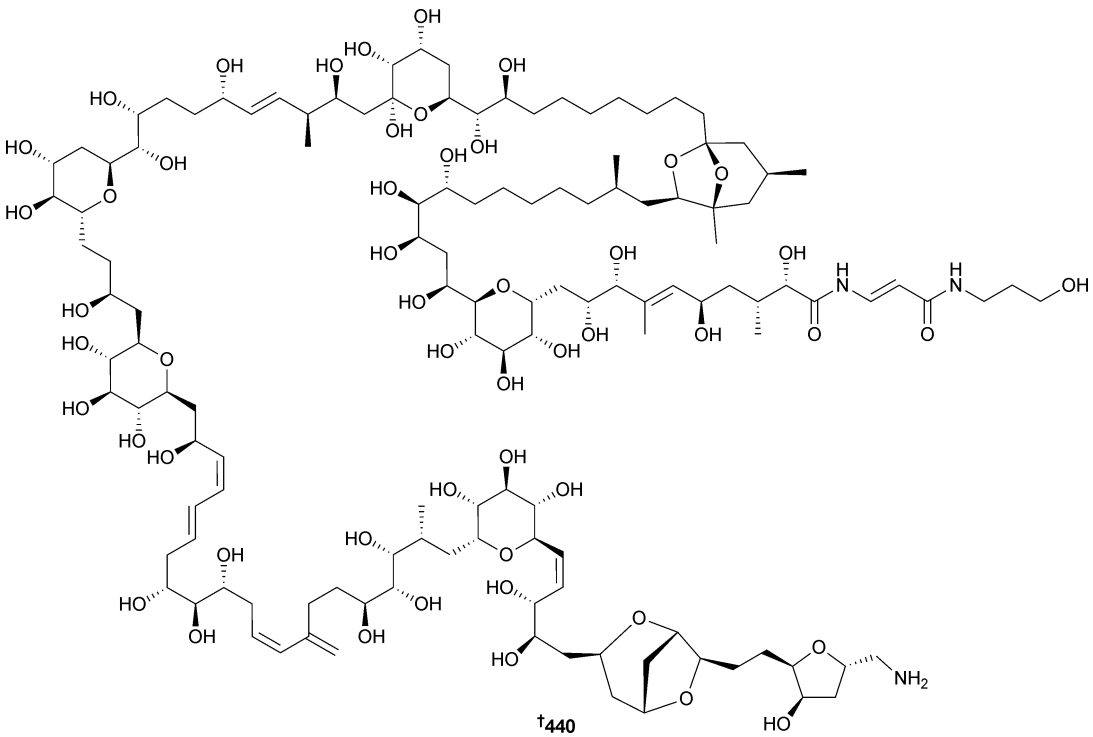
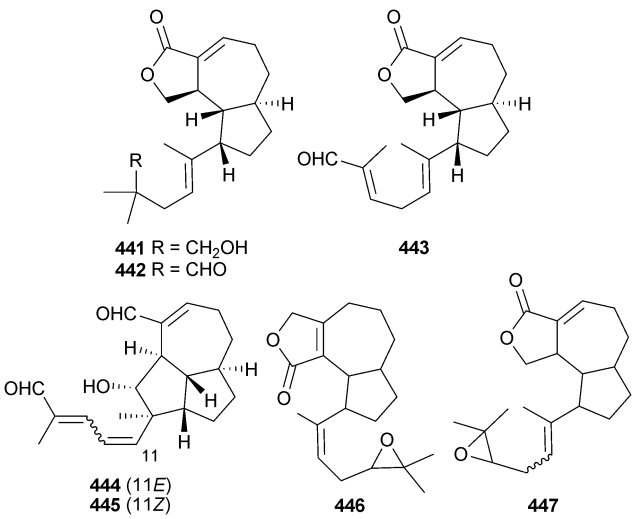


†440

ovatoxin-f was detected in a North Western Adriatic strain of *Ostreopsis cf. ovata* (Portonovo, Italy) but was not fully characterised.[354]

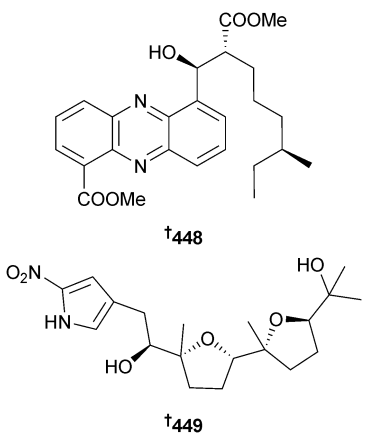
3.7 Ciliates

A number of diterpenes have been obtained from various strains of the ciliate *Euplotes rariseta*. One strain (Omaha Bay, New Zealand) provided the irregular diterpenoids omaholidenol **441** and omaholidenal **442**, while ubatubaolidenal **443**, ubatubadial A **444** and ubatubadial B **445** were obtained from a different strain (Ubatuba, Brazil). *Euplotes quinquecarinatus* (Mughsayl, Oman) yielded epoxyfocardolide **446** and *Euplotes parkei* (Margarita Is., Venezuela) the prenyl epoxyrarisetenolide **447**.[355]

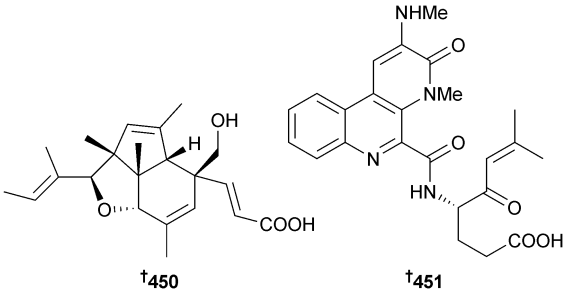


3.8 Synthetic aspects

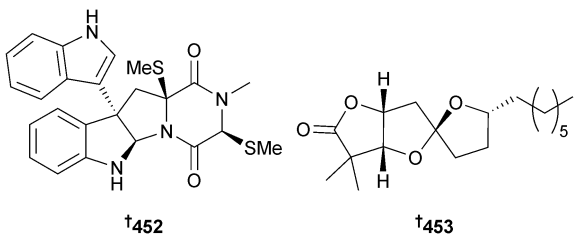
Asymmetric synthesis of streptophenazine G[356] has been achieved by alkylation and aldol reactions using chiral oxazolidinones as the key steps and resulted in revision of the published structure to **448**,[357] consistent with the structural revision of streptophenazine A reported previously *via* synthesis.[358] (−)-Heronapyrrole C, a farnesylated 2-nitropyrrole from an Australian *Streptomyces* sp.,[359] has been synthesised in eight steps from commercially available starting materials and is suggested to be the enantiomer of the natural product. The absolute configuration of naturally occurring heronapyrrole C is proposed as **449**.[360]



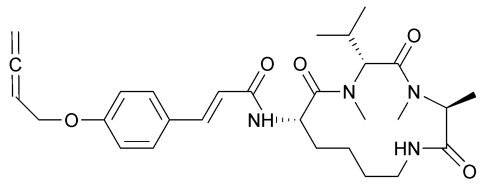
Total synthesis of the tricyclic polypropionate indoxamycin B, originally isolated from a marine-derived actinomycete,[361] has resulted in a stereochemical reassignment of the natural product to **450**.[362] A benzonaphthyridine alkaloid originally isolated from mangrove sediment derived *Streptomyces albogriseolus*[363] was synthesised and the absolute configuration determined as **451**.[364]



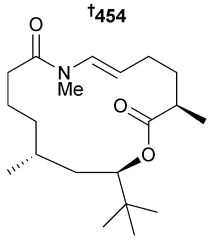
A synthesis of apiosporic acid, originally isolated from *Apiospora montagnei* (fungal endophyte of the North Sea alga *Polysiphonia violacea*),[365] has confirmed the absolute configuration as originally drawn.[366] (+)-Gliocladin B, a diketopiperazine metabolite of the fungus *Gliocladium* sp.,[367] has been synthesised in an enantioselective manner utilising a new regioselective Friedel–Crafts-based strategy that determined the absolute configuration as **452**.[368] Cephalosporolide H is a lactone from the marine fungus *Penicillium* sp.[369] Mismatch of spectral data from an earlier synthesis of the proposed structure with those of the natural compound indicated that the structure may need to be revised.[370] A stereocontrolled synthesis of the reported structure of cephalosporolide H and three diastereoisomers, *via* a zinc-chelation strategy for controlling the stereochemistry of oxygenated 5,5-spiroketals, led to a suggested structure for cephalosporolide H as **453**. This awaits comparison with an authentic sample for confirmation.[371]



Xyloallenoide A, an *N*-cinnamoylcyclopeptide isolated from the endophytic mangrove fungus *Xylaria* sp.,[372] has been synthesised and the absolute configuration determined as **454**.[373] Palmyrolide A is a neuroprotective macrolide obtained from an assemblage of the cyanobacteria *Leptolyngbya* and *Oscillatoria* spp.[374] Synthesis of (+)-*ent*-palmyrolide A has been achieved *via* a macrocyclisation reaction that established the absolute configuration of the natural product as **455**.[375,376] (−)-Palmyrolide A was subsequently synthesised *via* a protecting-group-free method.[376]

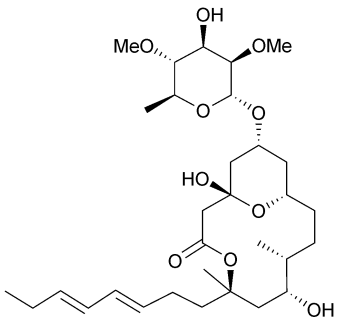


†454



†455

The aglycon of the originally assigned structure of lyngbouilloside, a glycosidic macrolide obtained from a Papua New Guinean *Lyngbya* sp.,[377] has been synthesised from commercially available 3-methylbut-3-enol. A mismatch of the NMR spectroscopic data against the original data strongly indicates that the configuration at C-11 of lyngbouilloside should be revised to **456**.[378] This is in accord with results of an earlier synthesis of the macrocyclic core[379] and also with the stereochemistry of lyngbyaloside B,[380] a metabolite obtained from a different species of *Lyngbya*, but with the same macrocyclic core as lyngbouilloside.[378]



†456

Veraguamide A is a cyclic hexadepsipeptide isolated from the cyanobacteria *Symploca cf. hydnoides* (Guam)[381] and *Oscillatoria margaritifera* (Panama).[382] Total synthesis of the proposed structure from three key fragments revealed that although the synthetic compound had a similar optical rotation to that reported for the natural product, there were significant differences in the NMR spectral data, particularly associated with the two *N*-methyl valine residues. The originally assigned structure may need revision.[383] A convergent total synthesis of lodopyridone, the unusual alkaloid originally isolated from *Saccharomonospora* sp., (sediment, La Jolla Submarine Canyon, USA),[384] was achieved in nine linear steps *via* cross-coupling of an iodopyridone fragment with a (quinolinethiazolyl)stannane.[385] Marinoquinoline A, a pyrroloquinoline alkaloid obtained from the gliding bacterium *Rapidithrix thailandica*,[386,387] has been synthesised from commercially available starting materials in six linear steps.[388] Synthesis of tirandamycin C, a tetramic acid originally isolated from a *Streptomyces* sp.,[389] has been completed[390] and the total synthesis of maremycin B, originally isolated from a marine *Streptomyces* sp.,[391] has been accomplished starting from L-isoleucine and *S*-methyl-L-cysteine.[392] Salinipyrone A, a polyketide of the Palauan actinomycete *Salinispora pacifica*,[393] has been prepared in 14% yield *via* an eight step procedure from a vinylketene silyl *N*,*O*-acetal.[394] Macrosphelide M, originally isolated from the fungus *Periconia byssoides* associated with the sea hare *Aplysia kurodai*,[395] has been synthesised from diacetone glucose.[396] As a positional isomer of macrosphelide E, this isomer has also been synthesised as part of a library of all 16 diastereomers of the natural products macrosphelides A and E.[397] (±)-Penostatin B, originally isolated from *Penicillium* sp. associated with the green alga *Enteromorpha intestinalis*,[398] has been synthesised utilising a diastereoselective Pauson–Khand reaction and a relay ring-closing metathesis.[399] 7a(*S*)-*p*-Hydroxyphenopyrrozin, sourced originally from the fungus *Chromocleista* sp. (sediment, Gulf of Mexico),[400] has been synthesised in an enantiospecific manner from L-proline utilising base-mediated cyclisation and oxygenation as key steps.[401] An improved method for the sulfenylation of 2,5-diketopiperazines utilising alkali metal hexamethyldisilazide bases has been employed in the synthesis of gliotoxin G,[258] a metabolite of the marine fungus *Penicillium* sp.[402] Balticolid, a 12-membered macrolide, originally isolated from an Ascomycetous fungus separated from driftwood,[403] has been synthesised utilising a Hoveyda–Grubbs II catalyst assisted ring-closing metathesis.[404] Also reported are the syntheses of phomolides G and H, nonenolides originally obtained from an endophytic *Phomopsis* sp. of the mangrove *Kandelia candel*,[405] from (*R*)-epichlorohydrin.[406] 7′,8′-Dihydroaigialospirol, a metabolite of the mangrove fungus *Aigialus* parvus,[407] was prepared in a highly convergent synthesis.[408] Apratoxin D, a cytotoxic cyclodepsipeptide obtained from *Lyngbya majuscula* and *Lyngbya sordida* from Papua New Guinea,[409] has been synthesised by a procedure which utilised an Evans *syn*-aldol and a Paterson *anti*-aldol reaction amongst the key asymmetric transformations employed.[410] The linear depsipeptide grassystatin A, originally isolated from *Lyngbya cf. confervoides*,[411] has been synthesised by a [4 + 6] strategy.[412] Total synthesis of gambieric acid A, a polycyclic ether metabolite of the dinoflagellate *Gambierdiscus toxicus*,[413] has been accomplished,[414] which reinforced the previously established revised stereostructure.[415] Amphidinolide F, originally obtained from the dinoflagellate *Amphidinium* sp.,[416] has been synthesised in 34 steps which included silver-catalysed dihydrofuran formation.[417]

3.9 Assorted bioactivities

The dibenzodiazepine alkaloid diazepinomicin, isolated as a metabolite of a *Micromonospora* sp. associated with the ascidian *Didemnum proliferum*,[418] has broad-spectrum antitumour activity. It has now been shown to be a potent antioxidant and an inhibitor of the proteases rhodesain and cathepsin L.[419] Prodigiosin,[420] a tripyrrole red pigment with immunosuppressive and anticancer activities was found to exhibit selectivity for

cells overexpressing the gene ErbB-2, so could show potential in human breast cancer therapy.[421] *Streptomyces praecox* (brown alga *Undaria pinnatifida*, S. Korean coast) produced the known (6*S*,3*S*)-6-benzyl-3-methyl-2,5-diketopiperazine (bmDKP)[422] and (6*S*,3*S*)-6-isobutyl-3-methyl-2,5-diketopiperazine[423] which both exhibited antifouling activity (inhibited zoospore settlement).[424] Several known alkaloids were obtained from *Bacillus pumilus* (black coral *Antipathes* sp., Otoque Is., Panama), of which 3-hydroxyacetylindole[425] and *N*-acetyl-β-oxotryptamine[426] were inhibitors of growth of *Trypanosoma cruzi* with moderate cytotoxicity to Vero cells.[427] Several known bacterial metabolites, including 2-undecen-1′-yl-4-quinolone,[428] 3-hexyl-6-pentyl-4-hydroxyl-2*H*-pyran-2-one[429] and 6-heptyl-3-hexyl-4-hydroxyl-2*H*-pyran-2-one[430] were isolated from *Alteromonas* sp. (seawater, Masan Bay, S. Korea) as potent algicides.[431] The diterpene lobocompactol was originally isolated from the soft coral *Lobophytum compactum*[432] but has now been obtained from *Streptomyces cinnabarinus* (seaweed, S. Korean Coast), where increased production was induced by co-culture with *Alteromonas* sp. Lobocompactol exhibited significant antifouling activity against the macroalga *Ulva pertusa* and the diatom *Navicula annexa* and inhibited growth of fouling bacteria.[433]

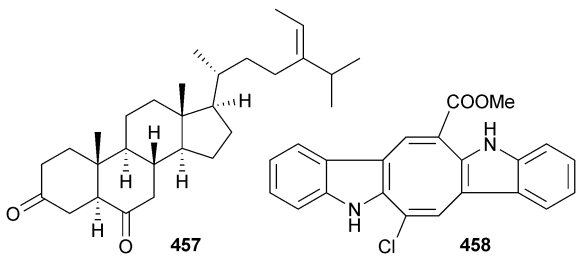
3.10 Biosynthesis

A series of genetic experiments involving the discovery and heterologous expression of the biosynthetic genes for marinopyrroles, 1,3′-bipyrrole metabolites of a *Streptomyces* sp.,[434,435] has indicated that two flavin-dependent halogenases catalyse the unprecedented *N*,*C*-bipyrrole homocoupling reaction.[436] Haterumalides are antitumour halogenated macrolides obtained from terrestrial plant-associated bacteria,[437,438] and subsequently from a marine sponge[439] and an ascidian.[440] The biosynthetic gene cluster for the potent oocydin A (haterumalide NA) was identified by genome sequencing, comparative genomics and chemical analysis and found to be organised into three transcriptional units encoding *trans*-acyltransferase polyketide synthases.[441] Several *Streptomyces* species[389,442,443] have yielded tirandamycins, metabolites that target bacterial RNA polymerase. Inactivation of the enzyme TrdE, a putative glycoside hydrolase within the tirandamycin biosynthetic cluster, leads to accumulation of pre-tirandamycin. *In vitro* and site-directed mutagenesis studies demonstrated that TrdE catalyses the installation of the $\Delta^{11,12}$ double bond during tirandamycin biosynthesis in an atypical manner.[444] Caerulomycins and collismycins are two groups of bacterial metabolites which contain a 2,2′-bipyridine core. Caerulomycins have been isolated from both terrestrial and marine[445] sources, whilst collismycins are terrestrial in origin. Cloning of the caerulomycin biosynthetic gene cluster enabled mining of a highly conserved gene cluster encoding collismycin biosynthesis in a *Streptomyces* strain previously unknown as a 2,2′-bipyridine producer. *In vitro* and *in vivo* experiments indicated that caerulomycins and collismycins share a common paradigm with an atypical hybrid PKS/NPRS system responsible for the 2,2′-bipyridine core formation.[446] Treatment of a strain of *Penicillium purpurogenum* (sediment, Bohai Bay, Tianjin, China) with the antibiotic gentamicin produced a mutant in which previously silent gene clusters were activated to produce antitumour compounds of four different chemical types: janthinone,[447] fructigenine A,[448] aspterric acid methyl ester[449] and citrinin,[450] demonstrating the potential of this approach to elicit dormant fungal metabolic potential.[451] Haloroquinone is a protein kinase B inhibitor and antitumour polyketide obtained from the fungus, *Halorosellinia* sp.[452] Feeding experiments on *Halorosellinia* sp. with [2-^{13}C]malonate and [1,2,3-$^{13}C_3$]malonate indicated that fifteen carbon atoms of the haloroquinone skeleton were derived from malonate, eight from the methylene group and seven from the carboxyl group, thus determining its origin *via* a polyketide pathway using malonyl-CoA as both the starter and the extender unit.[453] The biosynthesis of two *N*-acylated dihydropyrroles, (8*E*)-1-(2,3-dihydro-1*H*-pyrrol-1-yl)-2-methyldec-8-ene-1,3-dione and 1-(2,3-dihydro-1*H*-pyrrol-1-yl)-2-methyldecane-1,3-dione, originally isolated from terrestrial *Penicillium brevicompactum*[454] but subsequently also obtained from a marine-derived *Penicillium citrinum*,[455] has been investigated in the latter species. Feeding experiments utilising ^{13}C-labelled precursors established that the biosynthesis of both metabolites involves the incorporation of acetate, methionine and ornithine.[456] Reduction of emodin, a metabolite of both marine[457] and terrestrial[458] fungal origin, by sodium dithionite, resulted in the formation of two tautomeric forms of emodin hydroquinone. Subsequent conversion by the short-chain dehydrogenase/reductase (SDR) enzyme MdpC into the corresponding 3-hydroxy-3,4-dihydroanthracen-1(2*H*)-one implies that deoxygenation is the first step in the biosynthesis of the marine[459] and terrestrial[460] fungal metabolite monodictyphenone.[461] NotB, the enzyme which catalyses the indole 2,3-oxidation of the *Aspergillus* metabolite notoamide E[462] to notoamides C[462] and D[462] through an apparent pinacol-like rearrangement, has been characterised *in vitro*. Precursor incorporation experiments utilising [^{13}C]$_2$-[^{15}N]$_2$ quadruply labelled notoamide S,[463] demonstrated that notoamide S is a pivotal branching point in notoamide biosynthesis.[464,465] Stable-isotope labelling experiments on the endophyte *Fusarium incarnatum* (mangrove embryo *Aegiceras corniculatum*, unspecified source) indicated that the *Fusarium* processes coriolic acid, didehydrocoriolic acid and an epoxy fatty acid derived from linoleic acid by a process involving Δ^{15}-desaturation and 13-lipoxygenation.[466] The epoxy fatty acid was isolated in minute quantities as an inseparable mixture of diastereoisomers.[466] The ladder-frame polyether yessotoxin (YTX) is produced by the dinoflagellate *Protoceratium reticulatum*. Culture of *P. reticulatum* under an $^{18}O_2$ atmosphere and with supplementation of the culture media with [$^{18}O_2$]-acetate, followed by collision-induced dissociation tandem mass spectrometry (CID MS/MS) of the labelled yessotoxin, indicated that the ether oxygens were labelled from $^{18}O_2$ and the hydroxy oxygen on C-32 was derived from [$^{18}O_2$]-acetate. This supports the proposed biosynthetic mechanism of marine ladder-frame polyethers that a polyene precursor is oxidised by a monooxygenase after acetate condensation.[467] The biosynthetic origin of the okadaic acid water-soluble ester derivative DTX5c[468] was investigated by addition of sodium [1-^{13}C]- and

[2-^{13}C]-acetate to artificial cultures of the dinoflagellate *Prorocentrum belizeanum* and indicated that the polyketide backbone is interrupted by three "m-m" sequences in the ester side chain.[469] The finding in 2011 that the ascidian-derived didemnins are produced by an α–proteobacterium of the genus *Tistrella*[470] has been followed by another significant paper in 2012 reporting that *T. mobilis* (Red Sea and other sources) also produced didemnins. A putative didemnin biosynthetic gene cluster has been isolated from the genome of the Red Sea species. This locus encodes a 13-module hybrid NPRS–PKS enzyme complex for the synthesis of the acyl glutamine didemnins X and Y, precursors to didemnin B. Mass spectrometry of *T. mobilis* bacterial colonies captured the time-dependent extracellular conversion of didemnins X and Y to didemnin B.[471] The discovery of the didemnin biosynthetic gene cluster potentially obviates the supply problems that presently hinder the development of the didemnins as therapeutic agents as well as paving the way for the engineering of new didemnin congeners.

4 Green algae

There were just two new metabolites reported from publications on green algae in 2012. Research into *Tydemania expeditionis* (Yellow Sea, China) defined the new ketosteroid **457** along with three known sterols and established modest activity against prostate cancer cells.[472] The other new metabolite characterised was the weakly antifungal chloro-bisindole **458** from *Caulerpa racemosa* (Zhanjiang coastline, China) isolated along with caulerpin and two related caulerpin derivatives.[473]

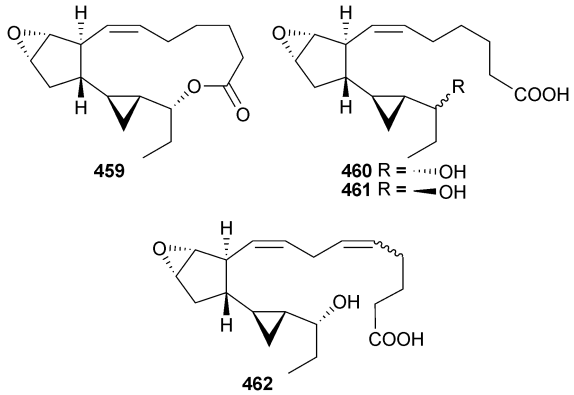


457 **458**

Included in the green algal literature for 2012 were a number of papers, that while not reporting new compounds, are worthy of comment. These include the finding that separate isoprenoid-24-alkyl sterol pathways have evolved in fungi and green algae which converge to yield ergosterol,[474] the role of caulerpin as a potential antiviral drug against HSV Type 1,[475] tetrapyrrolic pigments as photosensitisers for photodynamic therapy[476] and a careful evaluation of the antioxidant activity of a wide range of Hawaiian brown, red and green algae.[477] Also of interest was the identification of 208 volatile compounds from the green alga, *Capsosiphon fulvescens*, used by Koreans for centuries for its unique taste and flavour properties.[478]

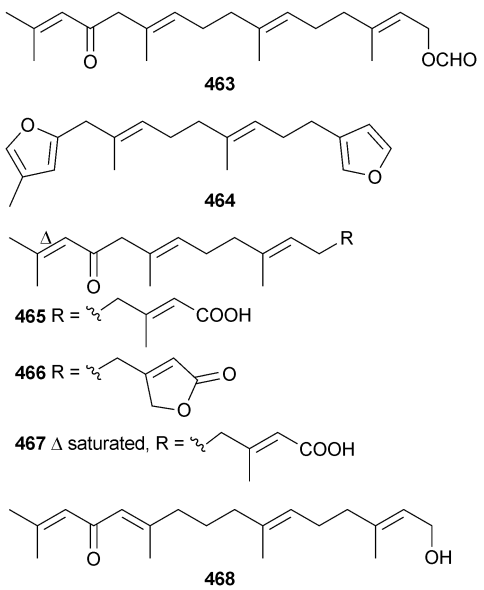
5 Brown algae

The chemistry of the Ochrophyta in 2012 was again dominated by terpenoids and phenolics and, as for the Chlorophyta, the number of new compounds characterised was relatively low. Further investigation into the chemistry of *Cymathere triplicata* (Deception Pass, Washington, USA) led to the characterisation of the unusual polycyclic oxylipins cymatherelactone **459** and cymatherols A–C **460–462** (isolated as the methyl esters).[479,480] A plausible biogenesis for **459–461** was offered.

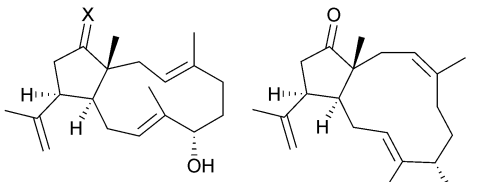


459 **462**

Two studies on *Bifucaria bifurcata* (Roscoff, France) defined the metabolic makeup of this alga with the isolation of the sesquiterpenoids formyleleganolone **463**, bibifuran **464** and four new eleganolone derivatives **465–468**.[481,482] Also isolated were eleganolone,[483] five previously described eleganolone derivatives[484–488] and 16-hydroxygeranylgeraniol[489] (isolated for the first time from this species) which collectively can be correlated in a hypothetical metabolic grid.[482]

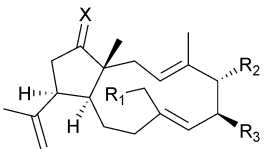


In a follow-up study the structures and relative configurations of a further 13 dolabellane diterpenoids **469–481** from the alga *Dilophus spiralis* (Elafonissos Is., Greece) were described along with the antibacterial properties of **469–477** and **481**. The absolute configuration of **469** was determined and extended by implication across the series.[490]

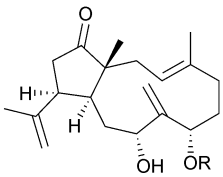


†**469** X = H,H
470 X = O

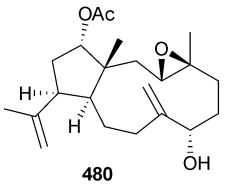
471



472 R_1 = OH, R_2 = R_3 = H, X = H,H
473 R_1 = OAc, R_2 = R_3 = H, X = H,H
474 R_1 = OAc, R_2 = R_3 = H, X = O
475 R_1 = R_2 = H, R_3 = OAc, X = O
476 R_1 = R_3 = H, R_2 = OAc, X = O



477 R = Ac
478 R = H



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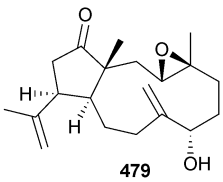

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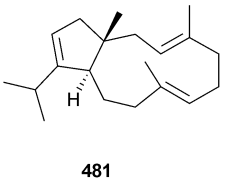
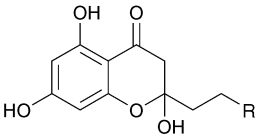
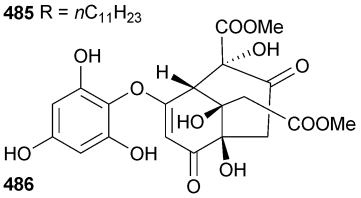


481

Investigation of the kinase and antibacterial activity of *Zonaria spiralis* (North Walkerville, Victoria, Australia) led to the isolation of the hemiketal spiralisones A–D, **482–485**. These are phloroglucinol-derived lipids and were isolated as racemates. The relative instability of the spiralisones, the zero optical rotation and the isolation of co-occuring chromones corresponding to dehydration of spiralisones B and D led to a biogenetic scheme, biomimetic syntheses of spiralisones A and D and raised the possibility that previously reported algal chromones could be artefacts of isolation.[491] Radical scavenging activity led to the isolation of sargussumol **486** from *Sargassum micracanthum* (Wando County, Jeonnam province, S. Korea).[492]



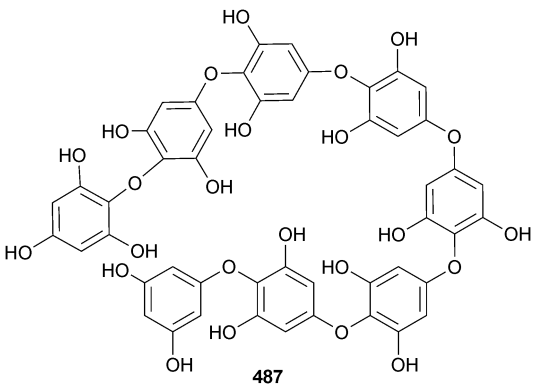
482 R = ^{s}(CH=CH)$_4$C$_4$H$_9$
483 R = ^{s}(CH=CH)$_5$
484 R = nC$_{13}$H$_{27}$
485 R = nC$_{11}$H$_{23}$



486

Sargussumol was the phenolic rather than the methyl ether (sargussumketone) previously isolated from *S. kjellmanianum*.[493]

From a survey of 15 algae from the Sea of Japan for α-amylase activity, the phlorotannin DDBT was found in *Sargassum patens* (Noto Peninsula, Japan). DDBT was a potent competitive inhibitor of α-amylase and also inhibited α-glucosidase suggesting a potential role as a natural nutraceutical to prevent diabetes.[494] DDBT was claimed as a new compound but had earlier been found in *Cystophora congesta*.[495] The phlorotannin octaphlorethol A **487** from the S. Korean brown alga *Ishige foliacea* (Jeju Is.) mediated glucose uptake and as such has potential as an antidiabetic,[496] while another Jeju Is. brown alga, *Ecklonia cava*, was the source of 2,7″-phloroglucinol-6,6′-bieckol **488**, a new antioxidant.[497]



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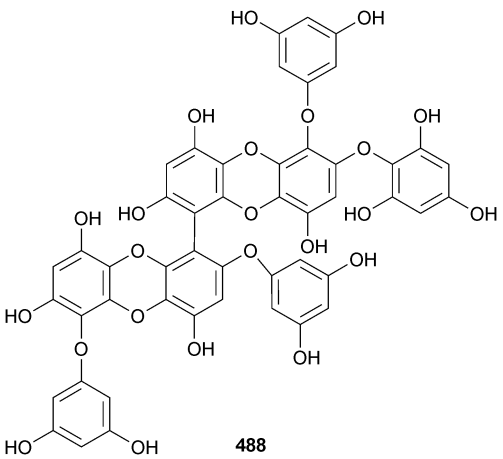
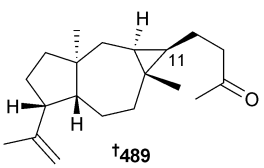


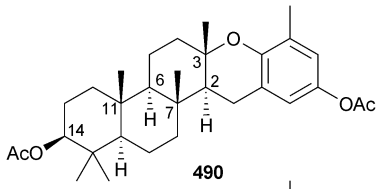
488

The absolute configuration of dilospirane B (*Dilophus spiralis*, Elafonissos Is., Greece)[498] has been assigned as **489** following conformational analysis and TDDFT calculations on the preponderant conformers (~92% of the total population) of the (11*R*)-enantiomer. This afforded a negative Cotton Effect comparable to that observed experimentally.[499]

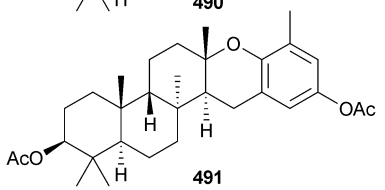


†**489**

In light of the confusion that has surrounded the absolute configurations of the meroditerpenoids taondiol[500,501] and epitaondiol[502] vibrational CD (VCD) approaches have been used to clarify the situation.[503] The diacetates were used in the study rather than the free alcohols which often show intermolecular solute–solute associations that complicate comparison of experimental and DFT calculated spectra. The calculations showed that the absolute configuration of taondiol diacetate **490** is (2*S*,3*S*,6*R*,7*R*,10*R*,11*R*,14*S*) and that of epitaondiol diacetate **491** is (2*S*,3*S*,6*S*,7*S*,10*R*,11*R*,14*S*) with single crystal X-ray analyses to support the relative configurations.



490

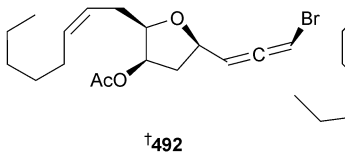


491

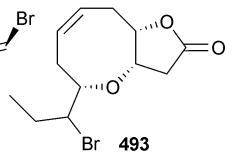
A stereoselective synthesis of the *trans*-hydrindane core of dictyoxetane[504] has been reported,[505] as has the development of "borono-sclareolide", a terpenyl radical precursor that can be produced on the multi-gram scale allowing rapid access to a wide variety of meroterpenoids. This was demonstrated by the synthesis of 10 meroterpenoids, the majority being of marine origin.[506] The C_{40} allenic-carotenoid fucoxanthin has been synthesised by a stereocontrolled route that also led to a longer chain (C_{42}) analogue.[507] The taxonomic implications of the re-isolation of five known diterpenoids of the dictyol series from *Dictyota guineensis* (Penha Beach, Brazil)[508] and of a known meroditerpenoid[509] from *Cystoseira nodicaulis* (Penmarc'h, Brittany, France) were considered.[510] The incidence of betaines in species of the Laminariales was studied[511] and two papers have been published on the biological properties of sargachromanol G from *Sargassum siliquastrum*[512] covering anti-inflammatory properties[513] and the expression of osteoclastogenic factors.[514] The tyrosinase inhibitory activity of dieckol from *Eklonia cava*[515] was examined *in silico* against mushroom tyrosinase and an effective binding site defined suggesting that dieckol has potential for further development as a pharmaceutical or cosmetic agent.[516] A particularly interesting techniques paper was the application of electrochemical methods to guide the isolation of antioxidants from crude samples. This was illustrated with the isolation of four known antioxidants from *Sargassum elegans* (Noordhoeck, Port Elizabeth, South Africa).[517]

6 Red algae

The 46 new compounds reported from red algae in 2012 is similar to the number reported from the previous year (42). Three bromoallenes, including the new dihydroitomanallene B **492**, were obtained from *Laurencia nangii* (Sabah, Malaysia).[518] Desepilaurallene **493** is a C_{12}-acetogenin extracted from *L. okamurai* (Rongcheng, China), along with four new sesquiterpenes described later in this section.[519] A different collection of *L. okamurai* (Weihai, Shandong Province, China) also contained a mixture of a C_{12}–acetogenin okamuragenin **494** and five new sesquiterpenes (see later).[520] An on-line/off-line HPLC–NMR study of an extract from *Plocamium angustum* (Pt. Lonsdale, Vic., Australia)[521] revealed the known halogenated monoterpene plocamenone, but with the revised structure **495** shown here, and the new isomeric compound isoplocamenone with the structure **496** previously ascribed to plocamenone.[522]



†**492**



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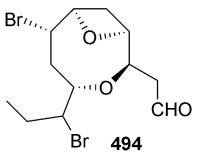

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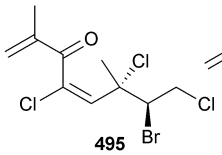

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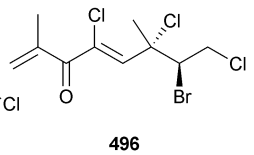
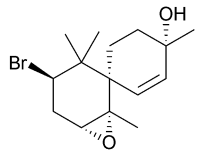


496

The brominated chamigrenes **497** and **498** and cuparene **499**, together with the known sesquiterpene **500**, but new as a natural product, were isolated from the same *L. okamurai* that yielded the C_{12}-acetogenin **493** described earlier. The sesquiterpene **500** had potent antibacterial activity.[519] In a separate paper, but resulting from this same collection of *L. okamurai*, three additional halogenated chamigrenes laurokamin A–C **501–503** were characterised.[523]



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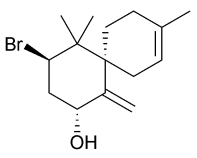

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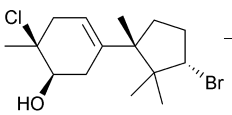

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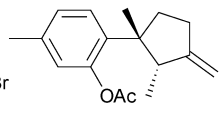

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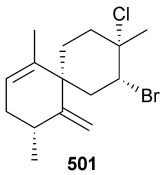

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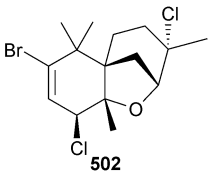

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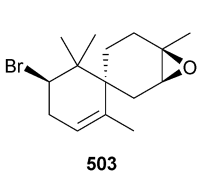
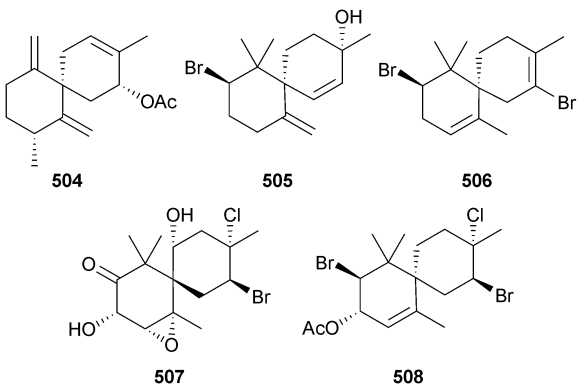


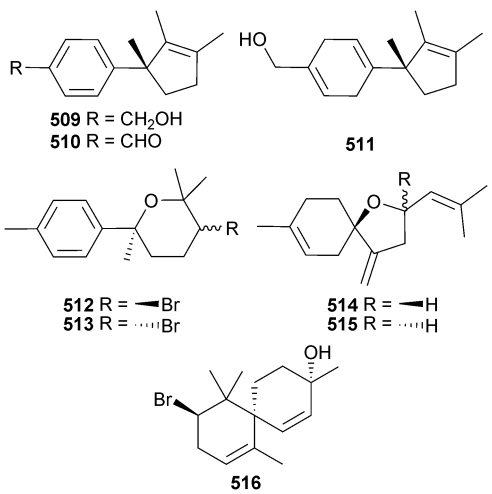
503

Four new chamigranes laurecomin A–D **504–507** and the sesquiterpene **508** were isolated from *L. composita* (Pingtan Is., China). Laurecomin B was the only compound showing antifungal activity.[524]



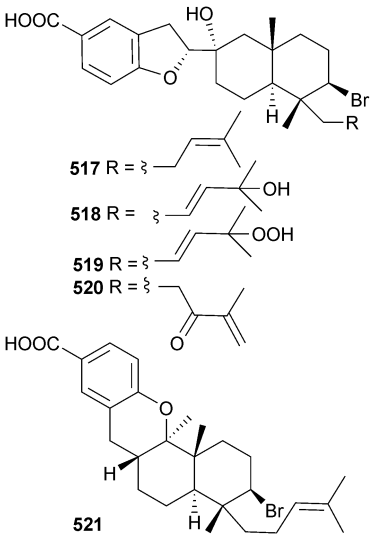
504 **505** **506** **507** **508**

A Red Sea (Jeddah, KSA) collection of *L. obtusa* yielded three new laurene sesquiterpenes **509–511** all of which had strong antibacterial activity, while **510** also had significant antifungal and antitumour activities.[525] Four new bisabolanes okamurene A–D **512–515** and the new chamigrane okamurane E **516** were obtained from the earlier-described *L. okamurai*.[520]



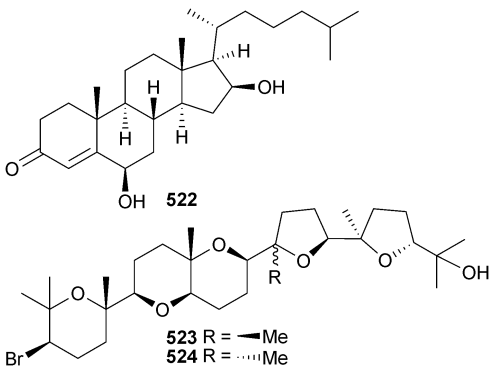
509 R = CH_2OH
510 R = CHO
511
512 R = —Br
513 R = ····Br
514 R = —H
515 R = ····H
516

The structure proposed for the sesquiterpene aldingenin B (*L. aldingensis*)[526] has been synthesised, but discrepancies between the spectroscopic data of the synthetic and natural material suggest that the claimed structure is incorrect.[527] From a Fijian (Mango Bay Resort, Viti Levu) collection of *Callophycus* sp., five new compounds of the diterpene–benzoate class, bromophycoic acids A–E **517–521**, were isolated. These compounds displayed a range of activities in antitumour, antimalarial and antibacterial assays.[528]



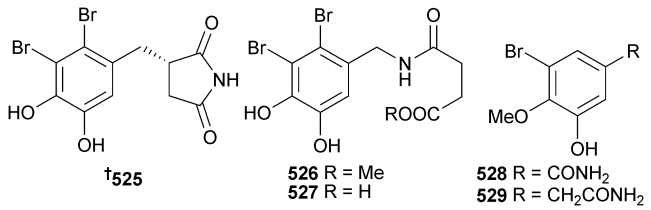
517 R = ≀
518 R = ≀
519 R = ≀
520 R = ≀
521

The antigenotoxic ketosteroid **522** was obtained from an extract of *Jania adhaerens* (Al-Shoaiba coast, Red Sea).[529] The two new cytotoxic oxasqualenoids saiyacenol A **523** and B **524** were obtained from *Laurencia viridis* (Callao Salvaje, Tenerife, Canary Is.).[530] These compounds share a significant part of their structures with aplysiol B, and with the definition of the stereocentre configurations in the saiyacenols well established, it was possible to confirm with more certainty the recently proposed structural revision for aplysiol B.[531]



522
523 R = —Me
524 R = ····Me

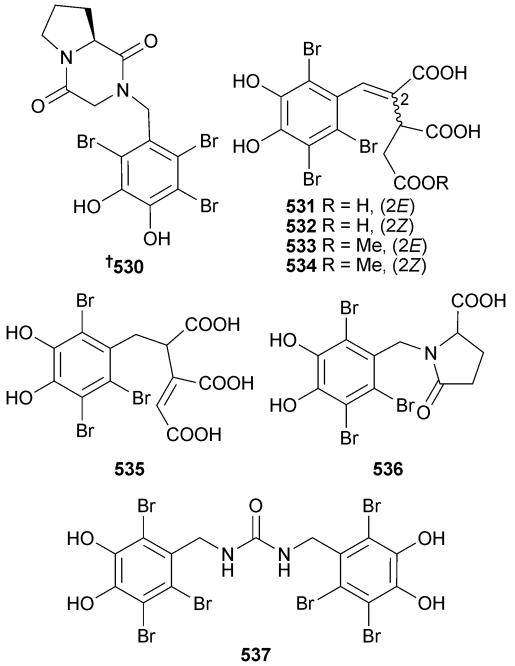
Bromophenols are frequently reported from red algae, and an additional 13 were described in 2012. The potently radical scavenging bromophenols **525–529** were obtained from *Rhodomela confervoides* (Dalian, Liaoning Province, China).[532]



†**525**
526 R = Me
527 R = H
528 R = $CONH_2$
529 R = CH_2CONH_2

A collection of *Symphyocladia latiuscula* (Qingdao, Shandong Province, China) provided a bromophenol coupled to a diketopiperazine **530**.[533] In another paper, this same collection of *S. latiuscula* was reported as having produced the symphyocladins

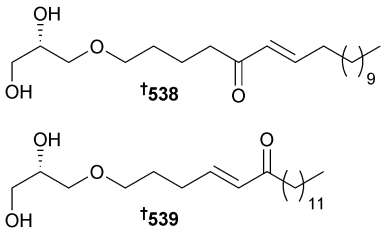
A–G **531–537**. Symphyocladin G showed modest antifungal activity.[534]



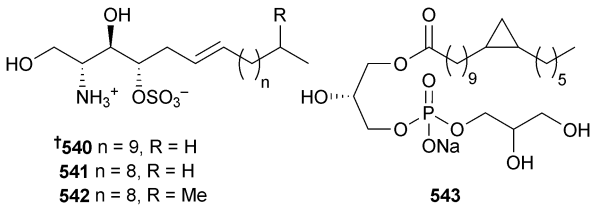
Several papers described new biological activities for red algal metabolites, including anti-HSV-1 and HSV-2 glycolipids from *Osmundaria obtusiloba*,[535] antitumour effects of elatol from *Laurencia microcladia*,[536] antinociceptive and anti-inflammatory extracts from *Bryothamnion triquetrum*[537] and anti-human rhinoviral activities of polybromocatechols from *Neorhodomela aculeata*.[538] Surface enhanced Raman spectroscopy combined with transposed Orthogonal Partial Least Squares (T-OPLS) provided chemical images of the antibacterial surface-active 1,1,3,3-tetrabromo-heptan-2-one on *Bonnemaisonia hamifera* at concentration levels of sub-femtograms per μm^2.[539]

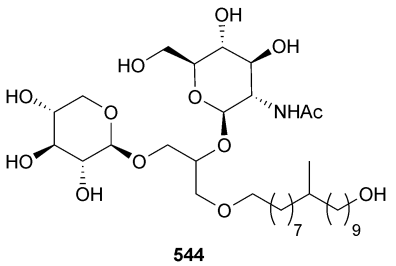
7 Sponges

The number of new compounds reported from marine sponges in 2012 (355) has increased by approximately 20% compared with 2011.[1] Pachastrissamine (*Pachastrissa* sp.),[540] also known as jaspine B, requires dual inhibition of both Forkhead box 03 (Fox03) and cyclin-dependent kinase 2 (Cdk2) to prevent melanoma cell growth.[541] Niphatenones A **538** and B **539** were isolated from *Niphates digitalis* (Pennville, Commonwealth of Dominica) and synthesised to permit bioactivity profiling. The enantiomers proved to be more active as androgen receptor inhibitors.[542]

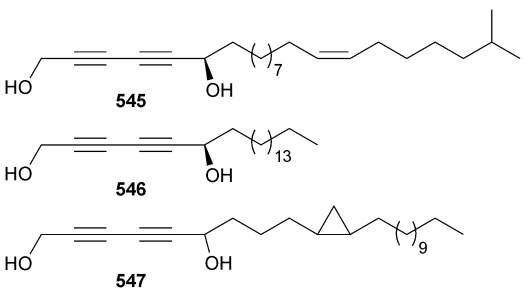


Leucettamols A and B (*Leucetta microrhaphis*)[543] act as non-electrophilic activators of transient receptor potential (TRP) ion channels and have potential as pain modulators.[544] A S. Korean *Spirastrella abata* yielded three sulfated sphingolipids **540–542** and one phosphorylated glycerol ether **543**.[545]

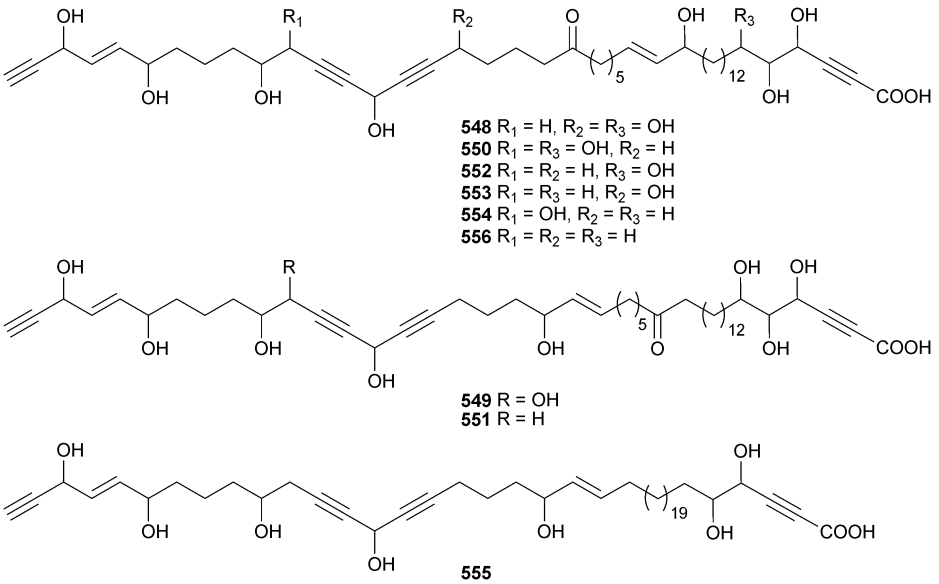




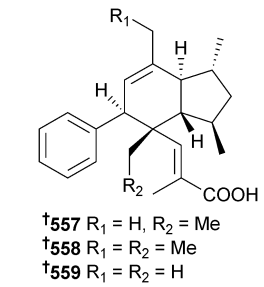
Myrmekioside E **544** is an acetylated glycolipid from *Myrmekioderma dendyi* (Epi Is., Vanuatu Archipelago) with moderate potency against lung tumour cells.[546] A Micronesian *Xestospongia* cave sponge was the source of three polyacetylenes **545–547** with low μM activity against *Pseudomonas aeruginosa* (*P. aeruginosa*),[547] while an extract of *Haliclona fulva* (Procida Is., Gulf of Naples, Italy) contained the nine acetylenes fulvyne A–I **548–556**.[548]

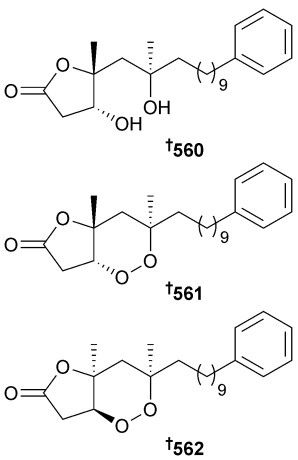


The structures of plakotenin **557** (*Plakortis* sp.),[549] homoplakotenin **558** and norplakotenin **559** (*Plakortis lita*)[550] have been revised following total synthesis and intensive spectroscopic characterisation.[551,552] Two comprehensive synthetic, chemical and spectroscopic investigations of various plakortolide congeners (*Plakinastrella clathrata*) have confirmed that

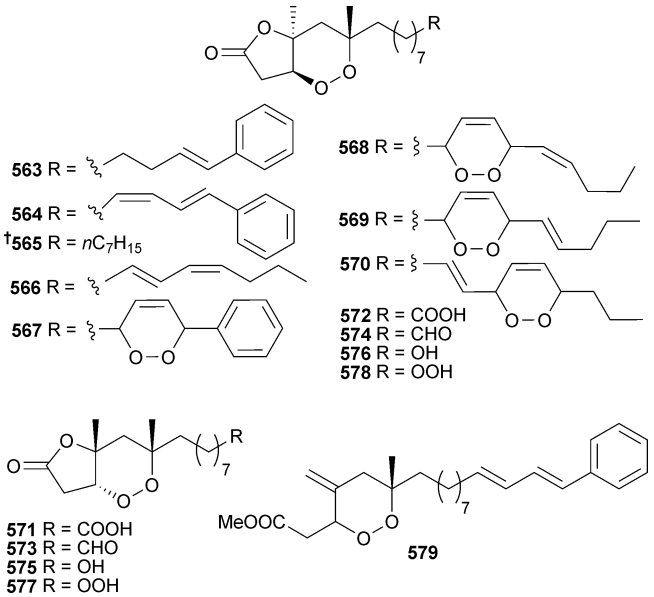


the originally reported plakortolides E (*Plakortis* sp.)[553] and I (*Plakortis simplex*)[554] are actually *seco*-plakortolide E **560** and plakortolide E **561**, respectively, and that a related but previously unnamed variant from *Plakinastrella* sp.[555] is plakortolide I **562**.[556,557] *Warning*: it was shown that optical rotation alone is not a reliable predictor of absolute configuration in this structural class.[556]

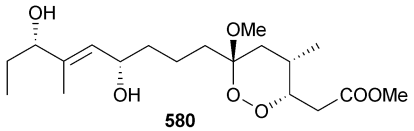




Further investigation of *P. clathrata* (Gneerings Reef, Mooloolaba, Australia) yielded plakortolides T–W **563–566**, plakortoperoxides A–D **567–570**, carboxyplakortolides 1 **571** and 2 **572**, and a series of other related metabolites **573–579** with **569–579** isolated as mixtures of diastereomers.[558]



Manadoperoxides E–K **580–586** and peroxyplakoric ester C **587** are potent antiprotozoals (*Trypanosoma brucei rhodesiense*) from *Plakortis lita* (Bunaken, Sulawesi, Indonesia).[559] Mycalamide E **588** and congeners (*Mycale hentscheli*, Pelorus Sound, New Zealand) are potent protein synthesis inhibitors that are not actively transported by drug efflux pumps in yeast.[560]



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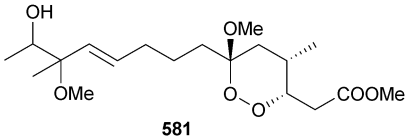

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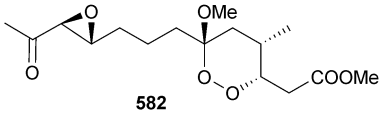

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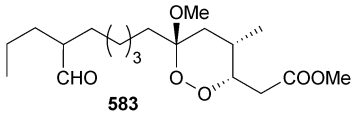

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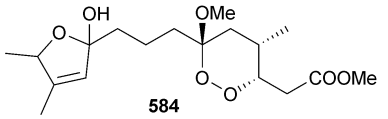

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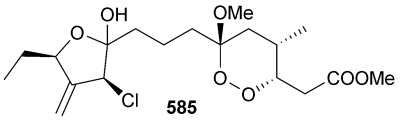

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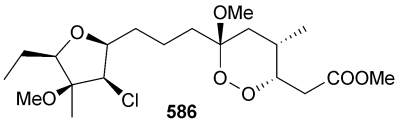

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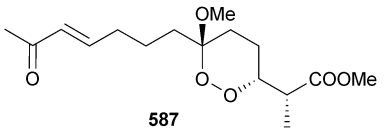

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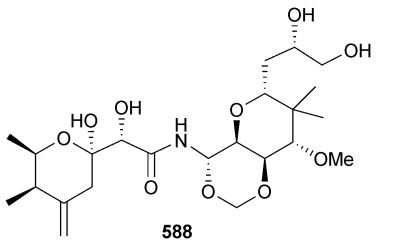
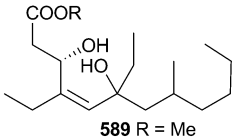


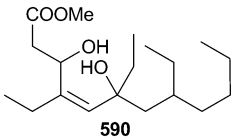
588

Investigations of *Plakortis simplex* (Yongxing Is., South China Sea) revealed the moderately antifungal woodylides A–C **589–591**,[561] and the less active simplexolides A–E **592–596** and plakorfuran A **597**.[562]

A Fijian *Plakinastrella mamillaris* contained plakilactones A–F **598–603** and gracilioether D **604**. Plakilactone C has potential



589 R = Me
591 R = H



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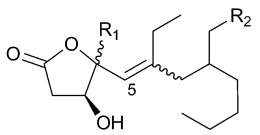
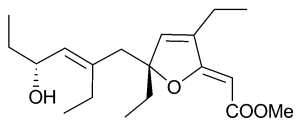
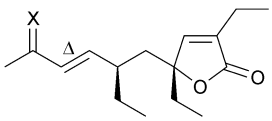


592 R_1 = ····Et, R_2 = H, (5*E*)
593 R_1 = ◄Et, R_2 = H, (5*Z*)
594 R_1 = ◄Et, R_2 = Me, (5*E*)
595 R_1 = ◄Et, R_2 = Me, (5*Z*)
596 R_1 = ◄Et, R_2 = H, (5*E*)

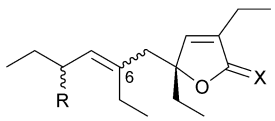


597

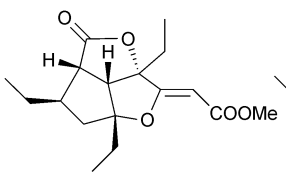
as an antidiabetic and anti-arthrosclerosis agent due to its covalent binding to the peroxisome proliferator-activated receptor γ (PPARγ), inhibiting adipocyte gene transcription.[563] Further investigation of the same sponge sample yielded gracilioethers E–J **605–610** with only gracilioether H being antimalarial (*P. falciparum*), highlighting the importance of the peroxide functionality for activity.[564]



598 X = H,H, Δ saturated
599 X = ◄OH,H
600 X = O



601 R = ····OH, X = O, (6*Z*)
602 R = ◄OH, X = O, (6*Z*)
603 R = ◄OH, X = O, (6*E*)
604 R = ◄OH, X = CHCOOMe, (6*E*)



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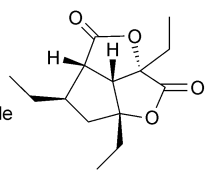

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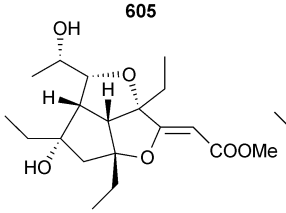

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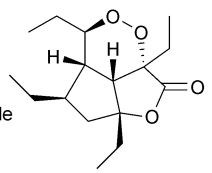

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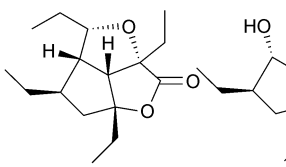

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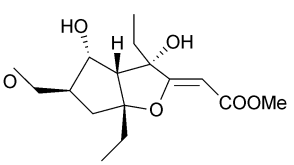
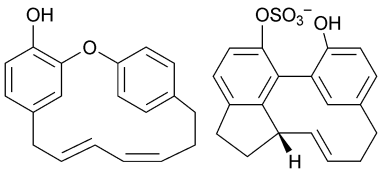


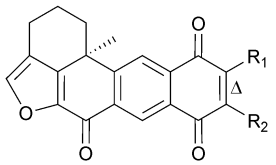
610

Tedarenes A **611** and B **612** are atropisomeric compounds from *Tedania ignis* (Sweetings Cay, Bahamas) with tedarene A inhibiting NO-production in LPS-induced macrophages.[565] The published structure of a dimethoxy binaphthyl compound from *Lendenfeldia* sp. has been shown to be incorrect,[566] and is likely a brominated biphenyl.[567]



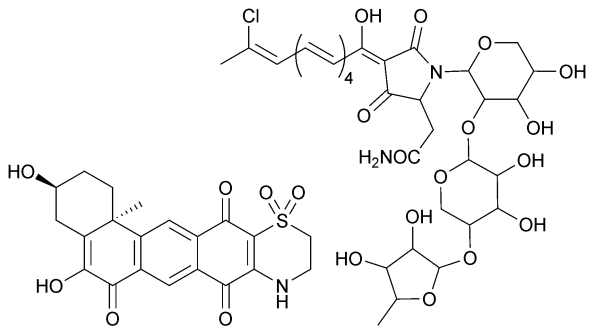
611 †612

A Malaysian *Petrosia alfiani* yielded 14-hydroxymethylxestoquinone **613**, 15-hydroxymethylxestoquinone **614** and 14,15-dihydroxymethylxestoquinone **615**, all of which activated the hypoxia-inducible factor-1 (HIF-1). Moreover, **613** enhanced respiration and decreased mitochondrial membrane potential suggesting its mode of action uncouples mitochondrial respiration.[568]

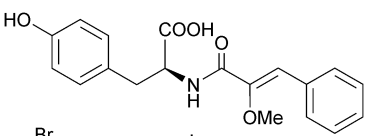


613 R_1 = H, R_2 = CH_2OH
614 R_1 = CH_2OH, R_2 = H
615 R_1 = R_2 = H, Δ saturated

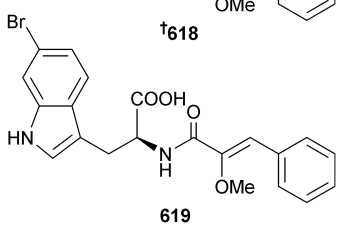
Xestosaprol N **616** has been reported from a *Xestospongia* sp. (Weno Is., Chuuk State, Federated States of Micronesia),[569] while the antifungal aurantoside K **617** was isolated from a species of *Melophlus* (Cicia, Lau group of Fiji).[570] Iotrochamides A **618** and B **619** (*Iotrochota* sp., Curacao Is., Queensland) were both moderately selective against *Trypanosoma brucei*.[571]



616 617

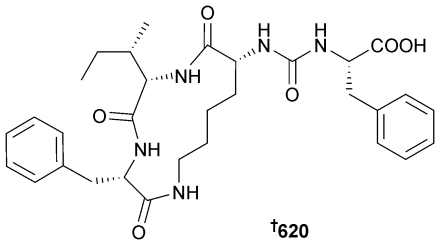


†618

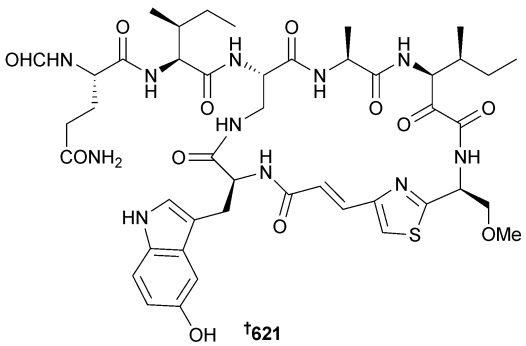


619

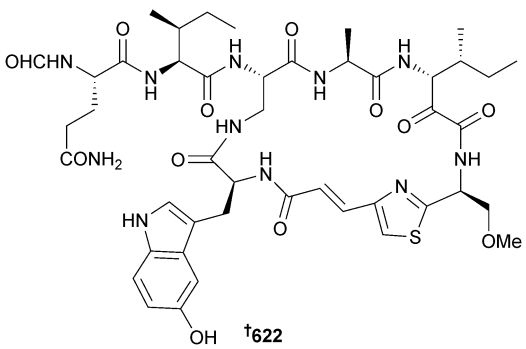
The total synthesis of (−)-irciniastatin B (*Ircinia ramosa*)[572] has been achieved.[573] The accepted structure of cyclocinamide A (*Psammocinia* sp.), originally reported in 1997 and revised in 2008,[574,575] has been disproven by synthesis leaving the structure of the natural product as a mystery.[576] Namalide **620** is a potent carboxypeptidase A inhibitor isolated from *Siliquariaspongia mirabilis* (Nama Is., Chuuk Lagoon, Federated States of Micronesia). The structure of **620** was confirmed by solid-phase synthesis.[577] The Lithistid sponge *Discodermia calyx* (Shikine-Jima Is., Japan) provided the moderately antiproliferative calyxamides A **621** and B **622**.



†620

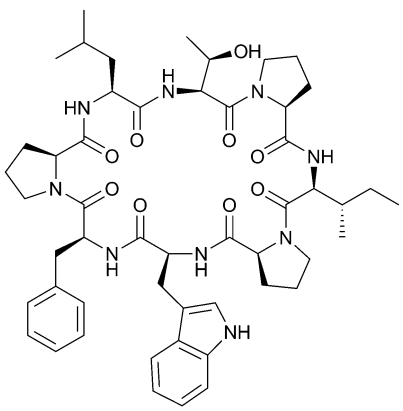


†621



†622

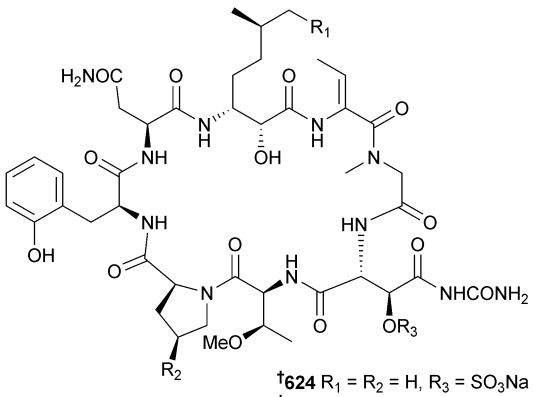
The presence of metagenomic DNA from the filamentous bacterium Candidatus *Enthotheonella* sp. that produces similar



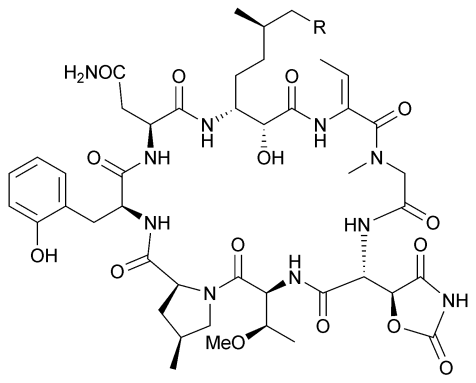
†623

cyclopeptides in other sponges suggested that the calyxamides are produced by a symbiont.[578] The proline-rich octapeptide stylissamide X **623** was reported from *Stylissa* sp. (Biak, Indonesia), and inhibited HeLa cell migration at sub-inhibitory concentrations.[579]

Droplet counter-current chromatography (DCCC) was used to isolate perthamides G–K **624–628** from a *Theonella swinhoei* (Solomon (Malaita) Is.). All of the perthamides isolated had some anti-inflammatory activity, suggesting structure activity relationships (SAR) were linked to the γ-methylproline, 3-amino-2-hydroxy-6-methylheptanoic acid and 2-amino-2-(2,4-dioxooxazolidin-5-yl)acetic acid side-chains.[580]

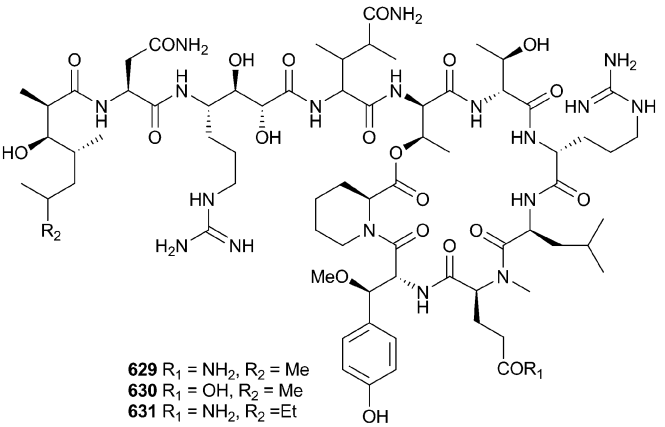


†**624** $R_1 = R_2 = H$, $R_3 = SO_3Na$
†**625** $R_1 = R_3 = H$, $R_2 = Me$
†**626** $R_1 = R_2 = Me$, $R_3 = H$

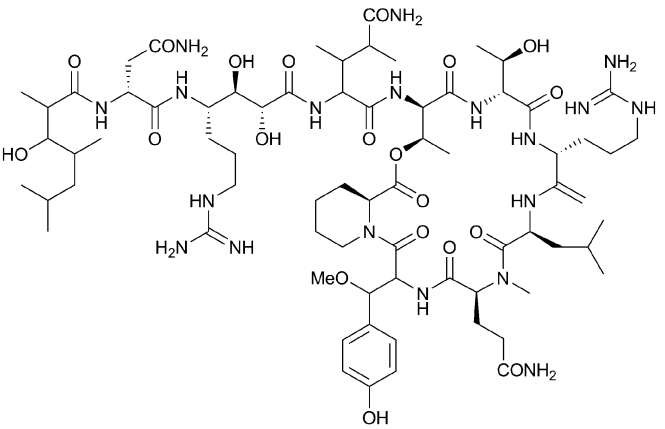


†**627** R = H
628 R = Me

The sponge *Neamphius huxleyi* (Milln Reef, Cape Grafton, Queensland) yielded neamphamides B–D **629–631** as potent and non-selective cytotoxins.[581] An earlier report had used the name neamphamide B to describe **632** from *Neamphius* sp. (Okinawa, Japan), which inhibited the growth of *Mycobacterium smegmatis*.[582] Neither report detailed the full stereochemical assignment of the isolated material, but they are different compounds as **632** is claimed to contain a D-Asn while **629** has L-Asn at the same position.

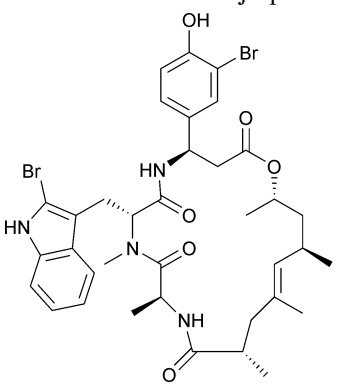


629 $R_1 = NH_2$, $R_2 = Me$
630 $R_1 = OH$, $R_2 = Me$
631 $R_1 = NH_2$, $R_2 = Et$



632

The sponge *Pipestela candelabra* (Guadalcanal, Solomon Is.) contained the mixed NRPS-PKS pipestelides A–C **633–635**, which are related to the well known jaspamides.[583]



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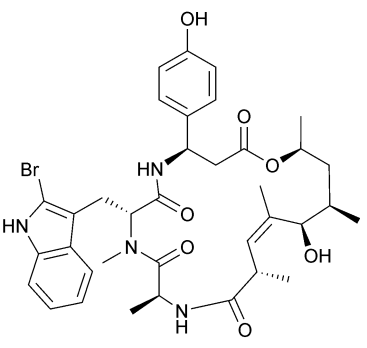

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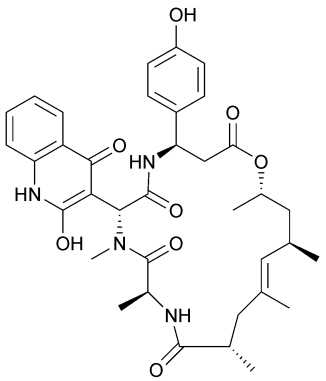
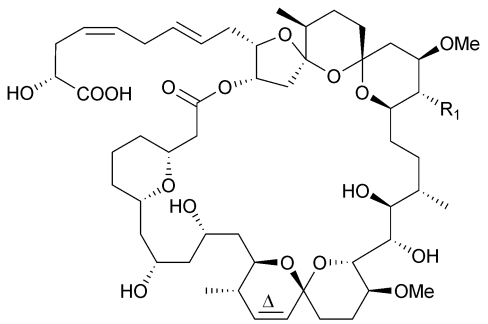
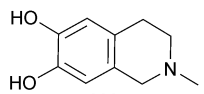


635

The absolute configuration of both leiodermatolide (*Leiodermatium* sp.)[584] and callipeltoside B (*Callipelta* sp.)[585] were confirmed as originally drawn by total synthesis,[586,587] while salarin C (*Fascaplysinopsis* sp.)[588] was a potent activator of apoptosis.[589] Spirastrellolides A **636** and B **637** were isolated from an *Epipolasis* sponge (Nagannu Is., East China Sea) as the free acids, although the methyl esters had been prepared previously to aid isolation of the natural products (*Spirastrella coccinea*).[590–592] The free acids are more cytotoxic than their methyl esters.[593]



636 R_1 = Cl
637 R_1 = H, Δ = saturated



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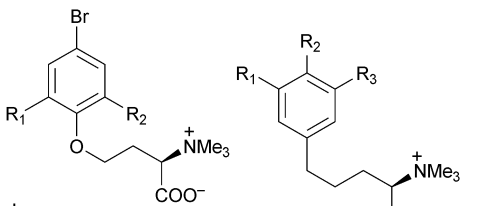
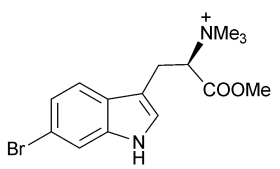


†**639** R_1 = R_2 = Br
†**640** R_1 = Br, R_2 = H
†**641** R_1 = R_2 = Cl
†**642** R_1 = Br, R_2 = I
†**643** R_1 = Br, R_2 = Cl

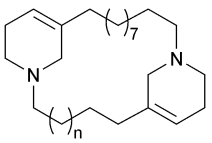
644 R_1 = R_3 = I, R_2 = OMe
645 R_1 = R_3 = I, R_2 = OH
646 R_1 = Br, R_2 = OMe, R_3 = I
647 R_1 = Br, R_2 = OH, R_3 = I



648

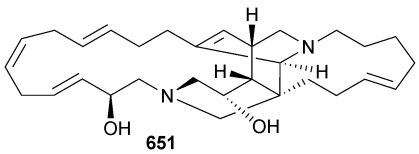
The first total synthesis of halichondrin B (*Halichondria okadai*)[594] has been achieved.[595] *N*-Methylnorsalsolinol **638** is a radical scavenging antioxidant from *Xestospongia* sp. (Bougainville Reef, Queensland),[596] while purpuroines A–J **639–648** are halogenated zwitterionic amino acid derivatives with antimicrobial and kinase inhibitory activities isolated from *Iotrochota purpurea* (Sanya, Hainan, China).[597]

Fuscain (*Phacellis fusca*)[598] has been synthesised.[599] The structures of haliclamines G **649** and H **650** have been reported from *Haliclona viscosa* (Kongsfjorden, Svalbard, Norway) and confirmed by synthesis.[600]



649 n = 7
650 n = 9

A Petrosid sponge collected from the Coral Sea (Queensland, Australia) yielded the potent antimalarials 22-hydroxyingamine A **651** and dihydroingenamine D **652** with activities in the low ng mL^{-1} range against various strains of *P. falciparum*.[601]



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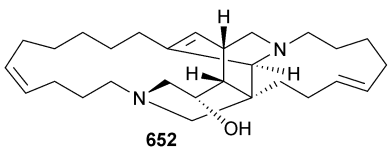
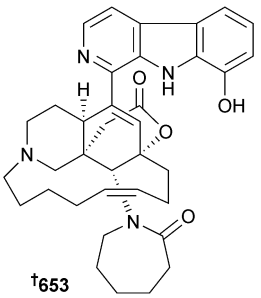


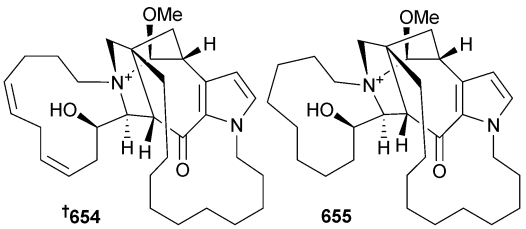
652

(−)-8,15-Diisocyano-11(20)-amphilectene (*Hymeniacidon amphilecta*)[602] and 7,15-diisocyano-11(20)-amphilectene[603] (*Hymeniacidon* sp.) are potent inhibitors (nM range) of thromboxane B_2 suggesting potential as neurological anti-inflammatory agents,[604] while bengamides A and B, originally isolated from a Jaspidae sponge,[605] are potent immune modulators inhibiting NFκB at non-toxic concentrations (nM range) in RAW264.7 cells. The isolation of bengamides from a myxobacterial source (*Myxococcus virescens*) suggests a possible microbial, not sponge, origin for this class of compound.[606]

Acantholactone **653** was isolated from an Indonesian *Acanthostrongylophora* sp. but the bioactivity profile could not be established due to a paucity of material.[607] The densanins A **654** and B **655** were reported from *Haliclona densaspicula* (Keomun Is., S. Korea) and inhibited NO production in LPS-stimulated BV2 monoglial cells.[608]

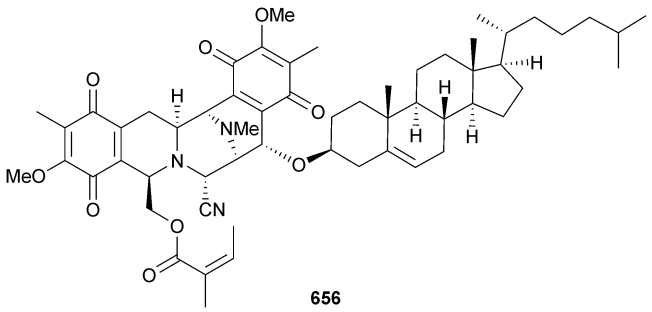


†653



†654 655

Renieramycin V **656** (*Xestospongia* sp.) is the first compound of the class to be conjugated to a sterol,[609] while pre-treatment of another *Xestospongia* sp. (Puerto Galera, Philippines) with KCN unsurprisingly yielded the cyano-derivatives renieramycin W–Y **657–659**.[610]



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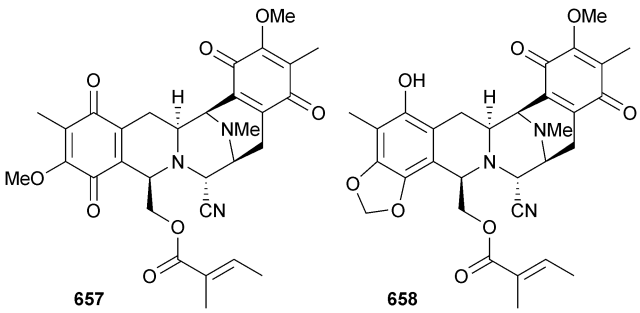
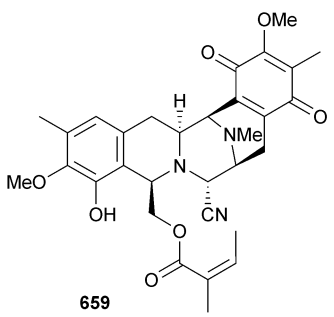
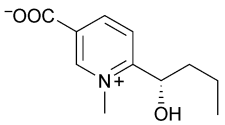


657 **658**



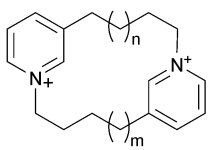
659

The sponge *Axinella polypoides* (Calvi, Corsica, France) was the source of a new betaine **660**.[611] The asymmetric total synthesis of nakinadine B (*Amphimedon* sp.)[612] has been accomplished, although the original report did not contain an optical rotation so the absolute configuration of the natural product cannot be confirmed.[613]

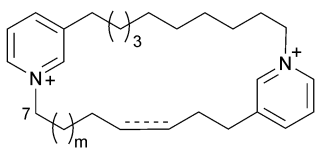


†660

Sponges continue to be a rich source of 3-alkylpyridinium alkaloids. Investigation of a *Haliclona* sp. (Sagyeri, Jeju Is., S. Korea) revealed cyclostellettamines N **661** and Q **662**, along with eight unnamed congeners **663–670**.[614] While cyclostellettamines N and Q have been reported as synthetic intermediates previously,[615,616] this is their first report as natural products.

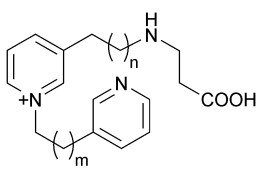


661 m = 7, n = 6
662 m = 8, n = 7
663 m = 7, n = 5
664 m = n = 6



665 m = 4, Δ^{12}, (*E*)
666 m = 4, Δ^{13}, (*Z*)
667 m = 5, Δ^{9}, (*Z*)
668 m = 5, Δ^{15}, (*Z*)
669 m = 6, Δ^{13}, (*Z*)
670 m = 6, Δ^{15}, (*Z*)

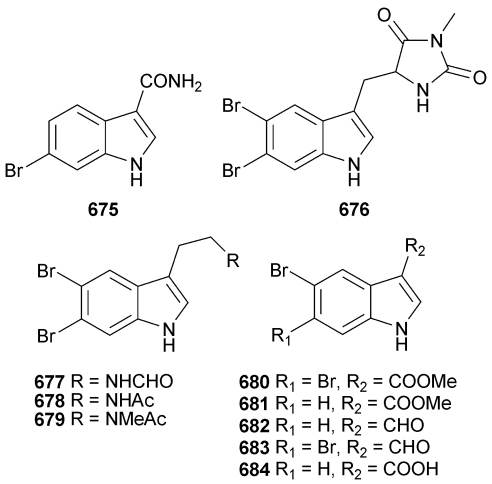
An Arctic *Haliclona viscosa* (Blomstrandhalvøya, Svalbard, Norway) yielded viscosalines B_1 **671**, B_2, **672**, E_1 **673** and E_2 **674**, with the structures established from NMR and comprehensive mass spectrometric fragmentation studies using different ionisation sources. The structures were confirmed by total synthesis.[617]



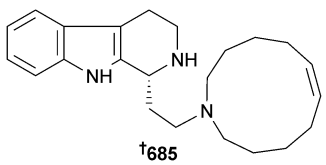
671 m = 11, n = 12
672 m = 12, n = 11
673 m = 12, n = 13
674 m = 13, n = 12

The proposed use of polymeric 3-alkylpyridinium alkaloids (*Reniera sarai*) as therapeutic adjuvants may be unwise due to their cardiotoxicity.[618] *Mycale fibrexilis* (Hainan Is., China) was

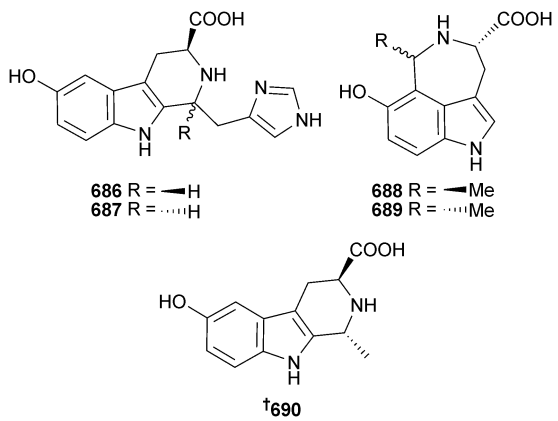
the source of the 6-bromo-1*H*-indole-3-carboxamide **675**,[619] while a Thai *Smenospongia* sponge (PP Is., Krabi Province) provided a series of brominated indole alkaloids **676–684**, isolated from a natural source for the first time.[620]



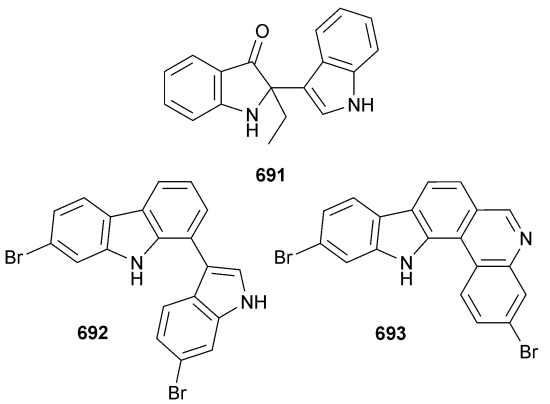
The synthesis of keramamine C **685** (*Amphimedon* sp.)[621] established the absolute configuration.[622]



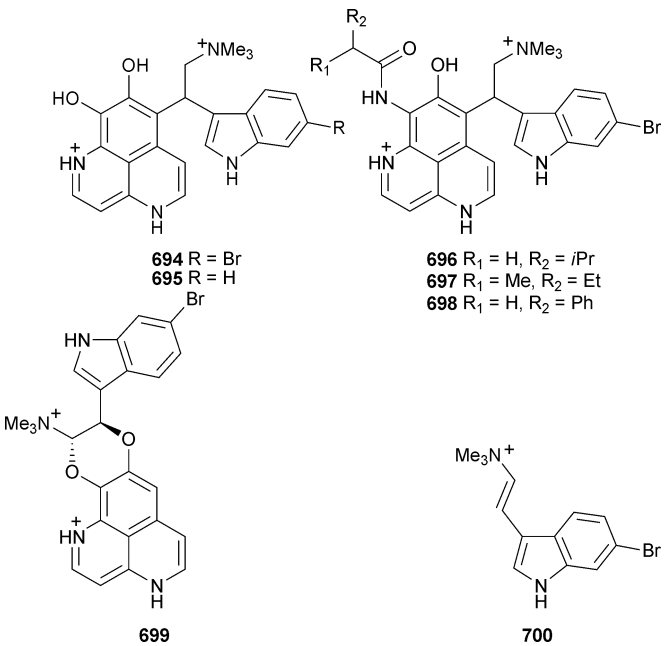
Hyrtioreticulins A–E **686–690** were reported from *Hyrtios reticulatus* (N. Sulawesi, Indonesia) with hyrtioreticulins A and B inhibiting the formation of the E1-ubiquitin-activating enzyme and having promise as anti-cancer proteasome modulators.[623]



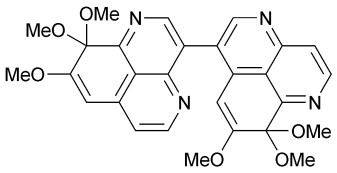
Heterologous expression of a biosynthetic gene cluster isolated from metagenomic DNA extracted from *Halichondria okadai* led to the isolation of the yellow pigment halichrome A **691**.[624] Two brominated β-carbolines **692** and **693** have been isolated from a species of *Penares* collected by dredging at 95 m in the South China Sea.[625]



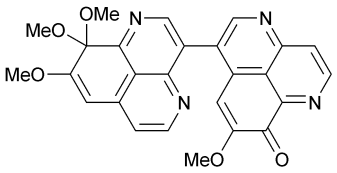
A *Suberites* sponge (Unten Port, Okinawa) was the source of nakijinamines A **694**, B **695**, F–I **696–699** and 6-bromoconicamin **700**. Nakijinamines A, B, F and I were isolated as racemates.[626]



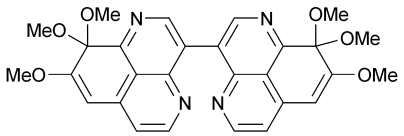
Suberitines A–D **701–704** were isolated from *Aaptos suberitoides* (Xisha Is., South China Sea), and are low micromolar inhibitors of P388 cells. They are thought to occur naturally *via* radical dimerisation.[627]



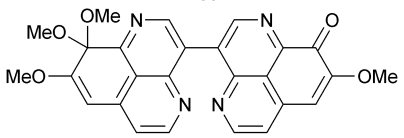
701



702

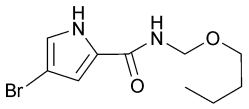


703

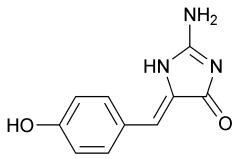


704

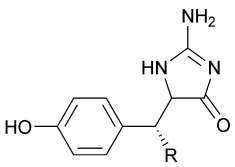
The bromopyrrole **705** was reported from *Agelas mauritiana* (Paracel (Xisha) Is.),[628] while phorbatopsins A–C **706–708** are anti-oxidant aminoimidazolines from *Phorbas topsenti* (Marseille, France).[629] Two new stevesines **709** and **710** and two debromolatonduines **711** and **712** have been isolated from an Indonesian *Stylissa* sp. (Derawan Is., Berau)[630]



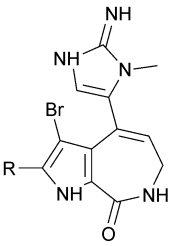
705



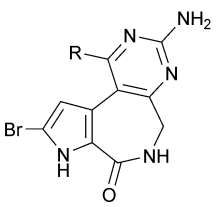
706



707 R = OH
708 R = H



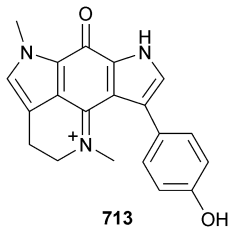
709 R = Br
710 R = H



711 R = COOMe
712 R = H

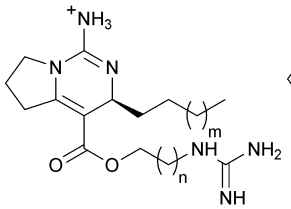
The original latonduines (*Stylissa carteri*)[631] are extremely potent correctors of ΔF508 protein misfolding by inhibition of the poly(ADP-ribose) polymerase (PARP) family, with latonduine A inhibiting PARP-3 in particular at the 400 pM level, whilst being totally inactive in all other assays tested. This makes the latonduines an important new lead for treatment of cystic fibrosis.[632] The bromopyrrole ageladine A (*Agelas nakamurai*)[633] has been used as an inherently fluorescent, pH-sensitive imaging molecule for transparent animals such as jellyfish.[634]

The pyrroloiminoquinone makaluvone (*Zyzzya* sp.)[635] has been synthesised,[636] while the related tsitsikammamine C **713** (*Zyzzya* sp., Rodda Reef, Queensland) was a potent antimalarial, inhibiting both chloroquine sensitive and resistant *P. falciparum* at the very low nM level.[637]

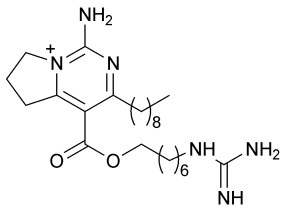


713

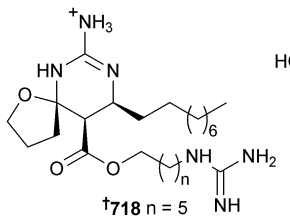
Eleven cytotoxic crambescins including the new congeners **714–721** have been reported from *Crambe crambe* (Villefranche-Sur-Mer, France).[638]



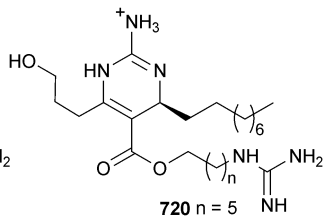
†**714** m = 9, n = 3
†**715** m = 10, n = 3
†**716** m = 6, n = 6



717

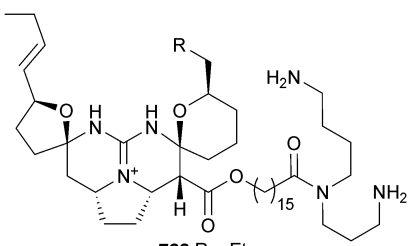


†**718** n = 5
†**719** n = 7



720 n = 5
†**721** n = 7

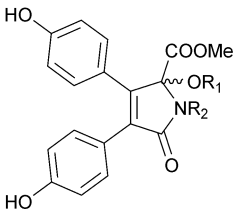
The structure of merobatzelladine B (*Monanchora* sp.)[639] has been confirmed by synthesis,[640] while the related monanchomycalins A **722** and B **723** were potent cytotoxins (low nM level) isolated from a dredged *Monanchora pulchra* (Sea of Okhotsk).[641]

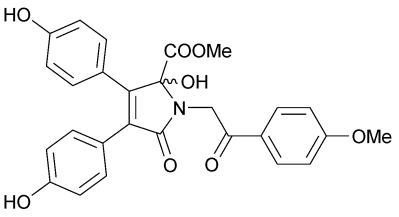


722 R = Et
723 R = H

Members of the kealiinine class (*Leucetta chagosensis*)[642] have been synthesised independently by two different groups,

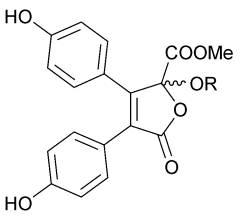
but with discrepancies in spectral data to those of the natural products noted. These discrepancies are likely due to different tautomeric forms.[643,644] An *Ianthella* sp. collected by trawling (Bass Strait, Australia) yielded ianthellidones A–H **724–731** and lamellarins O1 **732** and O2 **733**. The ianthellidones A–H were isolated as racemates.[645] The same sponge sample was also the source of the related dictyodendrins F–J **734–738**, with all but variant G being modest β-secretase (BACE) inhibitors making them potential anti-Alzheimer's agents.[646]

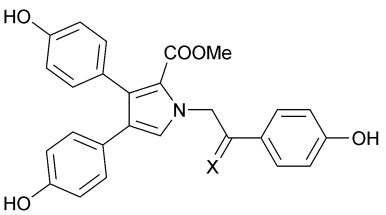




724 $R_1 = R_2 = H$
725 $R_1 = Et$, $R_2 = H$
726 $R_1 = H$, $R_2 = CH_2OMe$
727 $R_1 = H$, $R_2 = CH_2OEt$
728 $R_1 = H$, $R_2 = CH_2COOEt$

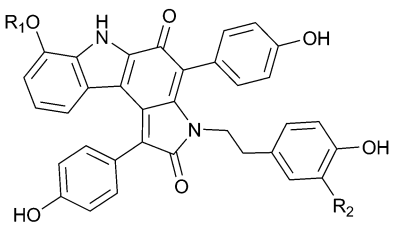
729



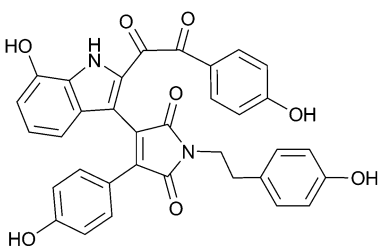


730 R = H
731 R = Me

732 X = O
733 X = H,OH

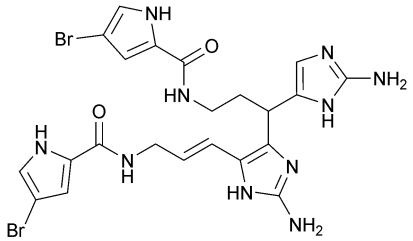


734 $R_1 = R_2 = H$
735 $R_1 = Me$, $R_2 = H$
736 $R_1 = H$, $R_2 = Br$
737 $R_1 = H$, $R_2 = I$



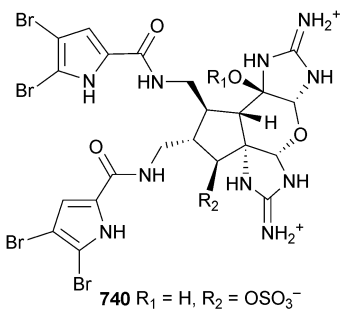
738

Didebromonagelamide A **739** was isolated from a Caribbean *Stylissa caribica* (Bahamas). Cell-free enzyme preparations from the same sponge and also *Agelas sceptrin* were able to catalyse the synthesis of benzosceptrin C (*Agelas* sp.)[647] and nagelamide H (*Agelas* sp.)[648] from oroidin (*Agelas oroides*).[649,650]

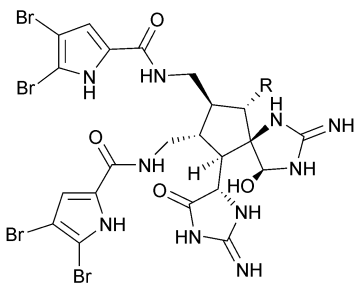


739

The "*meta*-biosynthetic" conversion of oroidin to the sceptrin and nagelamide families likely goes through a series of single electron transfer (SET) and radical processes.[651] The biomimetic SET-based syntheses of bromo- and dibromoageliferin (*Agelas* sp.)[652] were achieved.[653] An *Axinella* sponge (Great Australian Bight) yielded three new massadines **740–742**,[654] while *Axinella donnani* (Mauritius) was the source of donnazoles A **743** and B **744**, oxidised analogues of the postulated "preaxinellamine", the key intermediate to all dimeric pyrrole-aminoimidazole alkaloids.[655]

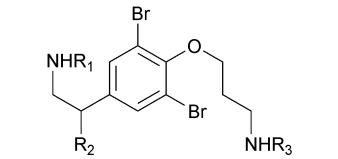


740 $R_1 = H$, $R_2 = OSO_3^-$
741 $R_1 = H$, $R_2 = OMe$
742 $R_1 = Me$, $R_2 = Cl$

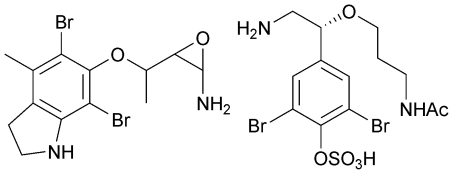


†**743** R = OH
†**744** R = Cl

Cavernicolin-1 and -2 (*Aplysina cavernicola*)[656] have been synthesised starting from 3,5-dibromoverongiaquinol (*Aplysina* sp.),[657,658] while ceratinines A–E **745–749** were reported from *Pseudoceratina arabica* (Hurghada, Egypt).[659] Ianthellamide A **750** is a modestly potent and selective inhibitor of kynurenine-3-hydroxylase isolated from *Ianthella quadrangulata* (Harrier Point, Orpheus Is., Queensland).[660]

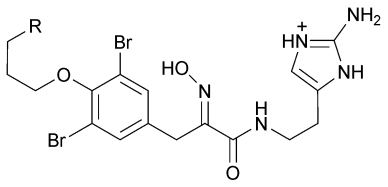


745 $R_1 = R_3 = H$, $R_2 = OMe$
747 $R_1 = R_2 = H$, $R_3 = CONH_2$
748 $R_1 = CHO$, $R_2 = H$, $R_3 = COCONH_2$
749 $R_1 = CHO$, $R_2 = H$, $R_3 = COOEt$

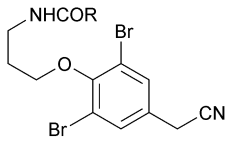


746 **750**

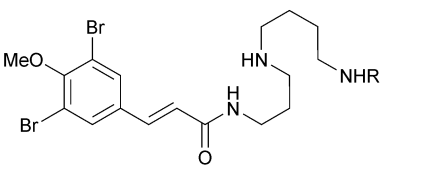
Tyrokeradines A–D **751–754** are bromotyrosine-derived alkaloids from an Okinawan Verongid sponge.[661] Examination of *Suberea ianthelliformis* (Manta Ray Bommie, Stradbroke Is., Australia) revealed the ianthelliformisamines A–C **755–757** that are selective inhibitors of *P. aeruginosa*.[662]

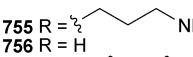
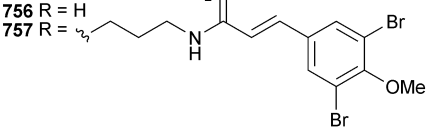


751 R = NHMe
752 R = NMe_2

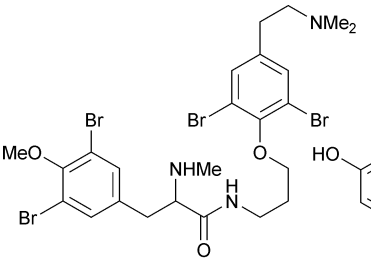


753 R = Me
754 R = Et



755 R = 
756 R = H
757 R = 

The syntheses of pseudoceramines A–D (*Pseudoceratina* sp.)[663] have been achieved,[664] as have the syntheses of psammaplin C and tokaradine A,[665,666] both from *Psammaplysilla purpurea*.[667] Aplysamine-2 (*Aplysina* sp.),[668] aplyzanzine A (*Aplysina* sp.),[669] anomoian A (*Anomoianthella popeae*),[670] purpurealidin E (*Psammaplysilla purpurea*)[671] and suberedamines A and B (*Suberea* sp.)[672] have all been synthesised for the first time, with the structure of anomoian A confirmed as **758**.[673] A *Pseudoceratina* sp. (Port Campbell, Victoria, Australia) contained aplysamine 7 **759**, purealins B–D **760–762**, (−)-purealidin R **763**, (−)-aerophobin 2 **764** and the racemic purealin **765**. Compounds **763** and **764** are the enantiomers of metabolites found from *Psammaplysilla purpurea* and *Verongia aerophoba*, respectively.[674–676]



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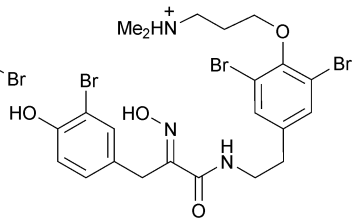

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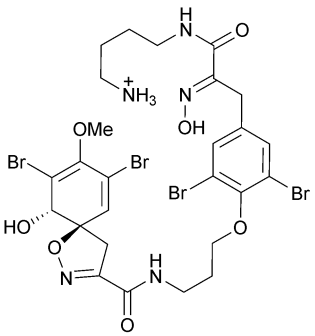

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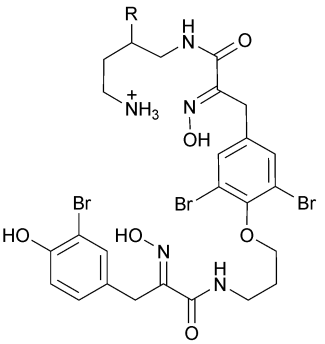
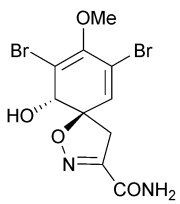
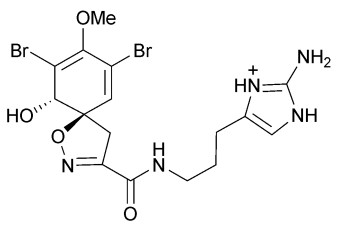


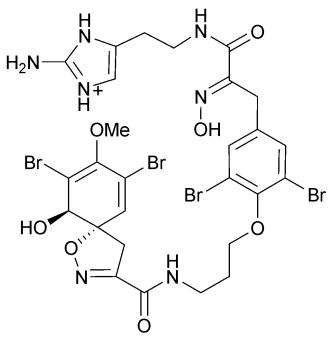
761 R = H
762 R = OH



763

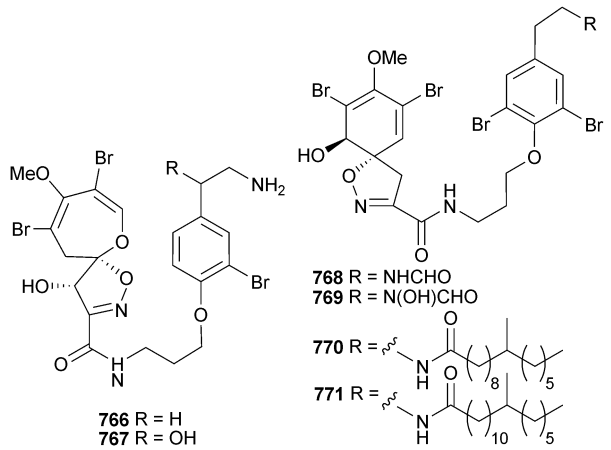


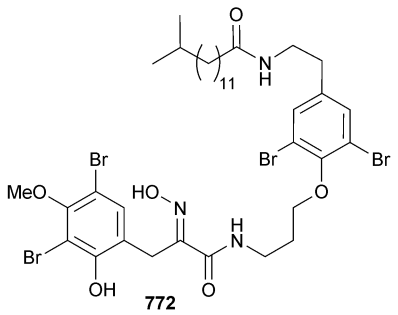
764



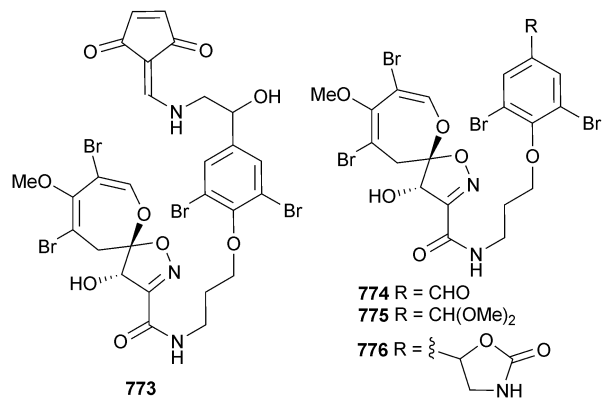
765

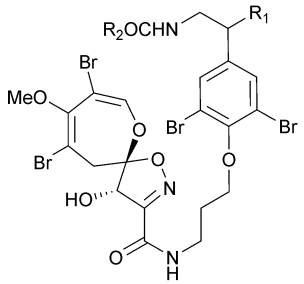
Psammaplysins I **766** and J **767** were reported from a "Twilight Zone" (50–1000 m depth) *Suberea* sponge collected in Guam,[677] while four individuals of *Suberea ianthelliformis* collected at various locations in the Solomon Islands yielded the five araplysillin congeners **768–772**. Araplysillin N-20 formamide **768** and araplysillin N-20-hydroxyformamide **769** are moderate antimalarials.[678]





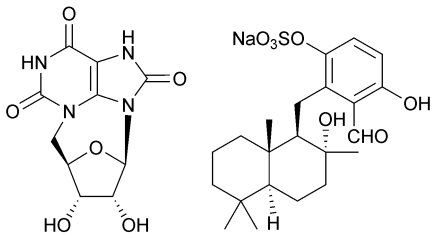
Twenty one psammaplysin variants **773–793** were isolated from *Aplysinella strongylata* (Tulamben Bay, Bali, Indonesia), although only 19-hydroxypsammaplysin E **773** showed any activity against *P. falciparum.*[679]

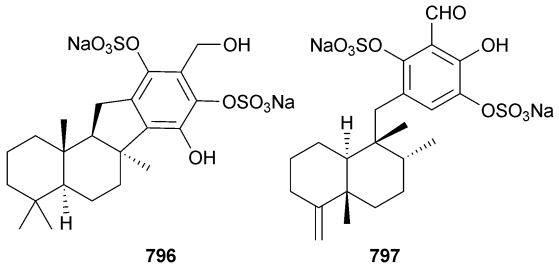


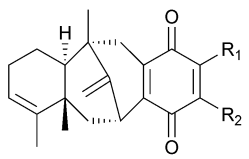


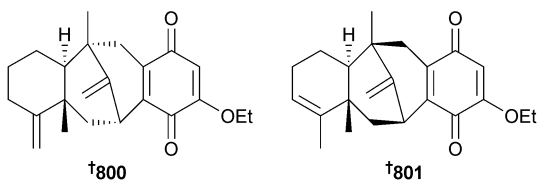
777 R_1 = H, R_2 = CH_2OH
778 R_1 = H, R_2 = $C_{12}H_{24}$*i*Pr
779 R_1 = H, R_2 = $C_{15}H_{31}$
780 R_1 = H, R_2 = $C_{17}H_{35}$
781 R_1 = OH, R_2 = $C_{17}H_{35}$
782 R_1 = H, R_2 = $C_{13}H_{27}$
783 R_1 = OH, R_2 = $C_{13}H_{27}$
784 R_1 = OH, R_2 = $C_{11}H_{22}$sBu
785 R_1 = H, R_2 = $C_{12}H_{24}$sBu
786 R_1 = OH, R_2 = $C_{12}H_{24}$sBu
787 R_1 = H, R_2 = $C_{14}H_{28}$sBu
788 R_1 = OH, R_2 = $C_{14}H_{28}$sBu
789 R_1 = H, R_2 = $C_{13}H_{24}$*i*Pr Δ^9 (9*Z*)
790 R_1 = OH, R_2 = $C_{13}H_{24}$*i*Pr Δ^9 (9*Z*)
791 R_1 = H, R_2 = $C_{15}H_{29}$ Δ^9 (9*Z*)
792 R_1 = H, R_2 = $C_{18}H_{35}$ Δ^{12} (12*Z*)
793 R_1 = OH, R_2 = $C_{18}H_{35}$ Δ^{12} (12*Z*)

The synthesis of dioxepine bastadin-3 (*Ianthella reticulata*)[680] has been achieved.[681] A new cyclonucleoside **794** has been reported from *Axinella polypoides* (Calvi, Corsica, France).[611] Siphonodictyal sulfate **795** and akadisulfates A **796** and B **797** are antioxidant merosesquiterpenoids from *Aka coralliphaga* (Quintana Roo, Mexico),[682] while dysideavarones A–D **798–801** are cytotoxic merosesquiterpenes from *Dysidea avara* (Xisha Is., South China Sea). The absolute configurations of dysideavarones A–D were determined by comparison of DFT-calculated and experimental ECD measurements.[683]

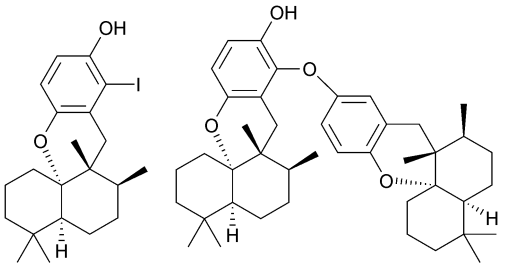






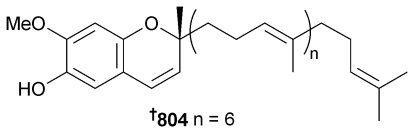


A *Smenospongia* sponge (PP Is., Thailand) was the source of the iodine-containing 6′-iodoauerol **802** and the dimeric 6′-aueroxyaureol **803**.[620] The total synthesis of akaol A (*Aka* sp.)[684] confirmed the absolute configuration as originally drawn.[685]

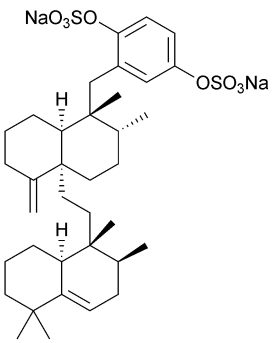


802 803

An *Ircinia* sponge (Weno Is., Chuuk State, Federated States of Micronesia) was the source of three linear polyprenyl hydroquinones **804–806.**[686] The asymmetric synthesis of (+)-akaterpin **807** (*Callyspongia* sp.)[687] established the absolute stereostructure as shown.[688]

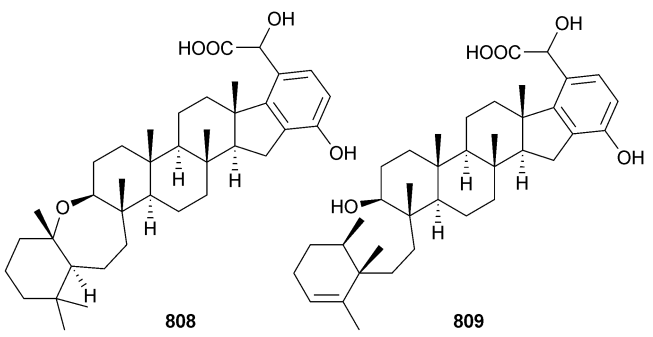


†**804** n = 6
†**805** n = 5
†**806** n= 4



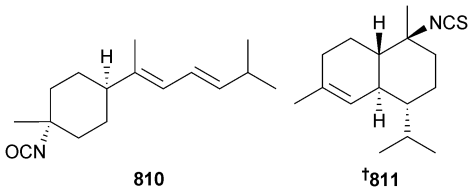
†**807**

The merotriterpenoids halicloic acid A **808** and B **809** were isolated from a *Haliclona* sponge (Culasian Point, Leyte, Philippines). Both compounds inhibited indoleamine 2,3-dioxygenase, which is required for tumour immune-response escape, but were unstable in deuterated DMSO.[689]



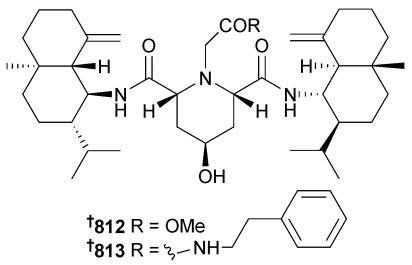
808 809

Rhaphoxya sp. (Blue Hole, Guam) provided the sesquiterpene theonellin isocyanate **810.**[677] The synthesis of 10-isothiocyanato-4-cadinene **811** (*Acanthella cavernosa*)[690] established the absolute configuration, although the spectroscopic data differed from those reported for a metabolite with the same assigned structure isolated from the nudibranch *Phyllidiella pustulosa*.[691] This study also synthesised the structure proposed for 10-*epi*-10-isothiocyanato-4-cadinene (*Stylissa* sp.).[692] However, discrepancies in the NMR data between the synthesised and reported compounds suggest that the natural product structure requires revision.[693]



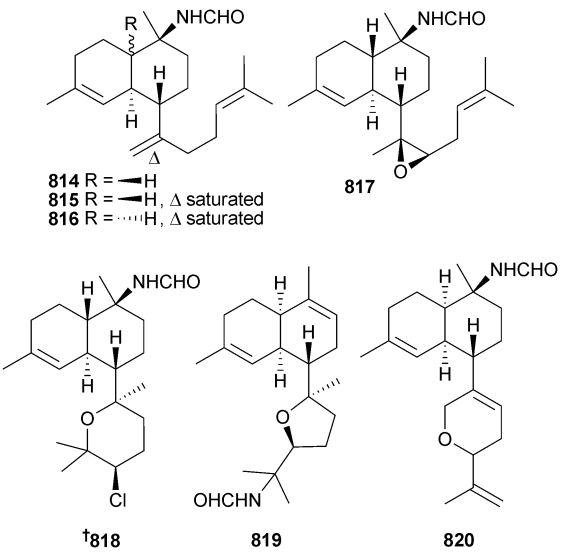
810 †**811**

Halichonadins K **812** and L **813** are sesquiterpene dimers from a *Halichondria* sponge (Unten Port, Okinawa). The absolute configurations of the compounds were determined by X-ray crystallography and chemical interconversion.[694] Racemic syntheses of luffarin X (*Luffariella geometrica*)[695] and cacospongionolide C (*Fasciospongia cavernosa*)[696] have been achieved.[697]



†**812** R = OMe
†**813** R = NH

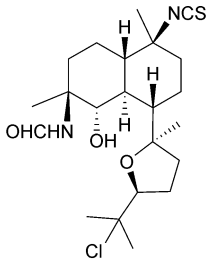
Cavernenes A–D **814–817**, kalihinenes E **818** and F **819** and kalihipyran C **820** are formamide diterpenoids from *Acanthella cavernosa* (Xisha Is., South China Sea).[698] Also obtained from *A. cavernosa* (Xisha Is., South China Sea) were the antifouling compounds kalihinols M–T **821–828.**[699]



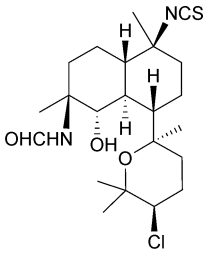
814 R = H
815 R = H, Δ saturated
816 R = H, Δ saturated

817

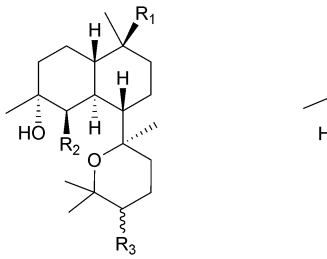
†**818** **819** **820**

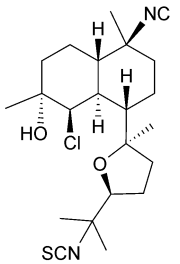


†821



†822

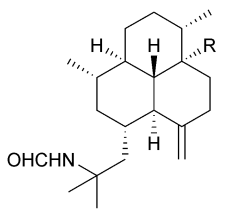




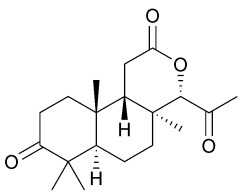
†828

†823 R_1 = NCS, R_2 = NC, R_3 = ◄Cl
†824 R_1 = NC, R_2 = NCS, R_3 = ····Cl
†825 R_1 = NC, R_2 = NCS, R_3 = ◄Cl
†826 R_1 = R_2 = NCS, R_3 = ◄Cl
†827 R_1 = NCS, R_2 = NHCHO, R_3 = ····Cl

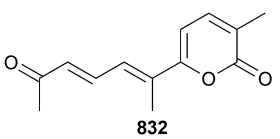
The absolute configurations of kalihinol A,[700] 10-*epi*-kalihinol I,[701] and kalihinol Y,[702] all from species of *Acanthella*, have been confirmed by synthesis.[703,704] The stereoselective synthesis of 7-isocyano-11(20),14-epiamphilectadiene (*Adocia* sp.),[705] a potent antimalarial, has been achieved,[706] while the isolation of two new formamido-amphilectane diterpenes **829** and **830** from a Thai *Stylissa massa* (Koh-Tao, Surat-Thani Province) have been reported.[707] Jaspiferin A **831** was isolated from *Jaspis stellifera* (Guangdong, South China Sea) along with an oxidative degradation product jaspiferin B **832**.[708]



829 R = NCO
830 R = NCS

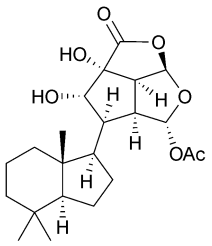


831

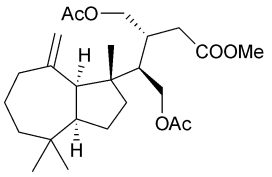


832

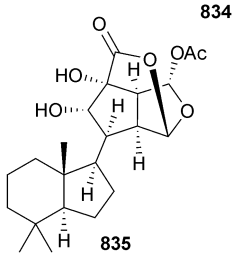
Chromodorolide D **833**, a heavily rearranged spongian diterpene, was reported along with **834** from an unidentified sponge (Cape Manza, Okinawa).[709] Chromodorolide D was also reported as chromodorolide E from an Australian *Dysidea* sp., along with a second structure **835** that was also called chromodorolide D.[710] Given the order in which the reports were accepted and published, **835** should be renamed chromodorolide E to reconcile the two separate papers.



833

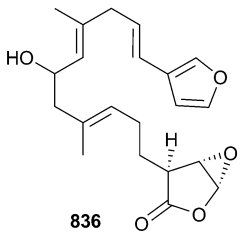


834

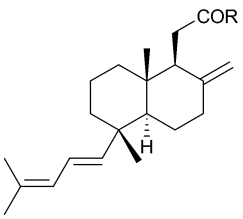


835

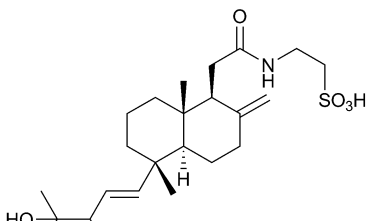
A linear C_{21} furanoterpene **836** was reported from *Coscinoderma matthewsi* (Gneerings Reef, Mooloolaba, Australia),[710] while *Clathria compressa* (Panama City Beach, Florida) was the source of three bicyclic C_{21} terpenoids **837–839**.[711]



836

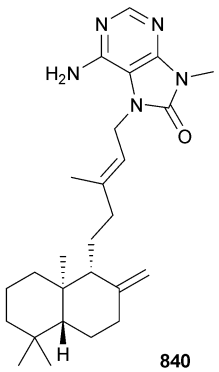


837 R = OH
838 R = $NHCH_2CH_2SO_3H$

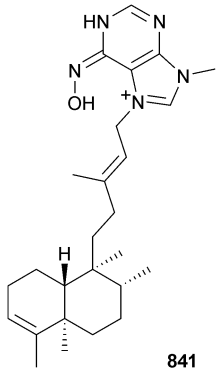


839

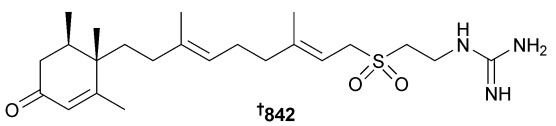
The cytotoxic diterpene alkaloids 8′-oxo-agelasine D **840** and ageloxime B **841** were isolated from *Agelas mauritiana* (Yongxing Is., South China Sea) along with a taurinated diterpenoid **842**.[628]



840

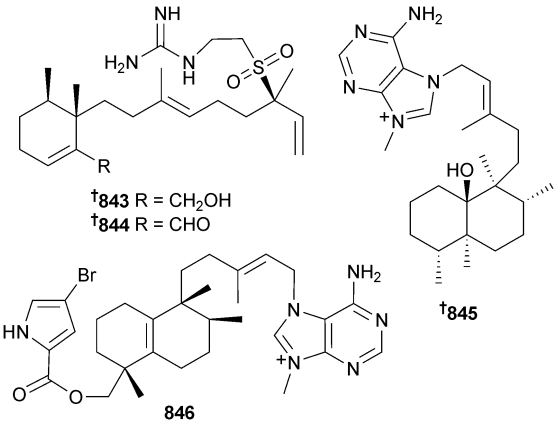


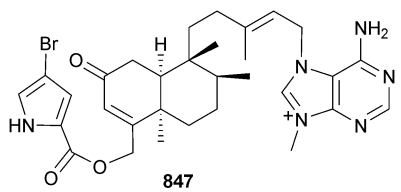
841

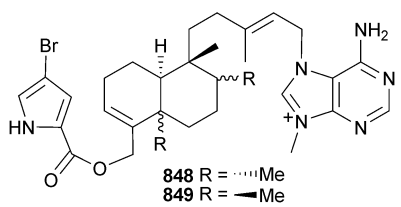


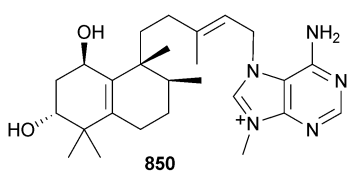
†842

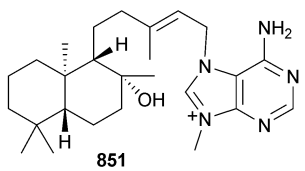
Agelasidines E **843** and F **844** are weakly antifungal compounds from *Agelas citrina* (Bahamas) that were isolated along with agelasine N **845**,[712] while agelasines O–U **846–852** are broadly active diterpene alkaloids isolated from an Okinawan *Agelas* sp.[713]

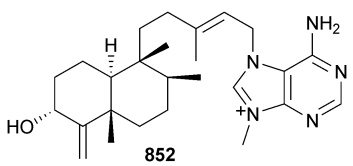




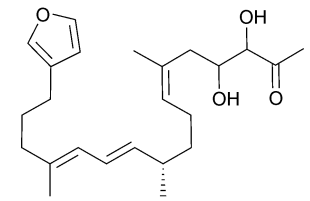


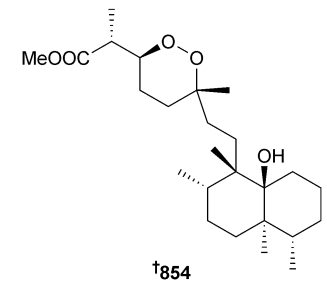




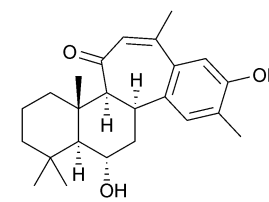


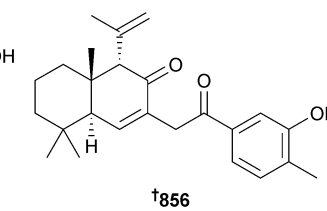
Sarcotin P **853** is a linear furano-norsesterterpenoid isolated from a *Sarcotragus* sp. (Cheju Is., S. Korea),[714] while diacarperoxide S **854** is a cytotoxic norsesterterpene peroxide from *Diacarnus megaspinorhabdosa* (Pula Baranglompo Is., Indonesia).[715] The total syntheses of (−)-alotaketal A (*Hamigera* sp.)[716] by two independent groups have confirmed the absolute configuration.[717,718]

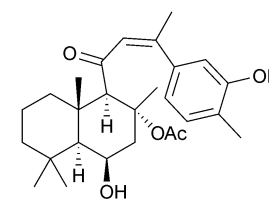


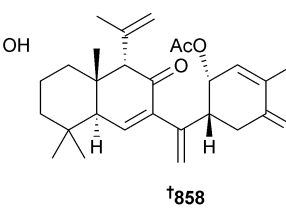


Four sesterterpenoids, phorone A **855**, isophorbasone A **856**, ansellone B **857** and phorbasone A acetate **858**, were isolated from a S. Korean *Phorbas* sp. Compounds **857** and **858**, described in the paper's supporting information, were low μM inhibitors of NO production in LPS-stimulated RAW 264.7 cells, while **855** and **856** are the first examples of two new carbon skeletons.[719]

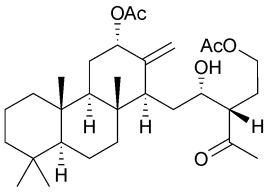




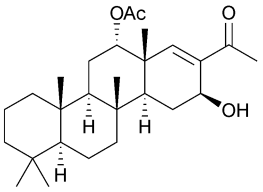




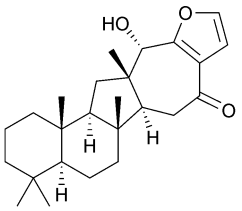
Flabelliferins A **859** and B **860** came from *Carteriospongia flabellifera* (Tutuba Is., Vanuatu). Both showed modest growth inhibition against human colon cancer cell lines,[720] while a



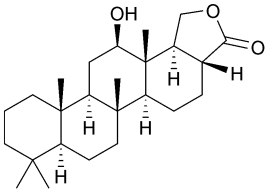
†859



†860



861

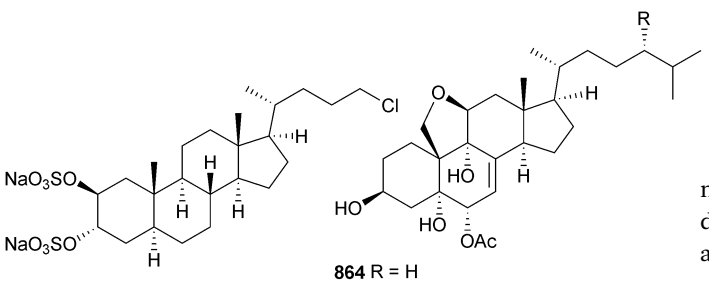


862

Hippospongia sponge (Taitung, Taiwan) was the source of hippospongides A **861** and B **862**.[721]

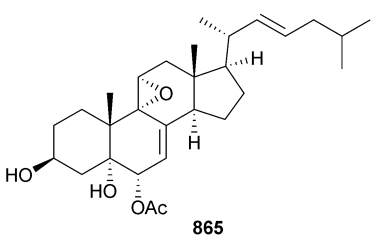
The archetypical anti-inflammatory scalarane sesterterpenoid scalaradial (*Cacospongia mollior*)[722] acted as a non-covalent binder in the active site of phospholipase A_2 and chelates Ca^{2+} but did not covalently bind to the enzyme through dial reactivity.[723] The total synthesis of solomonsterol B (*Theonella swinhoei*)[724] has allowed for SAR studies to be performed.[725]

Chalinulasterol **863** came from *Chalinula molitba* (Little San Salvador, Caribbean) and is the first chlorinated/sulfated sterol known.[726] A species of *Dysidea* (Ishigaki Is., Okinawa) was the source of dysideasterols F–H **864–866**, all of which inhibited human epidermoid carcinoma cells.[727]



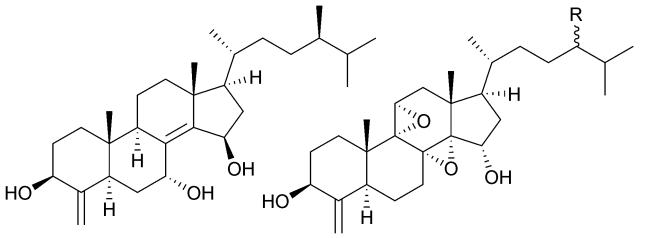
863

864 R = H
866 R = Me



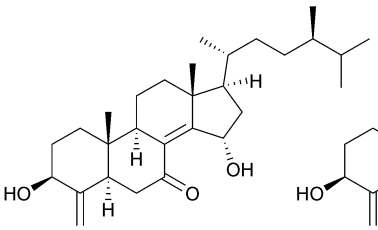
865

Theonella swinhoei from various locations in the Solomon Islands (Malaita and Vangunu Is.) have yielded conicasterols E **867**,[728] F **868**,[729] and G–K **869–873**,[730] along with theonellasterol I **874**,[729] and J **875**.[730] All are dual ligands of the pregnane X (PXR) and farnesol X receptors (FXR) with potential in modulating bile acid homeostasis in the liver and hence, metabolic disorders.[728–730]

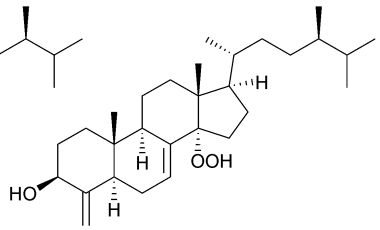


867

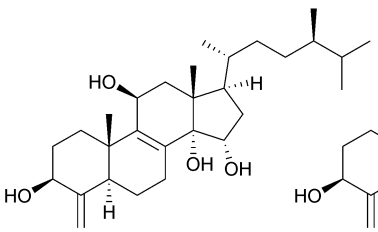
868 R = Me
874 R = Et



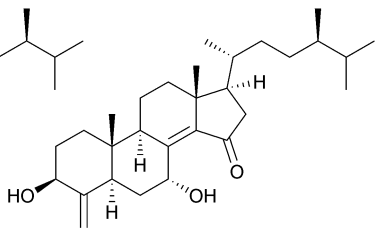
869



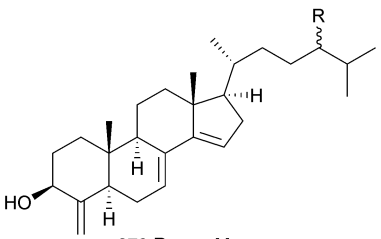
870



871

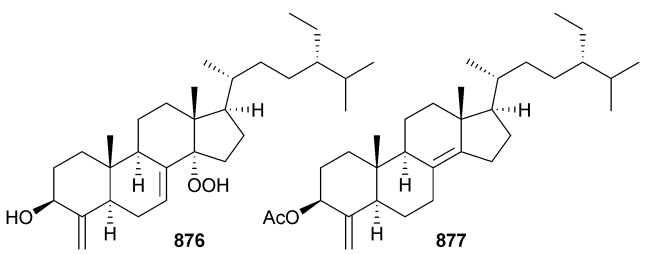


872



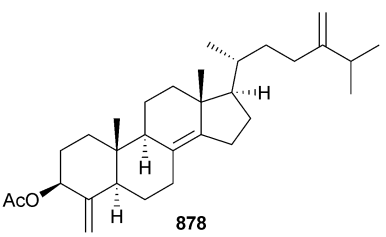
873 R = Me
875 R = Et

T. swinhoei (Pingtung, Taiwan) was the source of theonellasterol K **876**, acetyltheonellasterol **877** and acetyldehydroconicasterol **878**, with theonellasterol K being moderately active against a panel of cancer cell lines.[731]



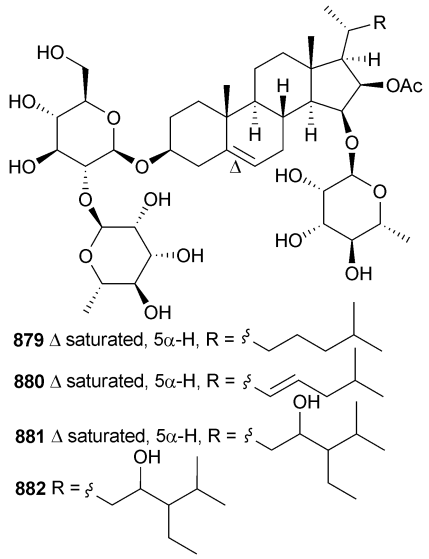
876

877

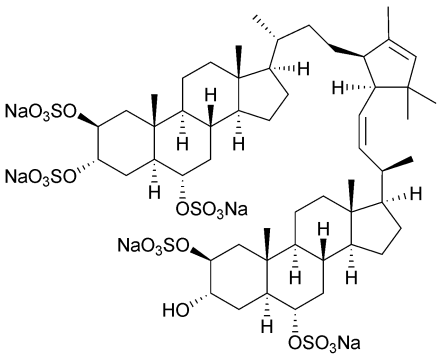


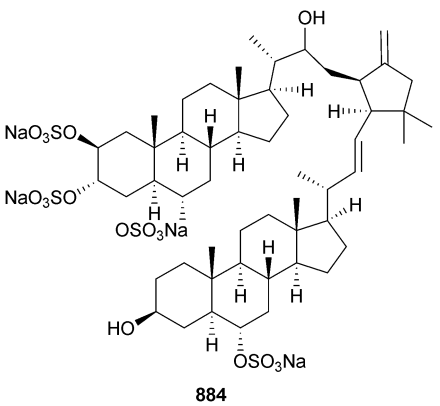
878

Acanthifoliosides G–J **879–882** were isolated from *Pandaros acanthifolium* (Marathon, Florida Keys) with acanthifolioside G activating the antioxidant response element in a dose-dependent manner without a significant increase in the activity of the detrimental xenobiotic response element.[732]

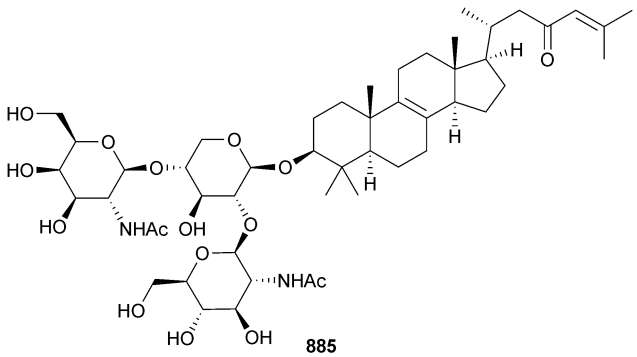


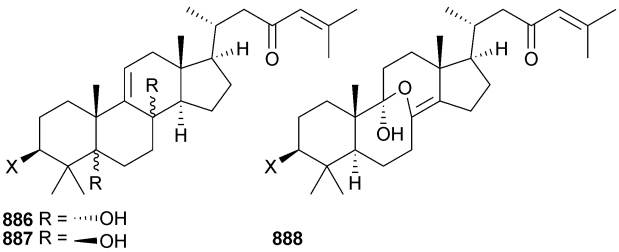
The sponge *Lissodendryx fibrosa* (North Sulawesi, Indonesia) was the source of manadosterols A **883** and B **884**, dimeric sterols that are potent inhibitors of the ubiquitin Ubc13-Uev1a complex and therefore have potential as anti-cancer agents.[733]

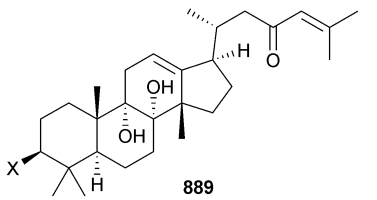


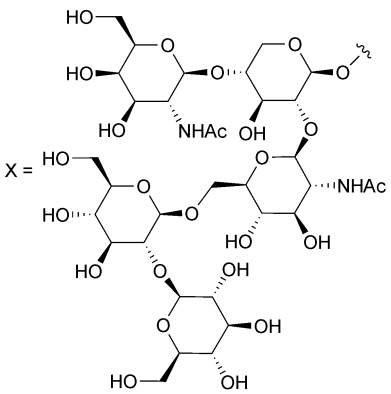


Geoditin A (*Geodia japonica*)[734] had antimelanogenic activity suggesting potential as a skin whitening agent,[735] while sarasinosides N–R **885–889** are nortriterpenoid glycosides from *Lipastrotethya* sp. (Chuuk State, Micronesia).[736]

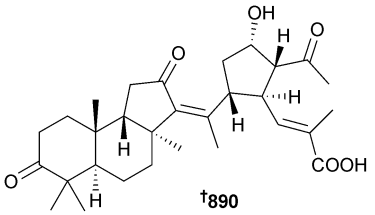




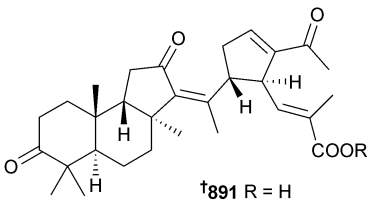




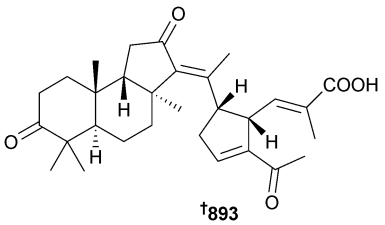
The isomalabaricane triterpenoids globostelletin J–R **890–898** were isolated from *Rhabdastrella globostellata* (Hainan Is., South China Sea), although in the paper there is no mention of the congener globostelletin S referred to in the title.[737]



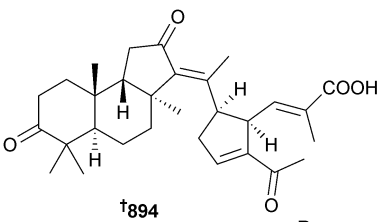
†890



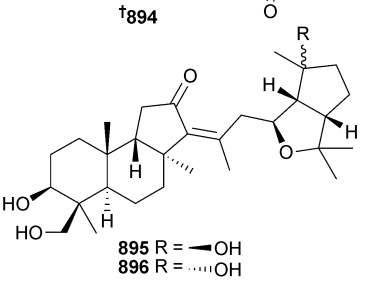
†891 R = H
†892 R = Me



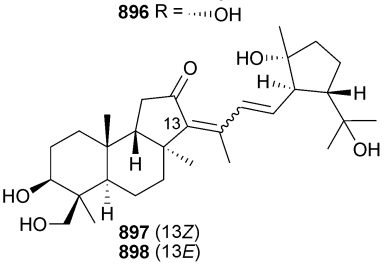
†893



†894

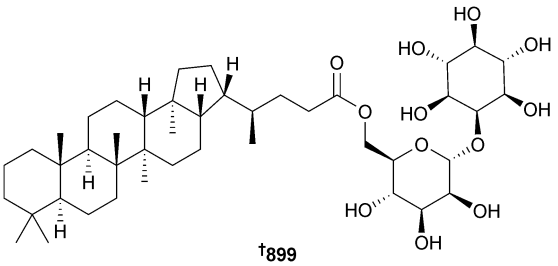


895 R = OH
896 R = OH



897 (13*Z*)
898 (13*E*)

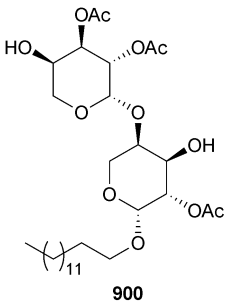
Plakortis lita (Manado, Indonesia) was the source of the hopanoid glycoside plakohopanoid **899**, although the terpenoid and carbohydrate components are reminiscent of bacterial secondary metabolites and it is likely that **899** is of symbiotic origin.[738]



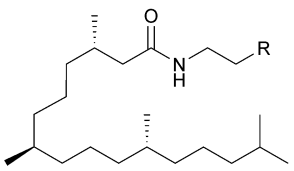
†899

8 Cnidarians

Although decreased from 2011, the number of new metabolites reported from cnidarians (213) is about the average number per year over the past decade. Sinularioside **900**, a bis-α-D-arabinopyranosyl myristyl glycolipid,[739] sinulasulfoxide **901** and sinulasulfone **902**[740] were isolated from *Sinularia* sp. (Manado, North Sulawesi, Indonesia), with sinularioside and sinulasulfoxide acting as moderate inhibitors of NO release from LPS-stimulated macrophages.

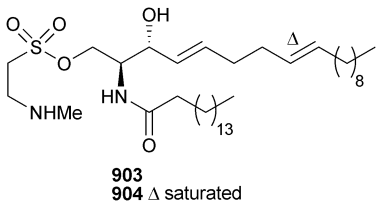


900



901 R = S(O)Me
902 R = S(O$_2$)Me

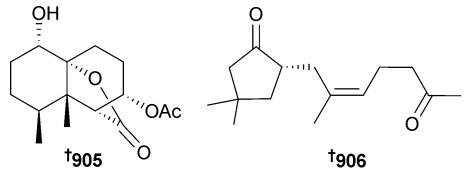
Brazilian collections (Paracuru Beach, near Fortaleza) of the zoanthids *Palythoa caribaeorum* and *Protopalythoa variabilis* yielded the sulfonylated ceramides palyosulfonoceramide A **903** and B **904**.[741] The structure elucidation of palyosulfonoceramides A and B was aided by comparison with two known co-metabolites; none of the four ceramides exhibited cytotoxicity.

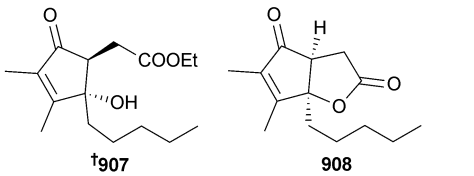


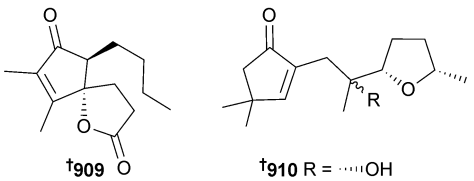
903
904 Δ saturated

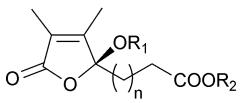
A new method of detection and quantification of palytoxin has been reported based on detection of the interaction of fluorescein-labeled Na,K-ATPase with palytoxin using fluorescence polarisation.[742] The method has a limit of detection of 2 nM. Paralemnolide A **905** is an unusual bisnorsesquiterpene from *Paralemnalia thyrsoides* (Taitong County, Taiwan)[743] and specimens of *Sinularia* sp. (Hainan Is., South China Sea) were the source of the cyclopentenones and butenolides sinularone A–I **906–914**.[744] Absolute configuration was assigned to several of the metabolites *via* comparison with calculated ECD, optical

rotation and chemical shifts. Sinularones A, B, G, H and I exhibited antifouling activity *in vitro* towards *Balanus amphitrite* (*B. amphitrite*).



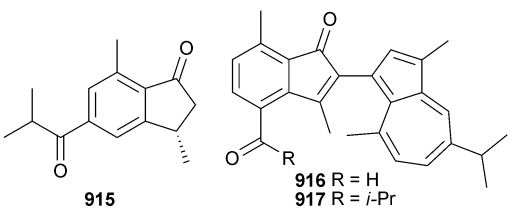


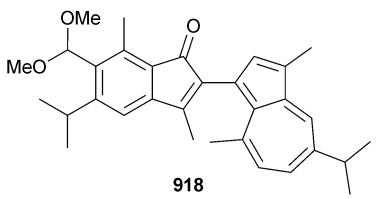


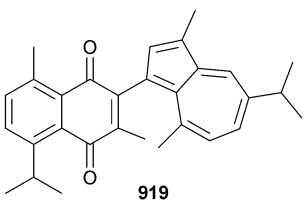


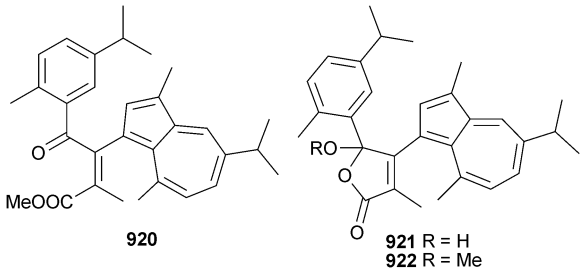
912 R_1 = H, R_2 = Et, n = 1
913 R_1 = Et, R_2 = Me, n = 1
914 R_1 = H, R_2 = Et, n = 11

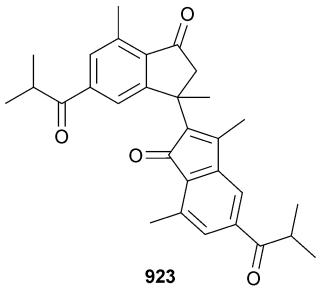
In addition to known congeners, fifteen new terpenes anthogorgienes A–O **915–929**, based on a guaiazulene sesquiterpene scaffold, were isolated from *Anthogorgia* sp. (Weizhou Is., China).[745] Absolute configurations were assigned to enantiomers **928** and **929** by CD analysis. Anthogorgiene G and known analogues exhibited antifouling activity (*B. amphitrite*) and antimicrobial properties.

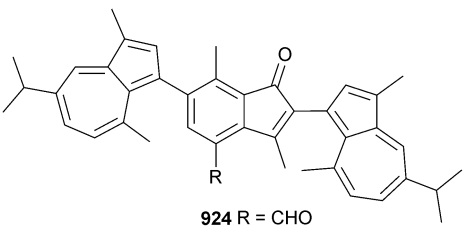


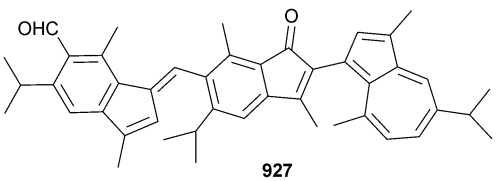


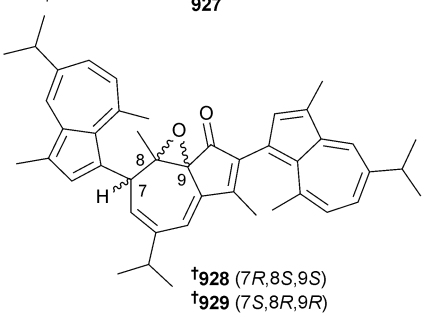




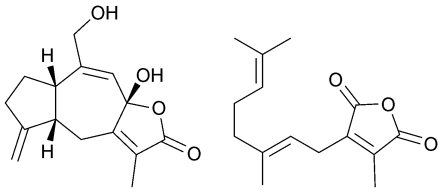




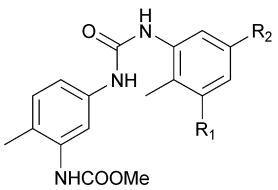




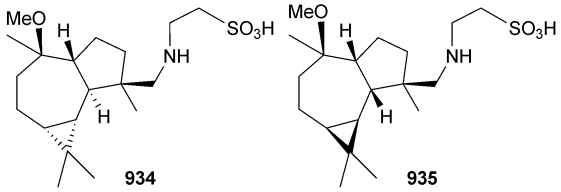
Menelloide E **930**, a germacrane-type sesquiterpene, and *seco*-germacrane anhydride **931**, previously reported from fruit of a Turkish plant,[746] were isolated from a deep-sea trawl collection of *Menella* sp. (southern coast of Taiwan).[747,748] Two carbamates obtucarbamate C **932** and D **933** and two sesquiterpene-taurine conjugates **934** and **935** were reported from *Melitodes squamata* (Sanya, Hainan Province, South China Sea).[749]



930 931

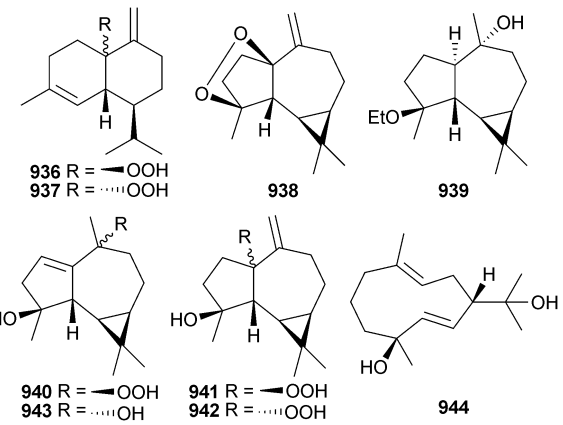


932 R_1 = NHCOOMe, R_2 = H
933 R_1 = H, R_2 = NHCOOMe



934 935

Of the two epimeric sesquiterpene hydroperoxides scabralin A **936** and B **937** (*Sinularia scabra*, Southern Taiwan), the former was found to exhibit mild antitumour activity and to reduce levels of iNOS protein in LPS-stimulated macrophages.[750] Sesquiterpenes lochmolin A–G **938–944** were reported from *Sinularia lochmodes* (northern coast of Taiwan); only lochmolin A was found to have an ability to reduce levels of COX-2 protein in LPS-stimulated macrophages.[751]



936 R = OOH
937 R = OOH

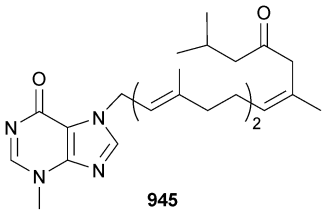
938 939

940 R = OOH
943 R = OH

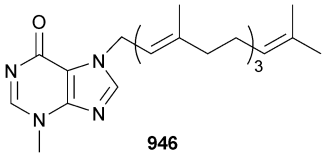
941 R = OOH
942 R = OOH

944

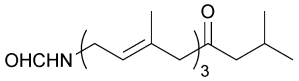
Prenylated purines **945**, **946** and formamide **947** (malonganenones I–K), and a number of previously reported congeners were isolated from *Euplexaura robusta* (Weizhou Is., South China Sea).[752] While **945–947** exhibited mild cytotoxicity, related co-metabolites malonganeones A, D and E[753,754] were more cytotoxic.



945

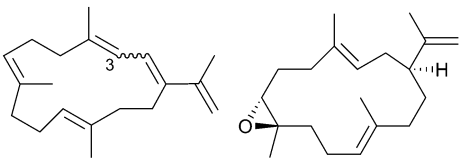


946



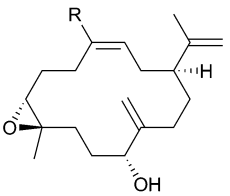
947

Two cembranes yalongene A **948** and B **949** were identified in extracts from *Sarcophyton trocheliophorum* (Yalong Bay, Hainan, South China Sea), with the former exhibiting cytoprotective effects towards cells injured with H_2O_2.[755] In addition to a number of congeners, epoxy-containing cembranes knightine **950** and related analogues **951** and **952** were isolated from *Eunicea knighti* (Santa Marta Bay, Colombian Caribbean Sea).[756] While only **951** and **952** and a related known co-metabolite inhibited quorum sensing in *Chromobacterium violaceum*, many of the cembranes inhibited biofilm formation for a number of different microorganisms.



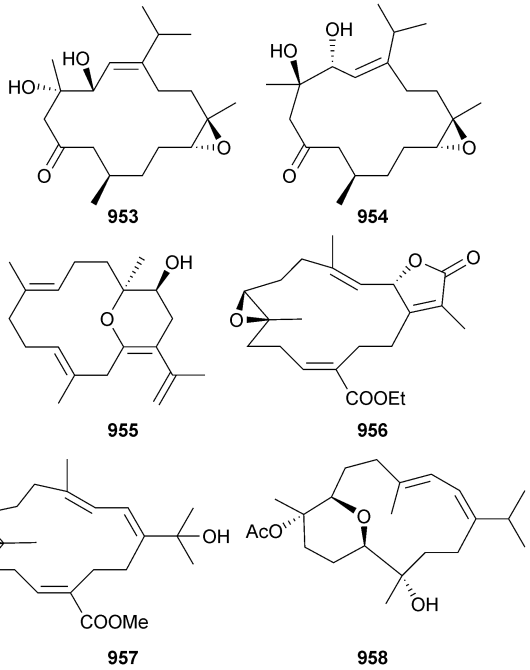
948 (3*E*)
949 (3*Z*)

†**950**

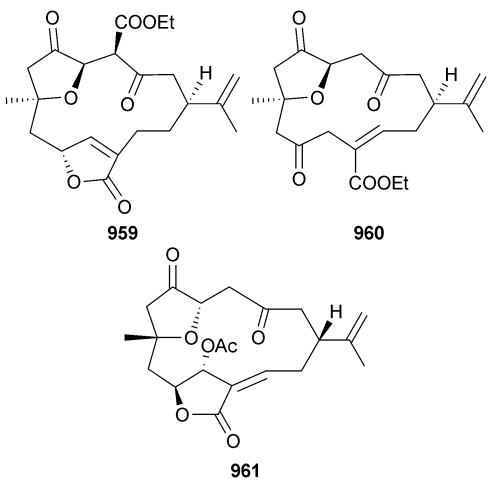


†**951** R = CHO
†**952** R = CH_2OAc

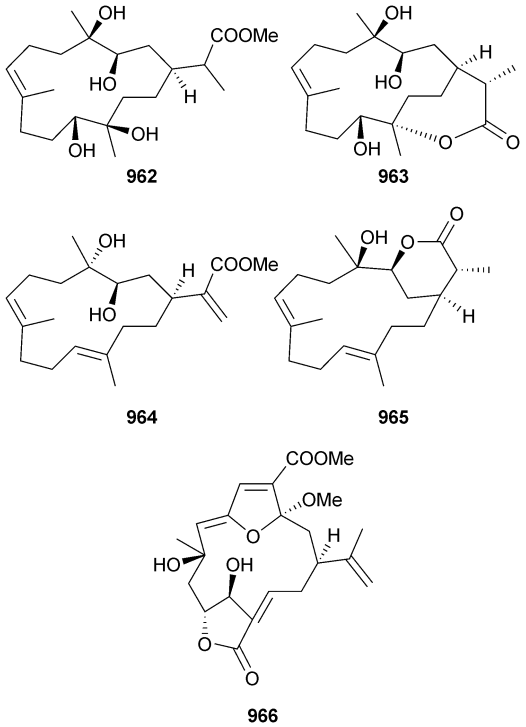
Epoxy-diol cembranes sicrassarine A **953** and B **954** (*Sinularia crassa*, Taitung County, Taiwan) were non-cytotoxic[757] while the C-4/C-14 ether linked cembrane lobocrassin F **955** (*Lobophytum crassum*, Northeast Taiwan) was a moderate inhibitor of elastase release from human neutrophils.[747] In contrast, cembranes **956** (a sarcophine analogue), **957** and **958** (ehrenbergol A and B) isolated from *Sarcophyton ehrenbergi* (Taitung County, Taiwan) exhibited cytotoxicity (P388 cells) and antiviral activity (human cytomegalovirus (CMG)).[758]



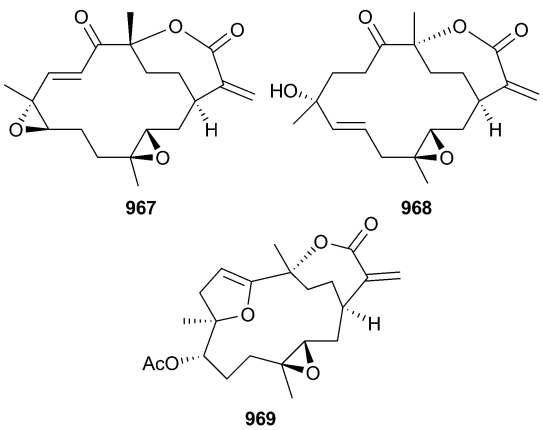
Of two cembranes sinumerolide A **959** and B **960** reported from *Sinularia numerosa* (Hainan Is., South China Sea) the latter contains the more usual combination of 5,8-epoxy linkage and C-4 norcembrane skeleton, while the former is unusual in possessing a complete C_{20} diterpene backbone.[759] One other example of a 5,8-epoxy-C-4-norcembrane, 5-epis-inuleptolide acetate **961** was reported as a moderately cytotoxic component of *Sinularia* sp. (Taitung County, Taiwan).[760]



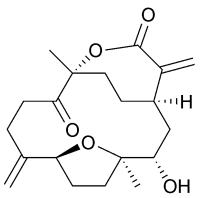
A collection of *Sinularia* sp. (Dongluo Is., Hainan, South China Sea) afforded sinuflexibilins A–E **962–966**, with the authors speculating about the potential artefactual nature of α-methoxyfuranocembranoid **966**.[761] Co-metabolite flexibilide[762] was the only compound in the study found to inhibit NF-κB activation.



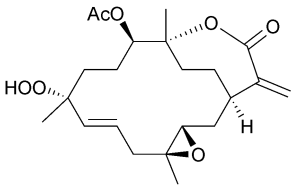
Cembranoid diterpenes flexibilisolide C–G **967–971**, flexibilisin C **972** and the ring opened 11,12-secoflexibillin **973** were reported from *Sinularia flexibilis* (Dongsha Atoll, South China Sea).[763] Flexibilisolide C, as well as several related co-metabolites, exhibited cytotoxicity and reduced the accumulation of iNOS and COX-2 pro-inflammatory proteins.



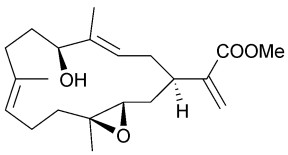
From a suite of new diterpenes sinumaximol A–I **974–982** and known congeners (*Sinularia maxima*, Nha trang Bay, Vietnam), sinumaximols B and C were found to inhibit IL-12, IL-6 and TNF-α production in LPS-stimulated bone marrow dendritic cells.[764]



970



971



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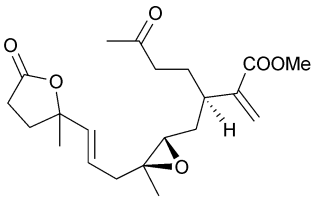
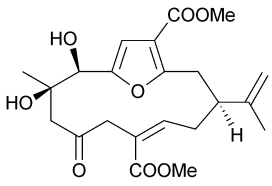


973



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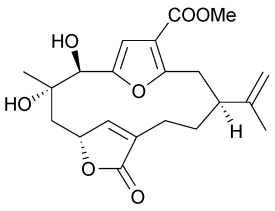

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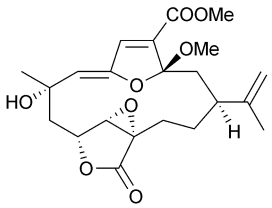

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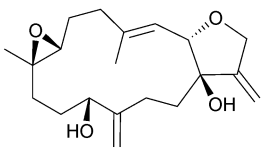

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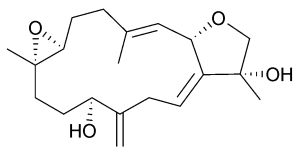
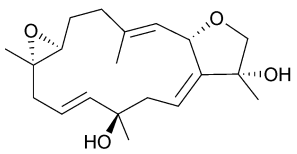


978



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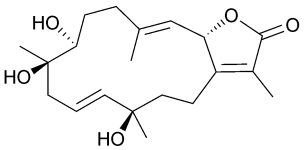

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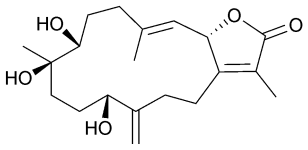
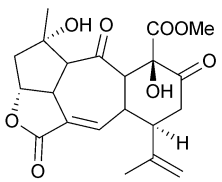
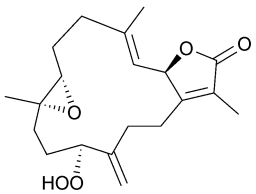


981

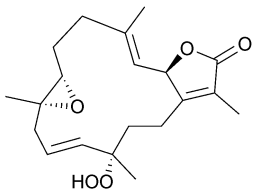


982

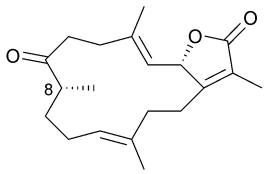
The structures of sarcophine hydroperoxide analogues **983** and **984** (*Sarcophyton glaucum*, Hurghada, Egyptian Red Sea) were secured by X-ray and CD analysis.[765] The NMR data of the co-metabolite 8-*epi*-sarcophinone **985** were different to those previously reported for the isomeric *iso*-sarcophinone[766] but could not be directly compared with earlier reported semi-synthetic isomers due to a lack of reported NMR data.[767] Metabolites **984** and **985** inhibited CYP450 1A and induced glutathione-*S*-transferase and quinone reductase activity.



†983

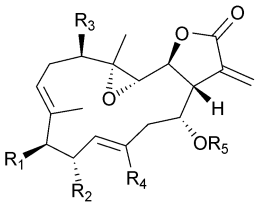


†984

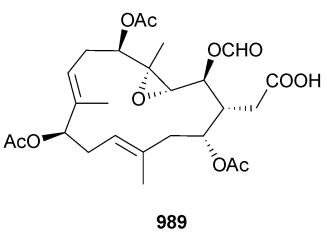


985

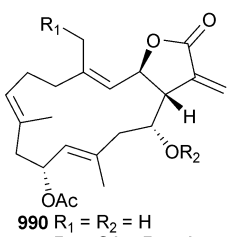
As would be expected, the α-*exo*-methylene-γ-lactone containing examples of michaolide L–Q **986–991** (*Lobophytum michaelae*, Ping-Tong County, Taiwan) exhibited more potent cytotoxicity than the *seco* analogue **989**.[768] Absolute configuration was assigned to michaolide L, though it should be noted that there is disagreement between configuration descriptors for C-4 and C-10 in the text *versus* the structure shown in the paper.



†**986** $R_1 = R_3 = R_5 = H$, $R_2 = OAc$, $R_4 = Me$
987 $R_1 = H$, $R_2 = R_3 = OAc$, $R_4 = Me$, $R_5 = Ac$
988 $R_1 = R_3 = OAc$, $R_2 = H$, $R_4 = CHO$, $R_5 = Ac$



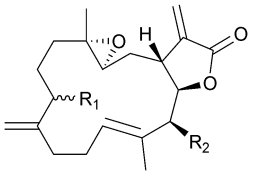
989



990 $R_1 = R_2 = H$
991 $R_1 = OAc$, $R_2 = Ac$

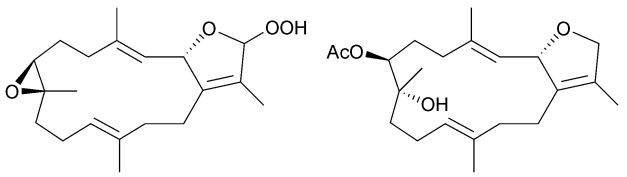
All three hydroperoxides sarcocrassocolide M–O **992–994** (*Sarcophyton crassocaule*, Dongsha Atoll, Taiwan) exhibited some degree of cytotoxicity towards tumour cell lines, with **992**

and **994** and to a lesser extent **993** also inhibiting the induction of iNOS protein.[769]



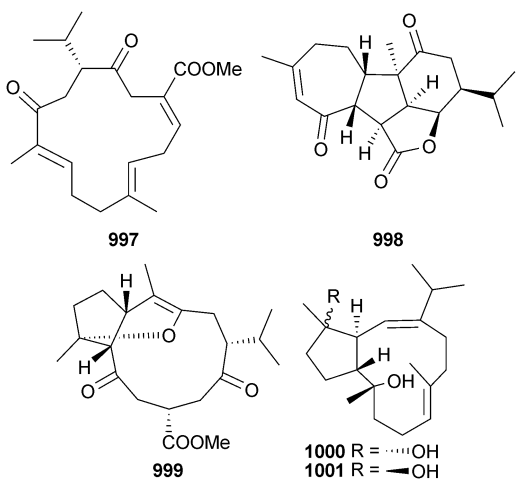
992 R_1 = ◄OOH, R_2 = OAc
993 R_1 = ····OOH, R_2 = OAc
994 R_1 = ◄OOH, R_2 = H

Dihydrofuranocembranoids sarcophytonin F **995** and G **996** (*Sarcophyton* sp., Dongsha Atoll, Taiwan)[770] are, respectively, the hydroperoxide and acetate derivatives of the co-metabolites sarcophytoxide and sarcophytonin C.[771] Sarcophytonin G can also be classified as *ent*-crassumol C.[772]



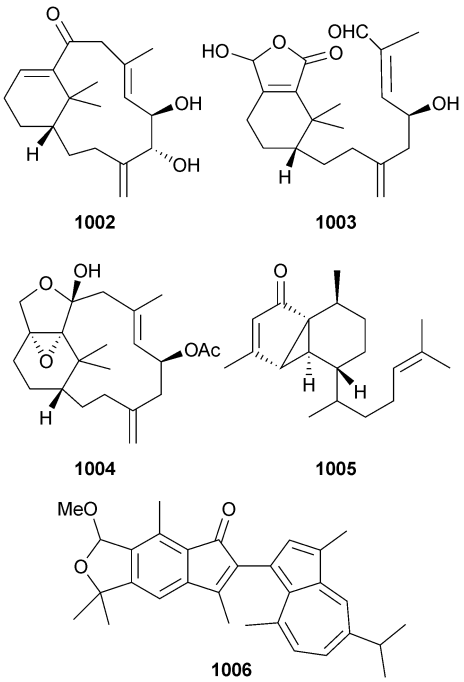
995 **996**

A structurally diverse set of diterpenes, the pavidolides A–E **997–1001**, were isolated from *Sinularia pavida* (Sanya Bay, Hainan Is., South China Sea). While pavidolides B and C were mildly cytotoxic, pavidolides C and D inhibited settlement of *B. amphitrite*.[773]



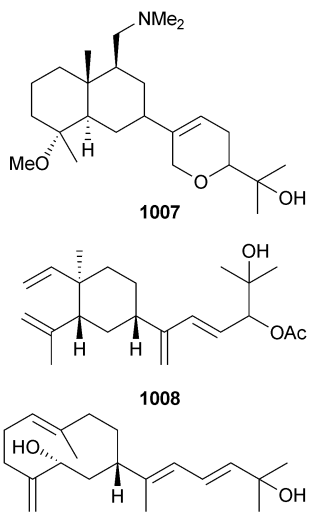
997 **998**
999
1000 R = ····OH
1001 R = ◄OH

Cespitularia taeniata (Green Is., Taiwan) was the source of norverticillane cespitulin E **1002**, secoverticillane cespitulin F **1003** and cespitulin G **1004**.[774] Cespitulin G was a moderate inhibitor of elastase release and superoxide production by stimulated human neutrophils. The serrulatane-skeletoned diterpene anthogorgiene P **1005** and triterpenoid anthogorgiene Q **1006** were isolated from *Anthogorgia* sp. (Weizhou Is., South China Sea) and the absolute configuration of the tricyclic core of anthogorgiene P was assigned.[775]



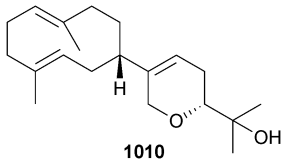
1002 **1003**
1004 **1005**
1006

Dimethylamino-naphthalene **1007** and lobane **1008** (*Sinularia* sp., Bowden reef, Great Barrier Reef, Australia) exhibited mild to moderate cytotoxicity towards three HTCLs.[776] Eunicidiol **1009** and known related diterpenes eunicol[777] and fuscol[777] were identified as potent topical anti-inflammatory metabolites of *Eunicea fusca* (Hillsboro Ledge, Florida).[778]



1007
1008
†**1009**

Extracts of *Lobophytum pauciflorum* (Taketomijima Is., Okinawa)[779] provided cyclolobatriene **1010** and the related metabolites lobatriene,[780] eunicol[777] and fuscol.[777] A low temperature (7 °C) NMR spectrum of **1010** identified three conformational isomers, while heating to 70 °C induced a thermal Cope rearrangement to lobatriene (identical by NMR and sign of $[\alpha]$). A similar rearrangement was induced for eunicol, converting it to fuscol. All four natural products showed moderate cytotoxicity towards a tumour cell line.

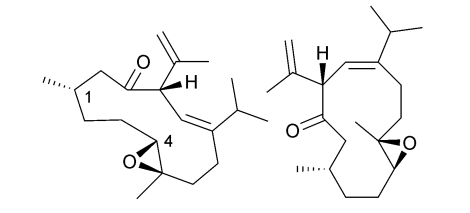


1010

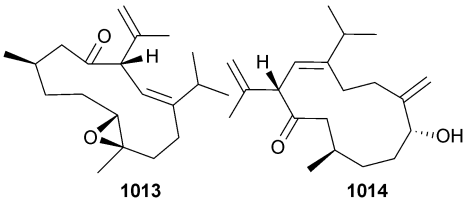
Two metabolites calyculone H **1011** and I **1012** (*Eunicea* sp., Old Providence Is., Colombia)[781] appear to be respectively the C-4,5-bis-epimers of previously reported calyculones C and A,[782] while triangulene C **1013** (*Sinularia triangula*, Taitung County, Taiwan) is another (possibly C-1) stereoisomer of calyculone C.[783] Calyculones A, B, C and H exhibited mild antimalarial activity, while calyculone A displayed strong cytotoxicity in testing at the NCI. In contrast, the related cubitane crassalone A **1014** (*Sinularia crassa*, Taitung County, Taiwan) exhibited no cytotoxicity towards a panel of tumour cell lines.[784]

Two separate studies of *Cespitularia* sp. (Zamami Is., Okinawa) afforded the mildly cytotoxic alcyonolide-type diterpenes **1015–1023**.[785,786]

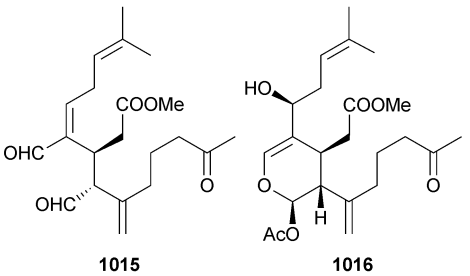
Twelve related diterpenes astrogorgin B–M **1024–1035** were isolated from *Astrogorgia* sp. (Beibuwan Bay, South China Sea).[787] Astrogorgin L was observed to undergo dehydration of the allylic alcohol functional group in $CDCl_3$ NMR solvent – the diene product was named astrogorgin N. Astrogorgins A–C exhibited moderate potency in a *B. amphitrite* antifouling bioassay.



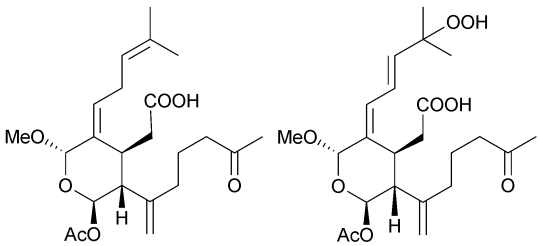
1011 **1012**



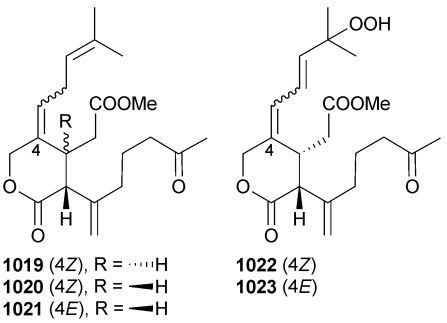
1013 **1014**



1015 **1016**

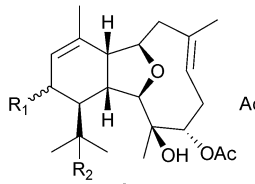


1017 **1018**

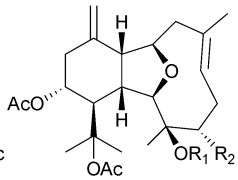


1019 (4*Z*), R = ····H
1020 (4*Z*), R = ◄H
1021 (4*E*), R = ◄H

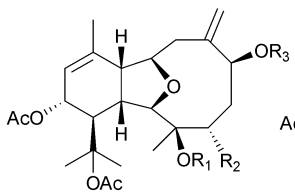
1022 (4*Z*)
1023 (4*E*)



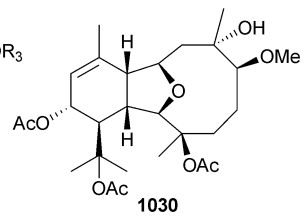
1024 R_1 = ····OAc, R_2 = H
1034 R_1 = ····OH, R_2 = H
1035 R_1 = ◄OAc, R_2 = OH



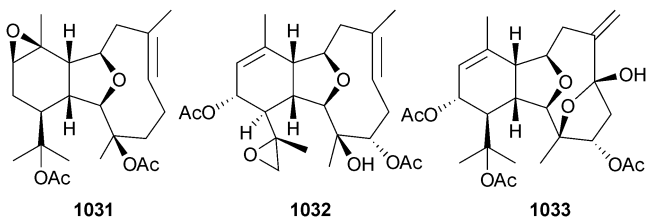
1025 R_1 = H, R_2 = OAc
1026 R_1 = Ac, R_2 = H



1027 R_1 = Ac, R_2 = R_3 = H
1028 R_1 = R_3 = H, R_2 = OAc
1029 R_1 = H, R_2 = OAc, R_3 = OH

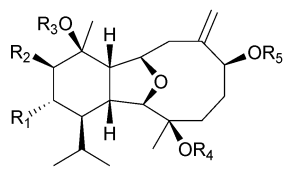


1030

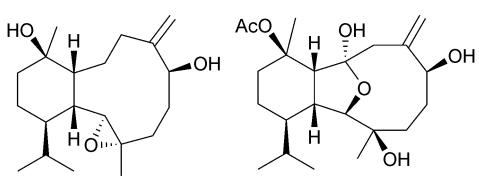


1031 **1032** **1033**

Duplicate structures were evident in the case of metabolites simplexin P–S **1036–1039** reported from *Klyxum simplex* (Dongsha Atoll, Taiwan).[788] Simplexin Q is identical to



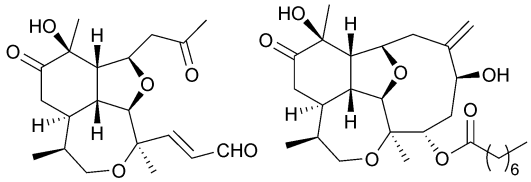
1036 R_1 = R_3 = R_5 = H, R_2 = OAc, R_4 = CO*n*Pr
1037 R_1 = OH, R_2 = R_5 = H, R_3 = Ac, R_4 = CO*n*Pr
1038 R_1 = R_5 = OH, R_2 = H, R_3 = R_4 = Ac
1039 R_1 = R_2 = R_4 = R_5 = H, R_3 = Ac,



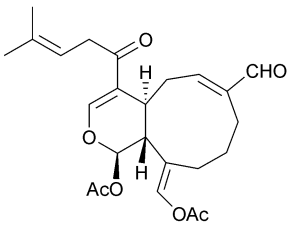
1040 **1041**

klysimplexin C,[789] while simplexin S is identical to cladieunicellin G concurrently reported from *Cladiella* sp. (Indonesia).[790] In addition, this latter study noted the presence of 6-*epi*-cladieunicellin F **1040** in the organism. The same specimen of *Cladiella* sp. also yielded the hemiketal congener cladieunicellin H **1041**.[791]

Seco-briarellinone **1042** and briarellin S **1043** are C-12 keto eunicellin diterpenes (*Briareum asbestinum*, Bocas del Toro, Panamanian Caribbean) that mildly inhibited the production of NO by LPS-stimulated macrophages.[792] Cristaxenicin A **1044** from *Acanthoprimnoa cristata* (dredging, Yakushima-Shinsone, Kagoshima, Japan) exhibited sub-micromolar activity towards the human protozoal targets *Leishmania amazonesis* (modest selectivity) and *Trypanosoma congolense*, but was less active towards *P. falciparum*.[793] Absolute configuration was assigned by comparison of calculated and experimental ECD spectra.

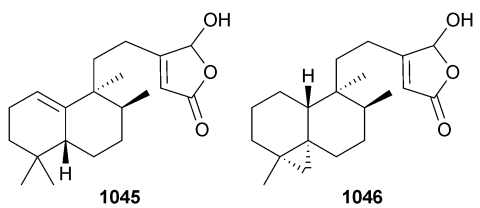


1042 **1043**

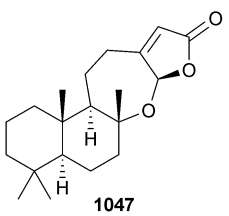


†**1044**

In three separate accounts, new halimane diterpenes **1045** (echinohalimane A) and **1046** (echinoclerodane A) and labdane **1047** (echinolabdane A) were reported from a single collection of *Echinomuricea* sp. (Taiwan)[794–796] with echinohalimane A inhibiting the release of elastase from stimulated human neutrophils.

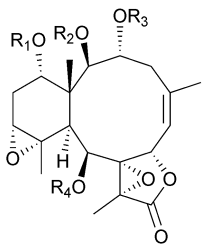


1045 **1046**



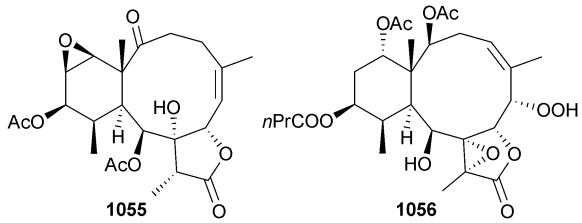
1047

Diepoxybriaranes briaroxalide A–G **1048–1054** (*Briareum* sp., Ishigaki Is., Okinawa) all share the same absolute configuration; the configuration of briaroxalide A was determined (derivative, X-ray) and related to the others by peracetylation.[797]

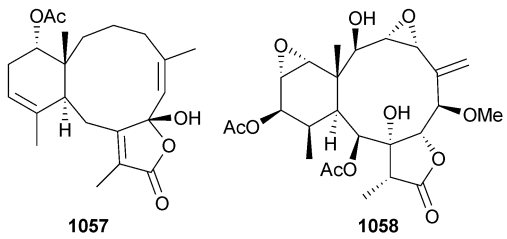


†**1048** $R_1 = R_3 = Ac$, $R_2 = R_4 = H$
†**1049** $R_1 = R_4 = Ac$, $R_2 = R_3 = H$
†**1050** $R_1 = R_3 = R_4 = Ac$, $R_2 = H$
†**1051** $R_1 = R_2 = R_3 = H$, $R_4 = Ac$
†**1052** $R_1 = R_2 = H$, $R_3 = R_4 = Ac$
†**1053** $R_1 = H$, $R_2 = R_3 = R_4 = Ac$
†**1054** $R_1 = R_2 = R_4 = Ac$, $R_3 = H$

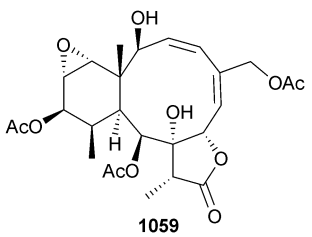
A southern Taiwanese collection of *Briareum* sp. afforded briarenolides E–I **1055–1059**.[798–800] Hydroperoxide briarenolide F was a strong inhibitor of superoxide generation by stimulated neutrophils.



1055 **1056**

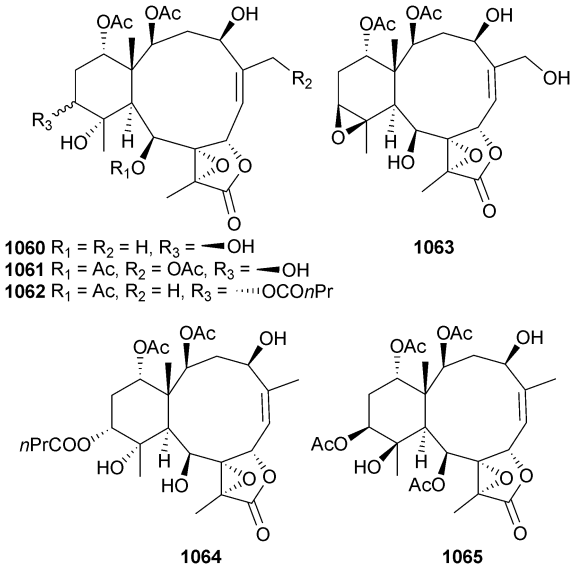


1057 **1058**

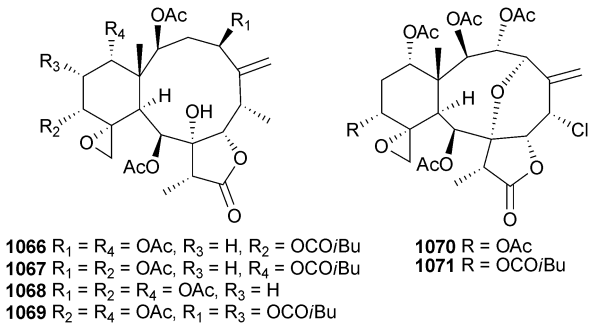


1059

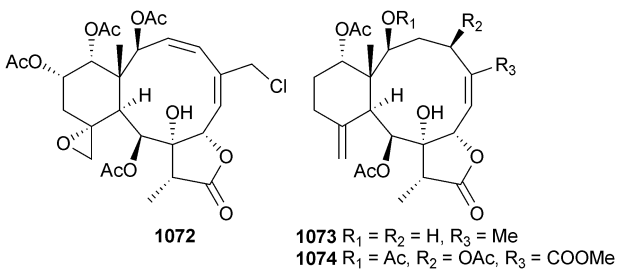
The 8,17-epoxybriaranes briacavatolide A–F **1060–1065** were all reported from *Briareum excavatum* (Orchid Is., Taiwan).[801,802] While none of the diterpenes exhibited cytotoxicity, briacavatolides C and F were modest inhibitors of CMG.



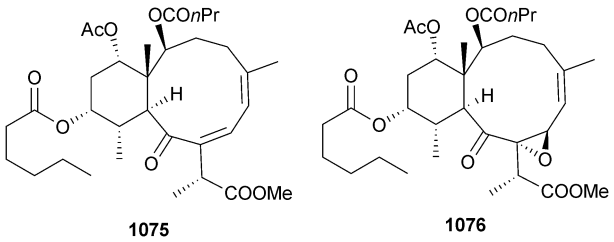
Of six 11,20-epoxybriaranes (gemmacolide T–Y **1066–1071**) isolated from *Dichotella gemmacea* (Beihai, China), gemmacolides V and Y exhibited the most pronounced cytotoxicity towards two tumour cell lines.[803]



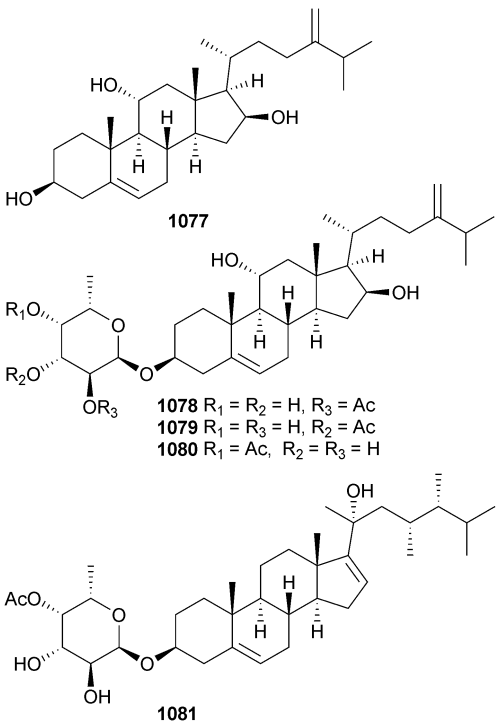
Investigation of *Junceella juncea* (Taitung County, Taiwan) secured three briaranes, juncenolide M–O **1072–1074**;[804] unfortunately the structure of juncenolide O is identical to that previously reported for juncin Z (*Junceella juncea*).[805]



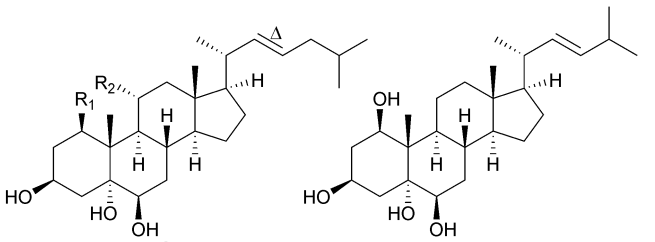
Briareolate esters J **1075** and K **1076** (*Briareum asbestinum*, Boca Raton, Florida)[806] are hexanoate esters of briareolate esters G and D,[807] respectively. Briareolate ester K was a weak growth inhibitor of human embryonic stem cells.



Sinularia crassa (Taitung County, Taiwan) yielded crassarosterol A **1077** and glycosides crassarosteroside A–D **1078–1081**; crassarosteroside A inhibited the expression of iNOS protein in stimulated macrophages.[808]

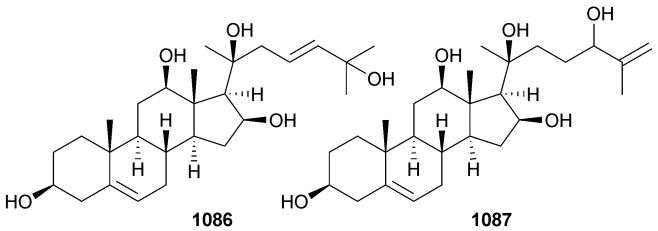


Of the four tetraols anthogorgsteroid A–D **1082–1085** isolated from *Anthogorgia* sp. (Beihai, South China Sea), anthogorgsteroid A appears to be identical to the previously reported sterol menellsteroid C[809] (*Menella* sp.).[810] Mildly cytotoxic pentaols **1086** and **1087** were isolated from *Subergorgia suberosa* (Naozhou Is., South China Sea).[811]



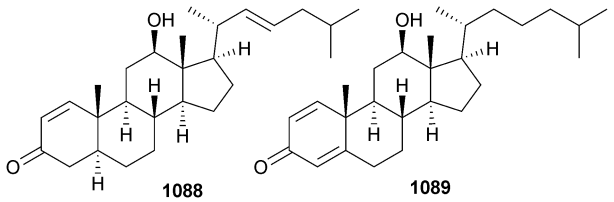
1082 R_1 = H, R_2 = OH, Δ saturated
1083 R_1 = H, R_2 = OH
1084 R_1 = OH, R_2 = H

1085



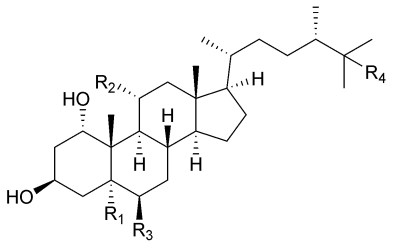
1086 **1087**

Two studies reported sterols with antagonistic activity towards FXR. In the first study, two new sterols **1088** and **1089** were isolated from *Dendronephthya gigantea* (Geo-je Is., S. Korea);[812] although three sterols were claimed to be new, one had in fact been reported the previous year from a Chinese specimen of *Astrogorgia* sp. (astrogorgol N).[813] Sterol **1088** was the most active of those isolated at inhibiting FXR trans-activation induced by chenodeoxycholic acid.

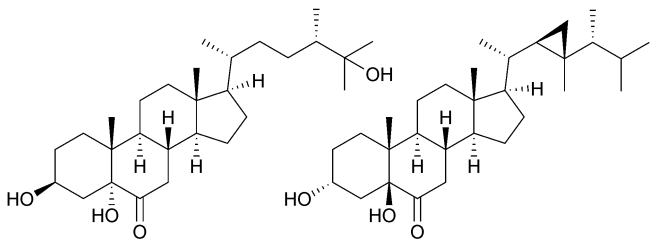


1088 **1089**

In addition to a number of known sterols, new examples **1090–1093** (new natural products) and **1094** were reported from *Sinularia* sp. (Bunaken Marine Park, Manado, Indonesia).[814] The most potent antagonist of FXR identified in this second study was gorgosterol.

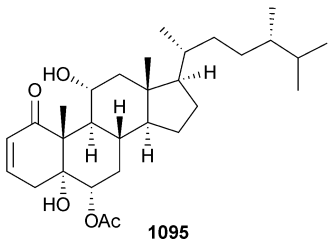


1090 R_1 = R_2 = R_3 = R_4 = H
1091 R_1 = R_2 = R_3 = H, R_4 = OH
1092 R_1 = R_3 = OH, R_2 = OAc, R_4 = H

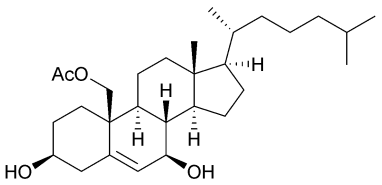


1093 **1094**

Extraction of *Echinomuricea* sp. (Taiwan) that had afforded a new labdane diterpene **1047** (see earlier) also yielded 6-*epi*-yonarasterol B **1095** which was notable for the ability to inhibit the generation of superoxide and the release of elastase from stimulated human neutrophils.[796] Three examples of C-19 oxygenated sterols, nebrosteroid N–P **1096–1098** (*Nephthea cabrolii*, Taitung County, Taiwan), were moderately cytotoxic towards a range of tumour cell lines.[815]



1095



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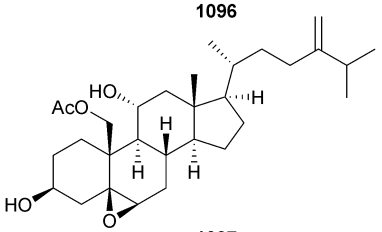

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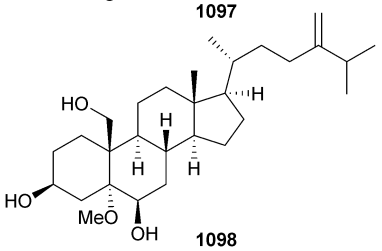
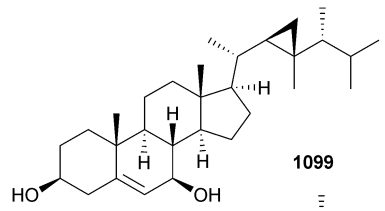
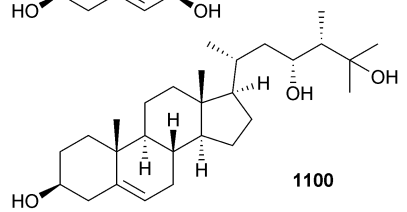


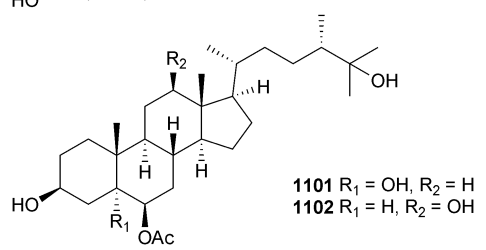
1098

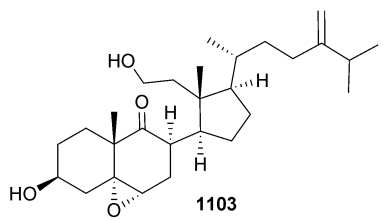
In addition to two cembranes **959** and **960** (see earlier), specimens of *Sinularia numerosa* (Hainan Is., South China Sea) also yielded the 7β-hydroxy analogue of gorgosterol **1099**,[759] while triol **1100** and tetraols **1101** and **1102** were characterised from extracts of *Sinularia* sp. (Weizhou Is., South China Sea).[816]

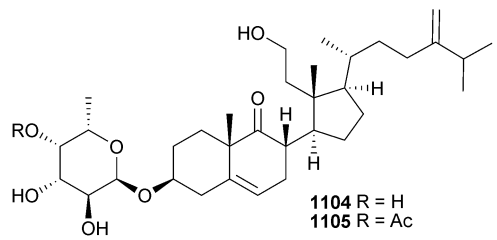
The 9,11-secosterol **1103** (*Sinularia granosa*, Pingtung, Taiwan) is an H-8, 5,6-epoxy diastereomer of a previously reported co-metabolite (*Sinularia lochmodes*);[817] both compounds exhibited cytotoxicity and inhibited expression of iNOS and COX-2 proteins in stimulated macrophages.[818] The first examples of 9,11-secosterol glycosides, sinularoside A **1104** and B **1105** (*Sinularia humilis*, South China Sea) exhibited growth inhibition properties towards two fungi, a microalga and a Gram-positive bacterium, but not a Gram-negative bacterium.[819]

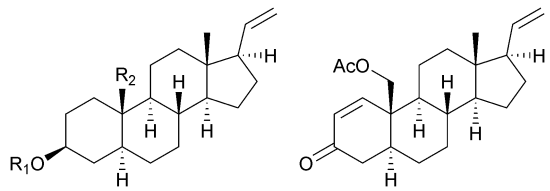


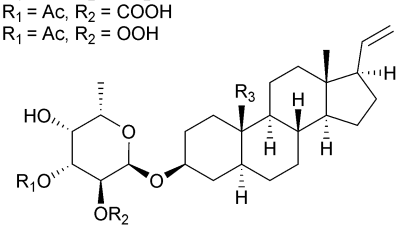






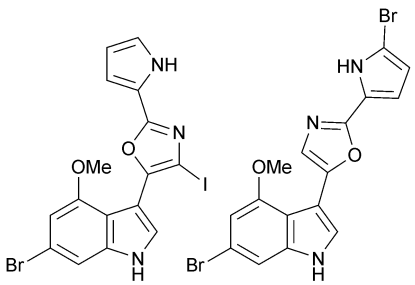






Of a diverse range of pregnanes, including new examples sclerosteroid A–I **1106–1114** (*Scleronephthya gracillimum*, Green Is., Taiwan), only sclerosteroids A, B and E inhibited expression of the pro-inflammatory proteins iNOS and COX-2 in stimulated macrophages.[820]

Mass-guided fractionation of the hydroid *Thuiaria breitfussi* (Bear Is., Arctic) identified the halogenated alkaloids breitfussin A **1115** and B **1116**. These structures were established using atomic force microscopy in combination with structure elucidation software and chemical shift calculations.[821]



The structure of a second γ-lactone 'trocheliophorolide B', originally reported from *Sarcophyton trocheliophorum*,[822] has been shown to be incorrect.[823] The trivial name trocheliophorol, ascribed to a cembranoid metabolite isolated from cultured specimens of *S. trocheliophorum*,[824] has been used before.[825] As a consequence the authors have changed the name to trocheliol.[826]

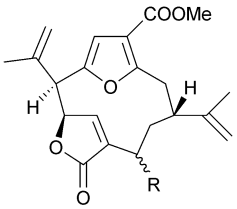
Syntheses of the modestly cytotoxic *seco*-caryophyllane rumphellaone A[827] and clovane rumphellclovane A[828] (*Rumphella antipathies*) have been reported;[829–831] the latter study used the filamentous fungi *Pestalotiopsis palustris* to biotransform synthetically prepared (1*S*,2*S*,5*S*,8*R*,9*R*)-2-methoxyclovan-9-ol into the soft coral metabolite, simultaneously establishing the absolute configuration.

Several studies have been reported on further biological investigation of purified cembranoids. Sinularin (*Sinularia flexibilis*)[832] inhibits the up-regulation of pro-inflammatory proteins iNOS and COX-2 as well as TGF-β in stimulated macrophages.[833] Such *in vitro* results also translated to *in vivo* studies, where sub-cutaneous application led to observable analgesic effects. While one study of 11-dehydrosinulariolide[834] noted an ability to induce apoptosis and act as an anti-proliferative and antimigration agent towards human melanoma cells,[835] a second study noted the same cembranoid significantly reduced 6-hydrodopamine-induced cytotoxicity and apoptosis of a human neuroblastoma cell line, mediated by caspase-3/7 and PI3K, suggesting a potential role as a neuroprotective candidate.[836] The related cembrane sinulariolide[837] exhibited antiproliferative, antimigratory and apoptosis-inducing activities, the latter *via* mitochondrial and p38MAP kinase pathways against human urinary bladder carcinoma cells.[838]

Investigation of the antiproliferative activity of an unnamed γ-lactone cembranoid (*Sinularia mayi*)[839] revealed

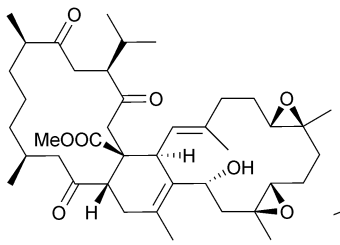
that it functions by activation of apoptosis *via* reactive oxygen species (ROS) generation, which has further downstream consequences of inhibiting signal transduction.[840] A semi-synthetic analogue of cembranoid sarcophine, sarcophine diol, inhibited mouse melanoma cell proliferation by arresting cell division at G_0 and by also activating apoptosis.[841]

A configurational reassignment of 11-gorgiacerol[842] (= 11-pseudopteranol?)[843] and 11-*epi*-gorgiacerol (aka 11-*epi*-pseudopteranol)[844] to those shown in **1117** and **1118** has been reported; the syntheses made use of a stereospecific photochemical ring contraction reaction.[845]

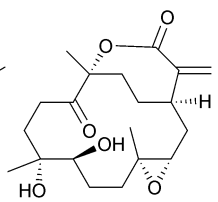


†**1117** R = ⋯OH
†**1118** R = ▬OH

The absolute configurations of bis-cembranoid ximaolide A[846] **1119** and cembrane (+)-sinulaparvalide A[847] **1120** were established by comparison of calculated ECD spectra (derived from X-ray structure conformation) with spectra observed for micro-crystalline solids.[62] Comparison with solution ECD spectra also allowed assignment of absolute configurations to ximaolide B and E, methyl tortuosoate (= methyl tetrahydrosarcoate)[848] and (+)-sinulaparvalide B.

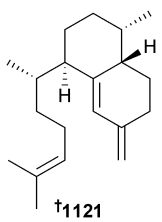


†**1119**



†**1120**

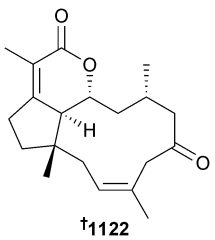
By stereospecific synthesis of a stereoisomer, the absolute configuration of elisabethatriene,[849] a diterpene representing the first committed step in pseudopterosin biosynthesis, has been corrected to that shown here, **1121**.[850]



†**1121**

Purified pterosins and *seco*-pterosins (*Pseudopterogorgia elisabethae*, Providencia Is., Colombia) demonstrated selective ability to inhibit the growth and biofilm of Gram-positive bacteria, suggesting that the natural products play a role in regulation of the gorgonian surface bacterial communities.[851] Further investigation of the antimycobacterial activity demonstrated by pseudopteroxazole[852] and homopseudopteroxazole[853] has identified a semi-synthetic histidine analogue with similar levels of potency and selectivity.[854] Theoretical studies suggested that the photochemical [2 + 2] cycloaddition reaction proposed for the biogenesis of the cyclobutane-containing diterpene plumisclerin A[855] could also be realised by a thermal step-wise proton-promoted process.[856]

The absolute configuration of clavulactone **1122** (*Sinularia* sp.)[857] has been established by enantioselective synthesis.[858] As indicated in the previous review in this series,[1] the structure of gemmacolide H[859] has been confirmed[860] as identical to the previously reported briarane 12-*epi*-fragilide G.[861]



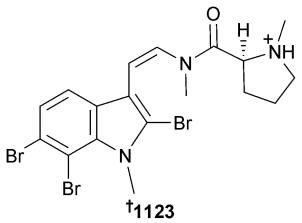
†**1122**

The structure of pregnane krempene B (*Cladiella krempfi*)[862] has been confirmed by synthesis from 3β-acetoxy-5-pregnen-20-one,[863] while two cholestane-dienones previously reported from *Minabea* sp.[864] and *Anthomastus bathyproctus*[865] have been prepared from (25*S*)-Δ^4-dafachronic acid.[866]

A systematic nomenclature for sea anemone toxins has been proposed, combining descriptors of biological activity, generic family name, genus and species of original source and relationship to known isoforms.[867] Further proof of the need of a consistent nomenclature system was demonstrated in a report on digital marine bioprospecting, whereby deep sequencing of transcriptomes of cold-water anemones *Bolocera tuediae* and *Hormathia digitata* and subsequent homology searching identified four highly similar and 15 additional new neurotoxin peptide candidates.[868] A concise synthesis of the guanidine hydantoin alkaloid parazoanthine A (*Parazoanthus axinellae*)[869] and the methyl ether analogue has been reported.[870]

9 Bryozoans

Only two investigations of bryozoan chemistry have been reported in the last year. A collection of *Amathia tortuosa* (northern New South Wales, Australia) provided the tribrominated indole alkaloid kororamide A **1123** which was marginally active against chloroquine-sensitive and resistant strains of *P. falciparum*.[871]



†1123

Total synthesis of the published structure of amathamide D, a metabolite of *Amathia wilsoni*,[872] indicated that the structure should be revised to that indicated by other researchers.[873] This revised structure was also synthesised.[874] Convolutamine H, a metabolite of *Amathia convoluta*,[875] was synthesised *via* a Grob fragmentation-aromatisation strategy.[874]

10 Molluscs

There was a pronounced increase in the number of new metabolites reported from molluscs when compared with recent years. The antioxidant activity detected in Japanese samples of the Pacific Oyster (*Crassostrea gigas*) was attributed to 3,5-dihydroxy-4-methoxybenzyl alcohol,[876] previously reported from the brown alga *Leathesia nana*.[877]

The new C-terminus pyroglutamate gonadotropin-releasing hormone related peptides Cg-GnRH-a **1124** and Cg-GnRH-G **1125** were isolated from French (Normandy) specimens of the Pacific Oyster.[878]

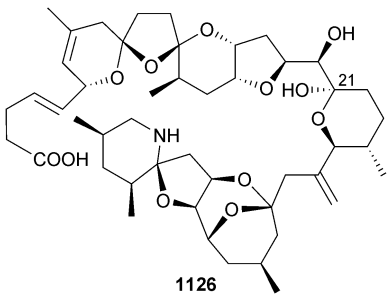
pQNYHFNSNGWQP-NH_2

1124

pQNYHFNSNGWQPG

1125

Optimised purification using extracts of *Mytilus edulis* (Bruckless, Donegal, Ireland) afforded sufficient quantities of the toxin azaspiracid-6 **1126**, previously characterised by MS,[879] to enable the characterisation by NMR spectroscopy.[880] While **1126** was stable in aqueous acetonitrile solution, storage in methanol formed a C-21 methyl ketal.



1126

A diverse array of fatty acid esters of pinnatoxin G were identified in extracts of *M. edulis* (Atlantic coast, Canada).[881] Specimens of the sea snails *Gibbula umbilicalis* (flat top shell) and *Monodonta lineata* (thick top shell) collected on the Portuguese coast were found to contain low levels of tetrodotoxin and/or analogues, highlighting these species as new toxin vectors.[882]

A number of new conotoxins continue to be isolated from snail venom. *Conus regius* (Plantation Key, Florida) yielded an α4/7-conotoxin, RegIIA **1127**, comprised of 16 residues with two disulfide bonds.[883] The structure was confirmed by synthesis and the 3D-conformation established by NMR methods. The peptide was a low nM blocker of α3β4 nAChRs. In contrast, the amidated 11-residue peptide pc16a **1128** (*Conus pictus*, Port Elizabeth, South Africa), which contained a rare cysteine framework XVI, was found to be inactive in a range of bioassays.[884]

GCCSHPACNVNNPHIC-NH_2

1127

SCSCKRNFLCC-NH_2

1128

A novel framework XXIII was present in two toxins im23a (42 residues) and im23b (43 residues) isolated from *Conus imperialis* (South China Sea).[885] The conformation of recombinant im23a was determined by NMR spectroscopy; the sequence and cysteine framework suggests that this peptide is the first member of the K-superfamily. Intracranial injections of either peptide caused excitatory symptoms. μ- and μO-Conotoxins are well known as blockers of voltage-gated sodium channels (VGSC) and nAChRs, making them of interest as potential analgesics.

A new μ-conotoxin congener, CnIIIC **1129** (*Conus consors*, Chesterfield Is., New Caledonia) was isolated, synthesised and tested against a range of skeletal muscle and VGSC targets.[886] Potent blocking of skeletal muscle (Na_V 1.4) and neuronal (Na_V 1.2) VGSCs was observed.

ZGCCNGPKGCSSKWCRDHARCC-NH_2

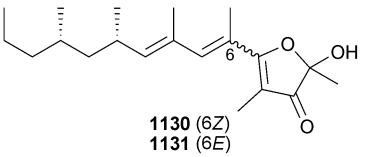
1129

A hydrophobic 32-residue peptide, μO-conotoxin MfVIA (*Conus magnificus*, unspecified location) preferentially inhibited Na_V 1.8 and Na_V 1.4 sodium channel isoforms.[887] Synthesis of the peptide made use of an interesting sequence of selective oxidative deprotections of cysteine residues that allowed for synthesis without requiring chromatographic purification of intermediates.

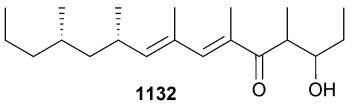
A combined proteomic/transcriptomic analysis of the venom duct of *Conus consors* (Chesterfield Is., New Caledonia) identified 105 components (of over 400 detected) covering A-, M- and O1-superfamily toxins, as well as unusual disulfide-free peptides and actinoprin- and hyaluronidase-like proteins.[888] However, the ability to automate such analysis is confounded somewhat by the complexity of post-translational modifications in *Conus* venoms. The interplay of three *Conus imperialis* venom duct proteins, protein-disulfide isomerase, peptidyl-prolyl *cis*–

trans isomerase and immunoglobulin-binding protein in directing the oxidative folding of cysteine-rich peptides has been studied.[889]

Investigation of the chemistry of *Siphonaria oculus* (Eastern Cape, South Africa) afforded new polypropionates **1130–1132**.[890] The potential artefactual nature of cyclic products **1130**, **1131** and a fourth known polypropionate was suggested when analysis of the crude mucous released from individual molluscs revealed ^{1}H NMR signals attributable to only **1132** in the extract.

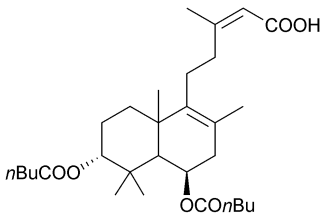


1130 (6*Z*)
1131 (6*E*)



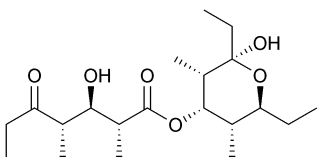
1132

The more structurally complex labdane diterpene **1133** was reported from specimens of the limpet *Trimusculus peruvianus* (Bahía de Pichidangui, Chile).[891] Enantioselective synthesis of *ent*-caloundrin B (*Siphonaria zelandica*)[892] confirmed the proposed relative and absolute configuration and in the presence of imidazole was found to isomerise to *ent*-siphonarin B.[893]

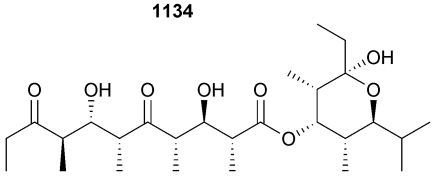


1133

The absolute configurations of the bis-γ-pyrone polyproprionate onchidione (*Onchidium* sp.)[894] and two methanolysis products have been assigned by analysis of X-ray diffraction data and TDDFT calculated ECD spectra.[895] *Dolabrifera dolabrifera* (El Escambron, Puerto Rico) afforded the known non-contiguous polyproprionate ester dolabriferol[896] and two new congeners dolabriferol B **1134** and C **1135**.[897] The artefactual nature of all three metabolites was suggested.

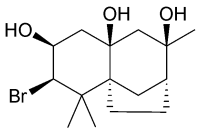


1134



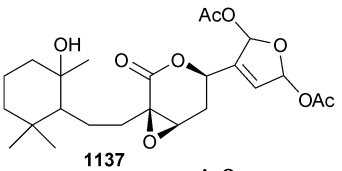
1135

Although not the first synthesis, a potential biomimetic synthesis of (−)-dolabriferol has been reported, utilising a retro-Claisen rearrangement of a 1,3-diketone to yield the non-contiguous polypropionate skeleton.[898] Dactylomelatriol **1136** (*Aplysia dactylomela*, La Gomera, Canary Is.) contains a rare sesquiterpene skeleton previously seen in a metabolite isolated[899] from a liverwort.[900]

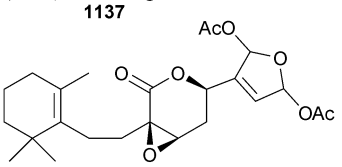


1136

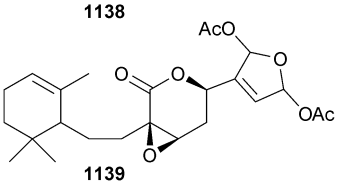
Use of either silica gel or $AgNO_3$-impregnated silica gel chromatography yielded diterpenes thuridillin D–F **1137–1139** from the sacoglossan mollusc *Thuridilla splendens* (Mooloolaba, Queensland).[901] Alkenes **1138** and **1139** may be purification artefacts of tertiary alcohol **1137**.



1137

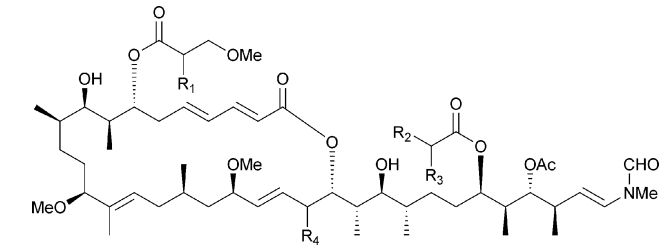


1138

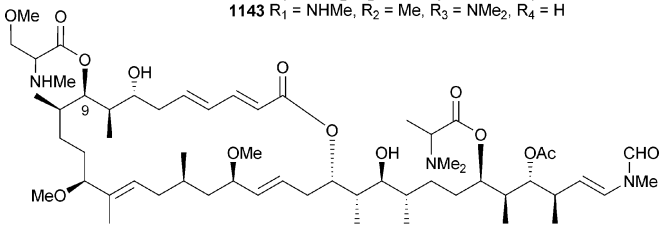


1139

Five new aplyronine congeners D–H **1140–1144** were reported as cytotoxic constituents of *Aplysia kurodai* (Mie Prefecture, Japan).[902] While aplyronines D–G were equipotent or more cytotoxic (HeLa S_3 cells) than aplyronine A,[903] aplyronine H was less cytotoxic highlighting that translocation of the di (or tri) methylserine residue to C-9 is detrimental to cell-based activity. Photoaffinity probes of aplyronine A have been used to identify two actin-related proteins Arp2 and Arp3 as target binding proteins.[904] As neither Arp2 nor Arp3 were covalently bound directly by the probes, it was suggested these proteins bind to the aplyronine A-actin complex or to oligomeric actin. Further evidence for the disconnect between actin-depolymerising activity and whole cell cytotoxicity of aplyronine A was observed for a synthetic hybrid combining the macrolactone of aplyronine A and the sidechain of the actin-depolymerising sponge metabolite mycalolide B.[905] While the hybrid was as potent as aplyronine A as an actin depolymeriser it was *ca*. 1000-fold less cytotoxic towards HeLa S_3 cells.[906]



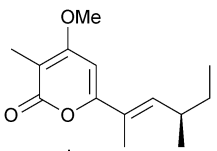
1140 $R_1 = R_3 = NMe_2$, $R_2 = R_4 = H$
1141 $R_1 = R_3 = NMe_2$, $R_2 = R_4 = Me$
1142 $R_1 = NMe_2$, $R_2 = Me$, $R_3 = NHMe$, $R_4 = H$
1143 $R_1 = NHMe$, $R_2 = Me$, $R_3 = NMe_2$, $R_4 = H$



1144

Biosynthetic incorporation studies have established that the C_3 units present in the opistobranch mollusc *Ercolania funerea* metabolite 7-methyl-cyercene[907] result from intact incorporation of propionic acid.[908] What is intriguing about this story is that the same metabolite is biosynthesised by the terrestrial fungus *Leptosphaeria maculans*/*Phoma lingam via* the acetate/SAM pathway.[909] The mollusc incorporation study made use of analysis of cross-peak volumes in HSQC and HMBC data to determine sites of isotopic enrichment.

SAR studies on the cytotoxic cyclic depsipeptide kulokekahilide-2 (*Philinopsis speciosa*)[910,911] have identified the importance of the cyclic structure (but not the ring size), and the configuration at 21-L-Ala and 24-D-MePhe as important determinants of potency.[912,913] *para*-Chloro-24-MePhe analogues were found to be particularly potent cytotoxins. The structures of α-pyrone polyketides aplysiopsene A–D (*Aplysiopsis formosa*)[914] have been confirmed by synthesis, with the absolute configuration of aplysiopsene D **1145** defined by synthesis of the enantiomer.[915]



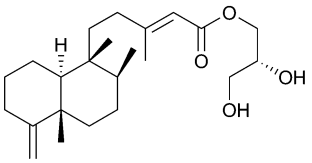
†**1145**

Also confirmed by synthesis are the structures of the 1,2,4-oxadiazole ring-containing alkaloids phidianidine A and B (*Phidiana militaris*).[916–918] In addition to a number of known PUFAs, heneicosa-5,8,11,14-tetraenoic acid (21;4 *n*-7) was reported as a new natural product from the opistobranch mollusc *Scaphander lignarius* (Arctic).[919] Mild, non-specific cytotoxicity was observed.

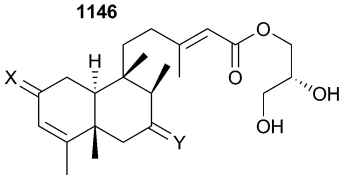
The biosynthesis of the aromatic polyketides previously reported from Mediterranean specimens of *S. lignarius*[920,921] has been investigated identifying the functional expression of a phenylalanine ammonia lyase (PAL), representing the first report of PAL in animal cells, and that biosynthesis is located specifically to the mantle border Blochmann's glands cells.[922]

The γ-pyrone tridachiahydropyrone (*Tridachia crispata*)[923,924] and two putative polyene precursors insert themselves into two phospholipid vesicle models of membranes, indicative perhaps of their location in molluscan cells.[925] Mass spectrometry imaging, using a perfluorinated siloxane-pretreated porous silicon support, of the hypobranchial gland of the mollusc *Dicathais orbita*, has established the spatial distribution of brominated precursors of Tyrian purple dye.[926]

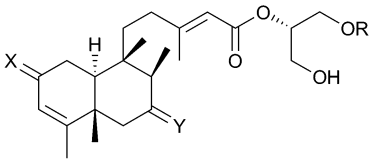
New indigoids, of undefined structure, were identified by LC-MS/MS (Orbitrap) analysis of dye from *Hexaplex trunculus* (French Mediterranean coast).[927] In addition to three previously reported palmadorin diterpene glyceride esters,[928] sixteen new congeners **1146–1161** were isolated from specimens of the nudibranch *Austrodoris kerguelenensis* (Anvers Is., Palmer Station, Antarctic).[929] Six of the diterpenes inhibited (μM) the growth of human erythroleukaemia cells, with the most potent analogue **1155** also inhibiting Jak2-STAT5 and Erk1/2 activation pathways.



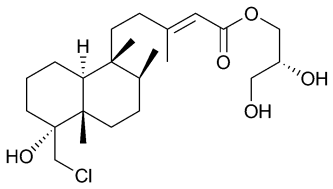
1146



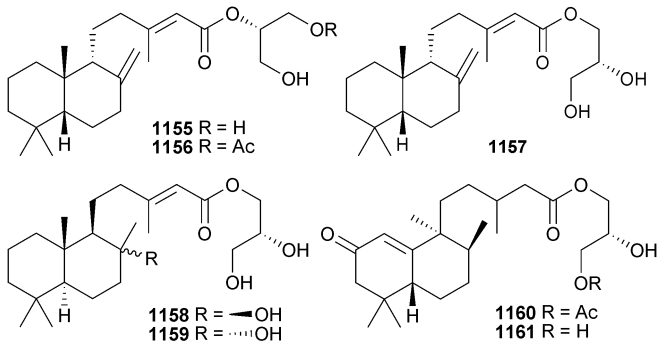
1147 X = O, Y = ◄OH,H
1148 X = H,H, Y = ◄OH,H
1149 X = O, Y = H,H
1150 X = Y = O



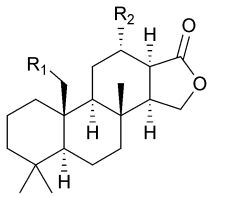
1151 R = Ac, X = H,H, Y = ◄OH,H
1152 R = H, X = O, Y = ◄OH,H
1153 R = H, X = Y = O



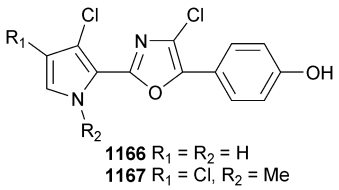
1154



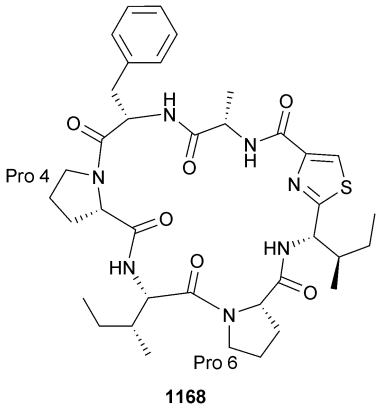
Investigation of the organelle distribution of metabolites in a single specimen of *Chromodoris albopunctata* (Inner Gneerings Reef, Mooloolaba, Queensland) yielded the sponge-derived diterpene **1162** and known analogues[930,931] from the internal organs, while **1163–1165** were isolated from the mantle extract.[932]



New phorboxazole congeners **1166** and **1167** were isolated from the dorid nudibranch *Aldisa andersoni* (Muttom Coast, India).[933] Both metabolites were feeding deterrents in a shrimp bioassay and mildly growth inhibitory to a panel of HTCLs, while **1167** was determined to exert cytostatic effects towards two of the tumour cell lines.



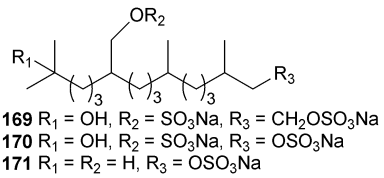
Tambjamine alkaloids C, E, F and BE-18591,[934–936] isolated from nudibranchs, ascidians or a bacterium, acted as efficient transmembrane anion transporters, releasing chloride from phospholipid vesicles.[937] Syntheses of the *Hexabranchus sanguineus* cyclic peptides[938] sanguinamide A **1168**[939] and B[940] have been reported. The *cis*,*cis* proline configuration originally proposed for sanguinamide A was corrected to Pro 4 *cis*, Pro 6 *trans* as shown – the resultant structure is stabilised by transannular hydrogen bonds making the natural product orally bioavailable in rats. In the case of sanguinamide B, final step macrocyclisation yielded the *cis*,*cis*-conformer as the dominant (kinetic control) product, while heating afforded a 1 : 1 mixture of the *trans*,*trans* natural product and *trans*,*cis*-conformer. The mixture of the latter two conformers inhibited *P. aeruginosa* fimbriae twitching motility.



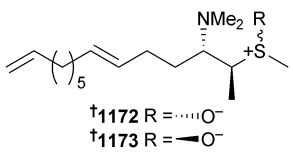
Analogues of (−)-jorumycin (*Jorunna funebris*),[941] with variation at the pendant methylene C-22, exhibited varied levels of potency towards a panel of HTCLs. A hippuric acid ester derivative exhibited broad spectrum nM potency.[942]

11 Tunicates (ascidians)

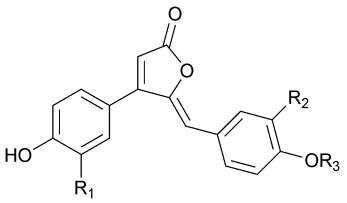
The 51 new tunicate-derived natural products presented in this review is one of the highest number reported per annum over the last decade. New alkyl sulfates **1169** and **1170** (*Aplidium elegans*) and **1171** (*Ciona edwardsii*) were reported from ascidians collected in the Bay of Naples.[943] While **1169** and **1170** exhibited cytotoxicity towards murine macrophage cells, **1171** was inactive, highlighting the importance of sulfate groups for biological activity.



Two unusual dimethylamino lipidsulfoxides aplisulfamine A **1172** and B **1173** were isolated from *Aplidium* sp. (Pozzuoli, Naples).[944] A comprehensive combination of nOe analysis, *J*-based configurational analysis, and calculated ^{13}C chemical shift and ECD data secured the absolute configurations of the alkaloids.

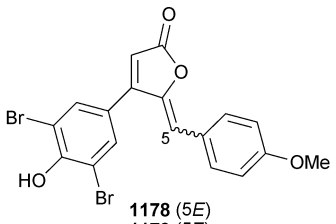


Three separate studies reported new congeners of the rubrolide and cadiolide families of furanones. In the first, South African specimens of *Synoicum globosum* (Algoa Bay) yielded known rubrolides E and F[945] in addition to new more highly brominated analogues **1174–1177**.[946] Variable levels of antibacterial activity were observed for all six metabolites.

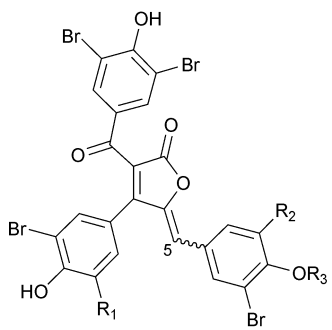


1174 R_1 = H, R_2 = Br, R_3 = Me
1175 R_1 = Br, R_2 = R_3 = H
1176 R_1 = Br, R_2 = H, R_3 = Me
1177 R_1 = R_2 = Br, R_3 = H

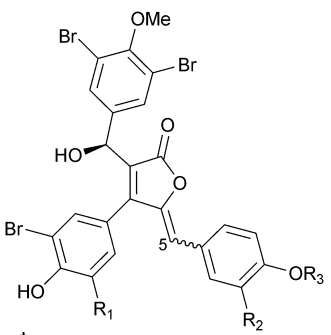
As well as rubrolide P **1178** and **1179** and **1177** (3′-bromorubrolide F, which the authors of this second study named rubrolide Q), a collection of *Pseudodistoma antinboja* (Tong-Yeong City, South Sea, S. Korea) also afforded four new cadiolide analogues C–F **1180–1184**.[947] Some of the latter examples, in addition to the known co-metabolite cadiolide B,[948] exhibited potent antibacterial activity towards MSSA and MRSA strains. As well as cadiolide E, related furanones cadiolide G **1185**, H **1186**,**1187** and I **1188** and diesters synoilide A **1189**,**1190** and B **1191**,**1192** (*Synoicum* sp., Chuja-do, S. Korea) were evaluated for antibacterial activity as well as activity in sortase A, isocitrate lyase (ICL) and Na^+/K^+-ATPase assays.[949] Cadiolides E, G–I exhibited antibacterial activity towards Gram-positive and Gram-negative bacteria, while the diesters were inactive, helping define an important SAR parameter. All metabolites exhibited activity towards the ATPase target, and all except cadiolide H were active against ICL but only cadiolide E inhibited sortase A (weak). Using calculated ECD data, the absolute configuration of **1185** was also assigned.



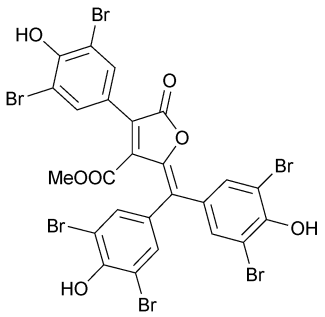
1178 (5*E*)
1179 (5*Z*)



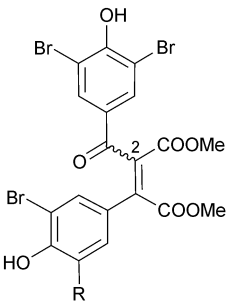
1180 R_1 = R_2 = R_3 = H, (5*Z*)
1181 R_1 = Br, R_2 = R_3 = H, (5*Z*)
1182 R_1 = R_3 = H, R_2 = Br, (5*Z*)
1183 R_1 = R_2 = H, R_3 = Me, (5*Z*)
1184 R_1 = R_2 = H, R_3 = Me, (5*E*)



†**1185** R_1 = R_3 = H, R_2 = Br, (5*Z*)
1186 R_1 = Br, R_2 = H, R_3 = Me, (5*Z*)
1187 R_1 = Br, R_2 = H, R_3 = Me, (5*E*)



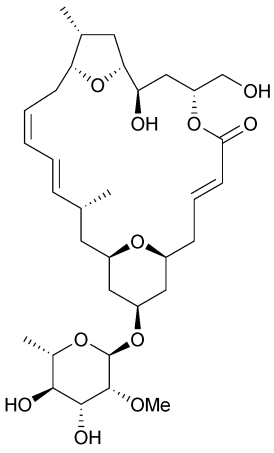
1188



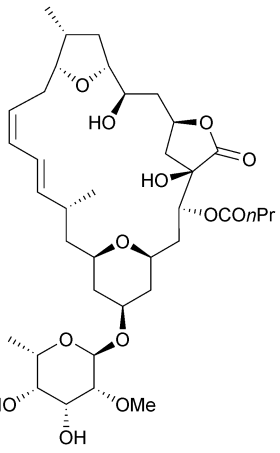
1189 R = Br, (2*Z*)
1190 R = Br, (2*E*)
1191 R = H, (2*Z*)
1192 R = H, (2*E*)

A small library of semi-synthetic analogues of eudistomin Y_2 and Y_3 was prepared and evaluated against the same set of biological targets used for the cadiolides; only one analogue exhibited increased cytotoxic potency, while all other analogues were less active than the natural products in the respective assays.[950] New efficient syntheses of rubrolides C and E have been reported.[951]

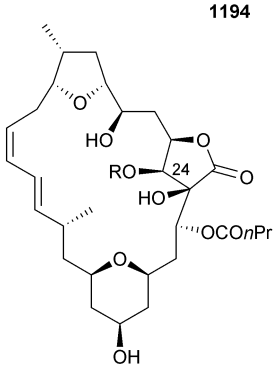
Potently cytotoxic macrolides mandelalide A–D **1193–1196** were isolated from *Lissoclinum* sp. (Algoa Bay, South Africa); relative configurations were assigned by extensive *J*-based and rOe analysis and absolute configuration was assigned to **1193** by a combination of sugar analysis (GC-MS) and rOe data.[952,953] Note that the structure diagram in the original paper[952] implying mandelalide C to be a hydroperoxide at C-24, is a typographical error, and that the macrolide is indeed a C-24 carbinol.[954]



†**1193**

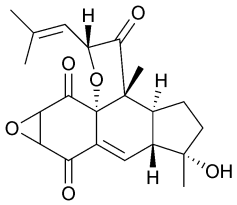


1194

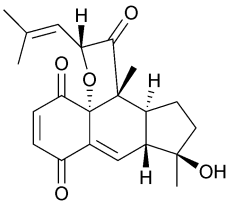


1195 R = H
1196 R = CO*n*Pr

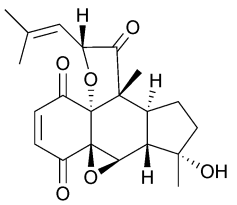
New rossinone congeners **1197–1199** (*Aplidium fuegiense*, dredge Western Weddell Sea, Antarctica) were localised in extracts of the ascidian internal organs.[955,956] Both rossinone B[957] and a mixture of meridianin alkaloids exhibited feeding deterrence towards the sea star *Odontaser validus* and amphipod *Cheirimedon femoratus*.[958]



1197

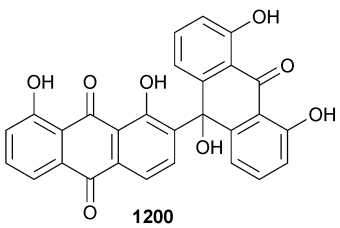


1198

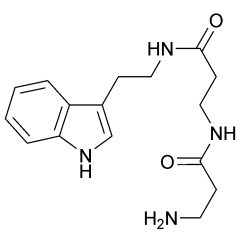


1199

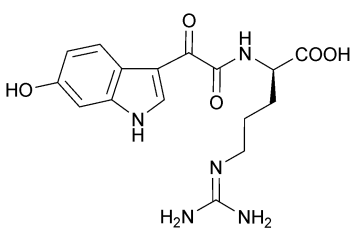
In contrast to the monomeric, presumed precursor 1,8-dihydroxy-9,10-anthraquinone, the anthrone-anthraquinone dimer albopunctatone **1200** (*Didemnum albopunctatum*, Swain Reefs, Great Barrier Reef) was equipotent towards chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum*.[959] While a previous study of an Australian collection of *Leptoclinides durus* afforded, amongst other metabolites, (+)-(*S*)-leptoclinidamine B,[960] Indonesian (Lembeh Strait, North Sulawesi) specimens of *L. dubius* have yielded leptoclinidamide **1201** and (−)-(*R*)-leptoclinidamine B **1202**.[961]



1200

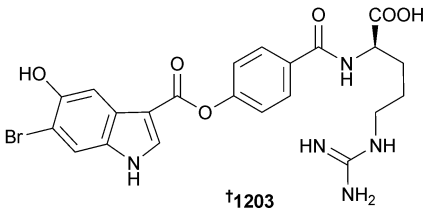


1201

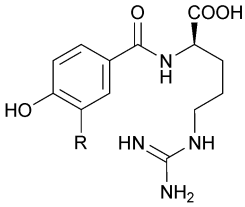


†**1202**

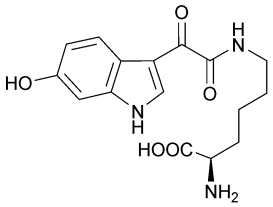
Further investigation of an extract of *Herdmania momus* (Jeju Is., S. Korea), from which anti-inflammatory amino acid derivatives had been previously identified,[962] afforded new congeners herdmanine E–L **1203–1210**, in addition to (−)-(*R*)-leptoclinidamine B.[963,964] The latter compound and herdmanine I and K all transactivated PPAR-γ in a cell-based luciferase reporter assay.



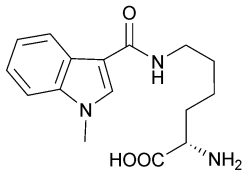
†**1203**



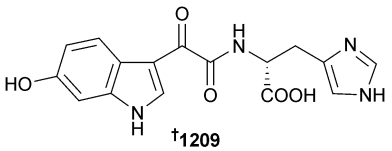
†**1204** R = Br
†**1205** R = OMe
†**1206** R = H



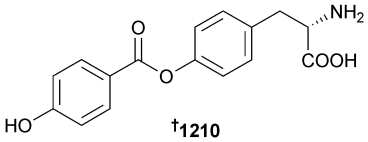
†**1207**



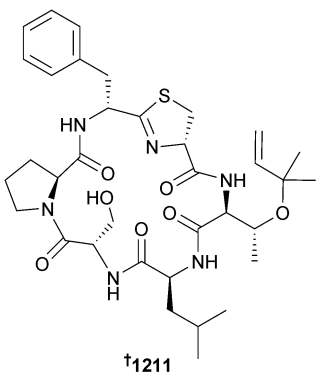
†**1208**



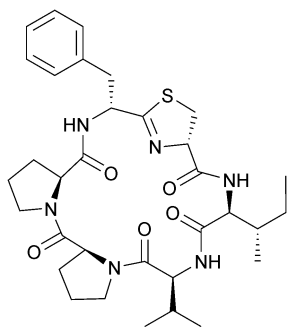
†**1209**



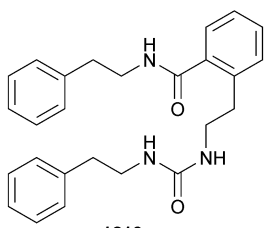
†**1210**



†**1211**



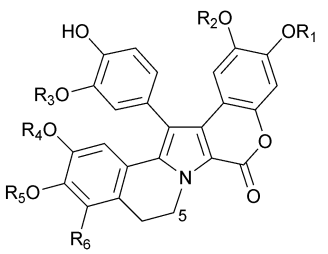
†**1212**



1213

Mollamides E **1211** and F **1212** and molleurea A **1213** were obtained from *Didemnum molle* (New Britain, Papua New Guinea) with NMR chemical shift and nOe data defining the proline conformations as *cis* in **1211** and *cis* and *trans* in **1212.**[965] These same two peptides have previously been identified as predicted products from the genome sequence of *Prochloron* spp., and detected by LC-MS in an ascidian[966] or in *E. coli* heterologously expressing the pathway.[967]

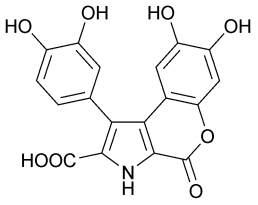
Australian collections of *Didemnum* sp. (Wasp Is., New South Wales, and Northern Rottnest Shelf, Western Australia) afforded an extensive number of lamellarin alkaloids including the new members lamellarin A1–A6 **1214–1219**.[968] Evaluation of the library identified examples exhibiting cytotoxicity towards a human carcinoma cell line and a P-gp-overexpressing variant, while addition to doxorubicin (P-gp substrate) in the same assays identified a permethylated semi-synthetic analogue as being the best inhibitor of P-gp activity.



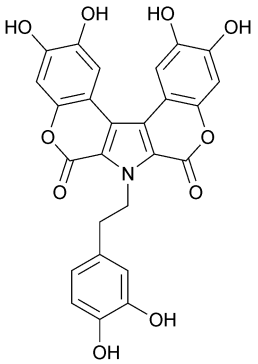
1214 $R_1 = R_2 = R_5 = R_6 = H$, $R_3 = R_4 = Me$
1215 $R_1 = R_2 = H$, $R_3 = R_4 = R_5 = Me$, $R_6 = OH$
1216 $R_1 = R_7 = H$, $R_2 = R_3 = R_4 = R_5 = Me$
1217 $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = H$
1218 $R_1 = R_2 = R_4 = R_5 = R_6 = H$, $R_3 = Me$, $\Delta^{5,6}$
1219 $R_1 = R_3 = R_4 = Me$, $R_2 = R_5 = R_6 = H$

Further investigation of the Northern Rottnest Shelf specimens of *Didemnum* sp. also yielded ningalins E–G **1220–1222.**[969] Ningalins C, D and G were potent inhibitors of CK1δ, CDK5 and GSK3β kinases.

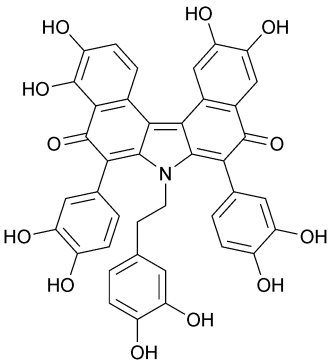
Biological evaluation of a mixture of two new staurosporine analogues **1223** and **1224** (*Eudistoma vannamei*, Ceara state, Brazil) identified the mixture as more potent than the parent compound.[970] Synthesis of the structure originally proposed for palmerolide C (*Synoicum adareanum*)[971] has required correction of configurations at C-9 and C-10 to those shown in **1225.**[972] Synthesis of the structure originally proposed for haouamine B (*Aplidium haouarianum*)[973] combined with re-examination/re-acquisition of NMR data for haouamine B peracetate requires the structure to be corrected to the *ortho*-diphenol (catechol) shown in **1226.**[974]



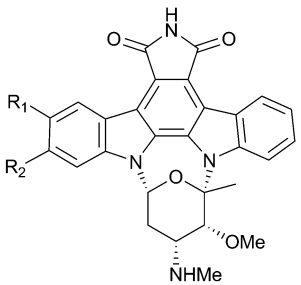
1220



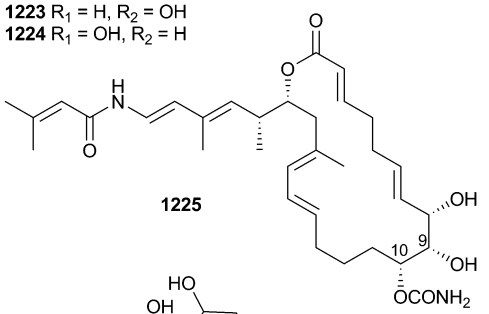
1221



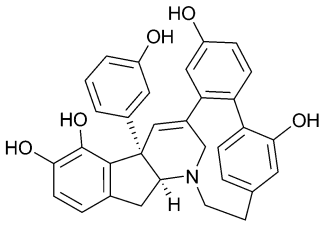
1222



1223 $R_1 = H$, $R_2 = OH$
1224 $R_1 = OH$, $R_2 = H$



1225



1226

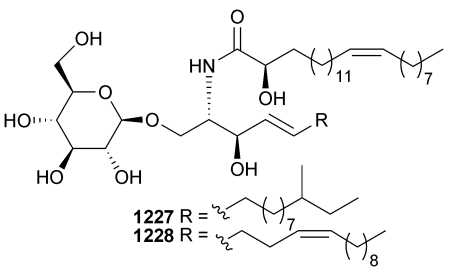
A stereoselective and convergent synthesis of lepadiformines A–C (*Clavelina lepadiformis* and *C. moluccensis*)[975,976] has been reported, confirming the absolute configuration of lepadiformine B.[977] A thorough investigation of different methods used to determine the absolute configuration of synoxazolidinone natural products (*Synoicum pulmonaria*)[978,979] has highlighted the value and reliability of VCD.[980] The structures

and absolute configurations of the brominated 1,2,3,4-tetrahydro-β-carboline alkaloids eudistomidin G–I (*Eudistoma glaucus*)[981,982] have been confirmed by synthesis[983] as have those of an iodinated nucleoside[984] originally reported from *Diplosoma* sp.[985,986]

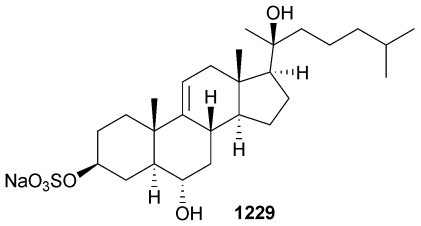
Biomimetic syntheses of the apoptosis-inducing prenylated thiazinoquinones thiaplidiaquinone A and B (*Aplidium conicum*)[987] have been reported.[988,989] Two different routes for the synthesis of the antimalarial pyrroloquinoline aplidiopsamine A (*Aplidiopsis confluata*)[990] have been reported,[991] with one[992] of the studies also identifying the natural product as a moderate inhibitor of rat and human PDE4. Total synthesis of the structure proposed for didemnaketal A (*Didemnum* sp.)[993] gave a product that exhibited different NMR spectra compared to those reported for the natural product, calling into question the original stereochemical assignments.[994]

12 Echinoderms

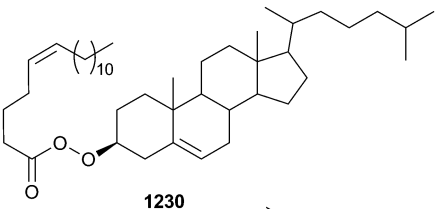
The 37 new metabolites reported from echinoderms in 2012 is a modest increase from the number reported in 2011. Known sulfated alkanes 2,6-dimethylheptyl sulfate, octyl sulfate and decyl sulfate as well as new sulfated alkenes (5*Z*)-dec-5-en-1-yl sulfate and (3*E*)-dec-3-en-1-yl sulfate were isolated from the sea cucumber *Apostichopus japonicus* (commercially supplied).[995] All of the metabolites exhibited moderate to potent cytotoxicity and antibiotic activity towards *E. coli*. Cerebrosides **1227** and **1228** were obtained as pure entities for the first time (*Cucumaria frondosa*, undefined location),[996] with **1227** having previously been reported as a component of a mixture from *Stichopus japonicus*.[997]

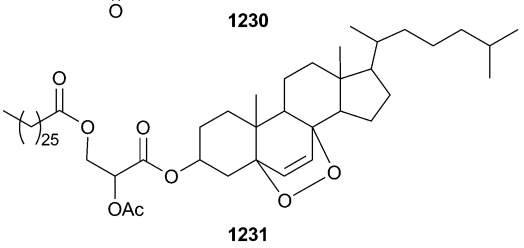


Crude preparations of cerebrosides from the sea cucumber *Acaudina molpadioides* (Zhejiang Province, China) and the starfish *Asterias amurensis* (S. Hokkaido, Japan) exhibited pronounced *in vitro* and *in vivo* antitumour activity and appear to function by induction of apoptosis *via* a mitochondrial-mediated pathway.[998] A series of complex ganglioside molecular species PNG-1 (disaccharide), PNG-2A and PNG-2B (tetraosides) were reported from the starfish *Protoreaster nodosus* (Katsuren, Okinawa).[999] The sterol sulfate mithrotriol **1229** was isolated as a non-cytotoxic component of the starfish *Mithrodia clavigera* (Maldives Is.).[1000]

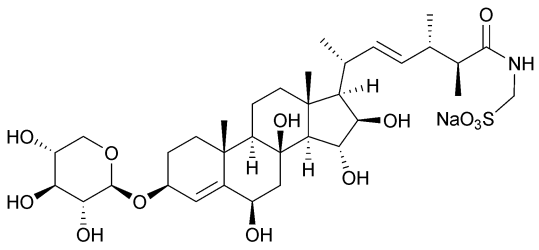


An unusual peroxy-ester lucunterperacetate **1230** and the more classical peroxy-bridged sterol peroxylucunterine **1231** were reported from the urchin *Echinometra lucunter* (Dakar, Senegal).[1001]

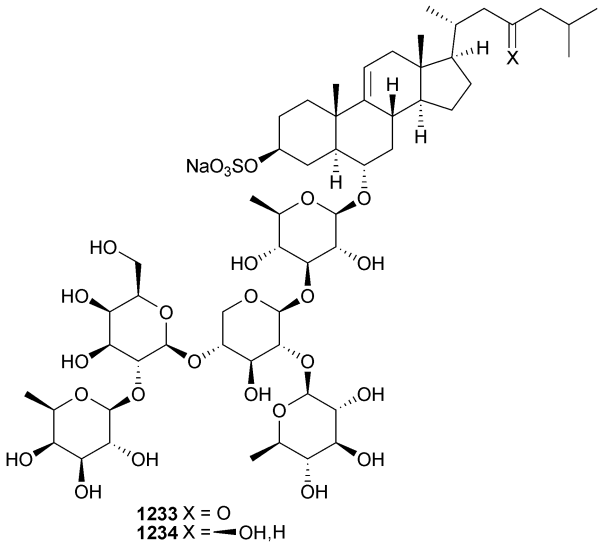




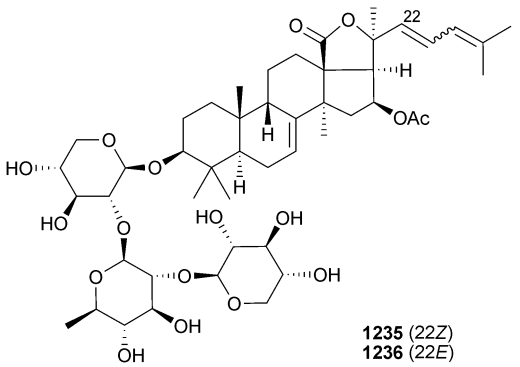
An amidotaurine β-D-xyloside, fisherioside A **1232**, was isolated from the starfish *Leptasterias fisheri* (Sakhalin Is., Sea of Okhotsk),[1002] while pentaosides lethasteriosides A **1233** and B **1234** were reported from *L. fusca* (Posyet Bay, Sea of Japan).[1003] Lethasterioside A, while being weakly cytotoxic, had pronounced ability to inhibit colony formation of tumour cells in a soft agar clonogenic assay.



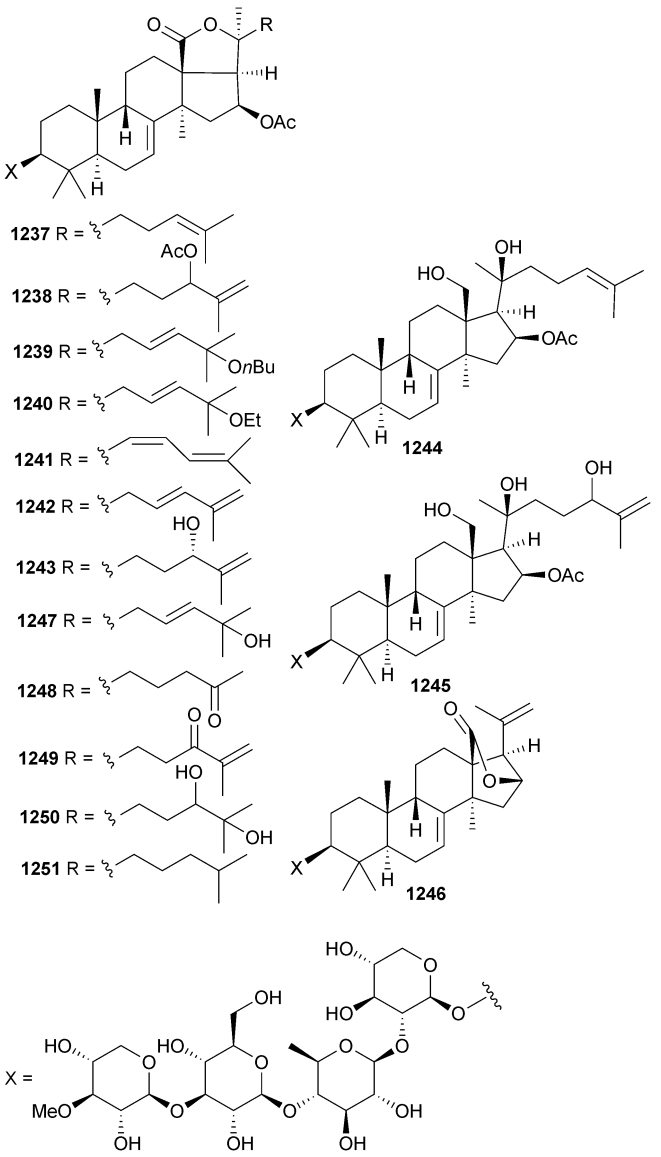
In five separate accounts, a series of tri-, tetra- and pentaosides were reported from the same collection of the sea cucumber *Eupentacta fraudatrix* (Peter the Great Gulf, Sea of Japan). Of the two side-chain isomeric triosides, cucumarioside B_1 **1235** and B_2 **1236**, only the latter demonstrated cytotoxicity and haemolytic activity (mild).[1004] Minor metabolite tetraosides cucumarioside A_1–A_{15} **1237–1251** all incorporated the same tetrasaccharide unit.[1005–1007] Cucumariosides A_1, A_5,



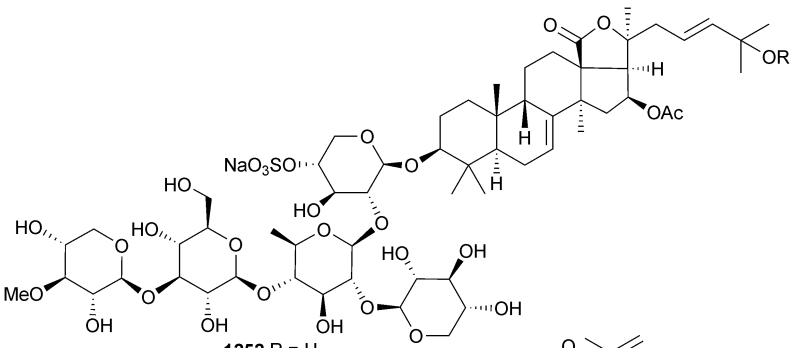
A_{10} and A_{11} are desulfated derivatives of previously reported cucumariosides G_1, G_3, G_2 and G_4, respectively[1008–1011] and cucumarioside A_{15} appears to be identical to a previously reported starfish metabolite.[1012] Cucumariosides A_1, A_2, A_6, A_8 and A_{13} were the most active of the series in a range of biological studies assessing cytotoxicity, antifungal and haemolytic activities. Out of the three pentaosides cucumarioside H_2–H_4 **1252–1254**, there was more pronounced cytotoxicity and haemolytic activity for the likely artefactual ethyl ether, cucumarioside H_4.[1013]



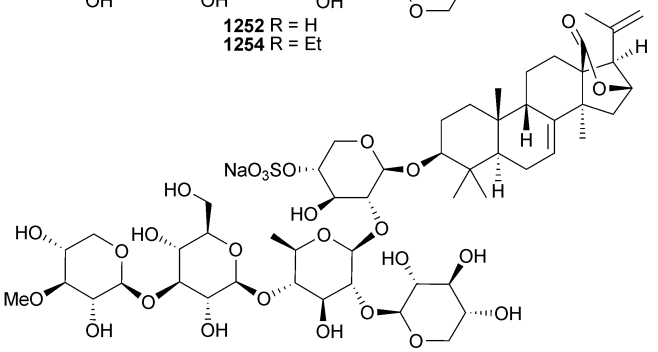
The sea cucumber *Apostichopus japonicus* is used as a food and a tonic in China – investigation of constituents of specimens (Dalian coast, Bohai Sea of China) identified penta- and hexaosides **1255**, holotoxin D–G **1256–1259**[1014] and holotoxin D_1 **1260** and 24,25-dihydroxyholotoxin A_1 **1261**.[1015] Broad spectrum antifungal activity was observed for holotoxins D–G and holotoxin D_1, with indications that the presence of a lactone and a double bond in the sidechain at C-25 increases activity.



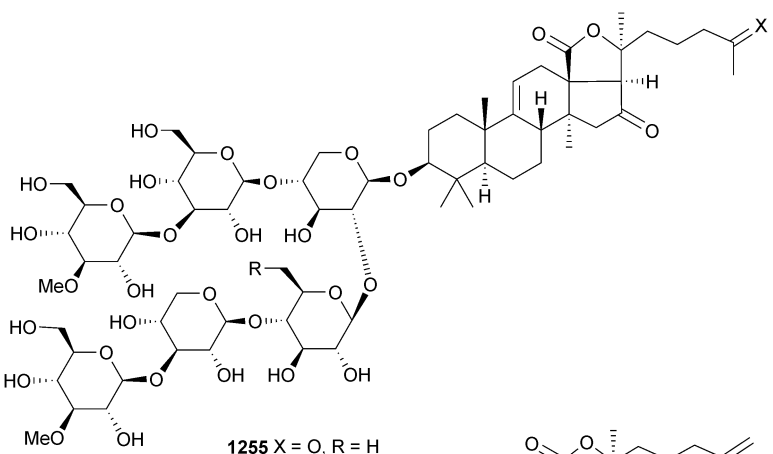
The antifungal properties of the closely related hexaoside, bivittoside D (*Bohadschia vitiensis*),[1016] have also been investigated[1017] while tetraosides echinosides A and B (*Actinopyga echinites* and *Holothuria polii*)[1018] demonstrated schistomicidal activity *in vitro*.[1019] The antitumour effects of the echinosides A and B have also been investigated, establishing that each echinoside can induce apoptosis in human HepG2 cells *via* the mitochondrial pathway, induce cell cycle arrest in G_0/G_1 phase and reduce tumour growth *in vivo* (ip dosing).[1020] Interestingly, desulfated echinoside B suppressed NF-κB expression, while echinoside A did not. The related tetraoside neothyonidioside[1021] (*Australostichopus mollis*) demonstrated antifungal activity by binding to ergosterol, leading to altered membrane curvature and fusion capability.[1022]



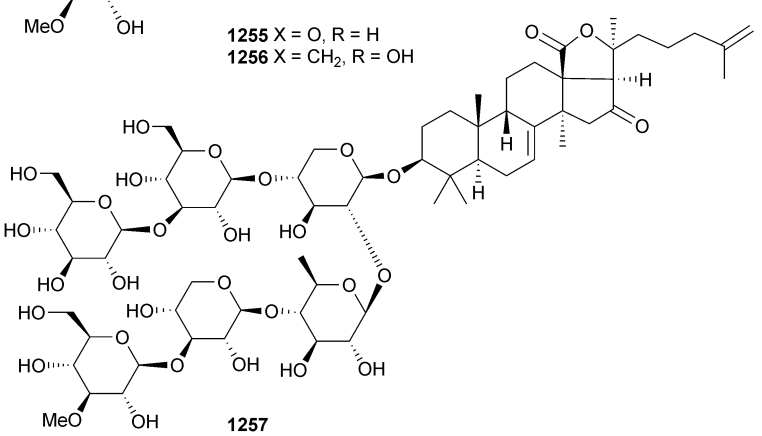
1252 R = H
1254 R = Et



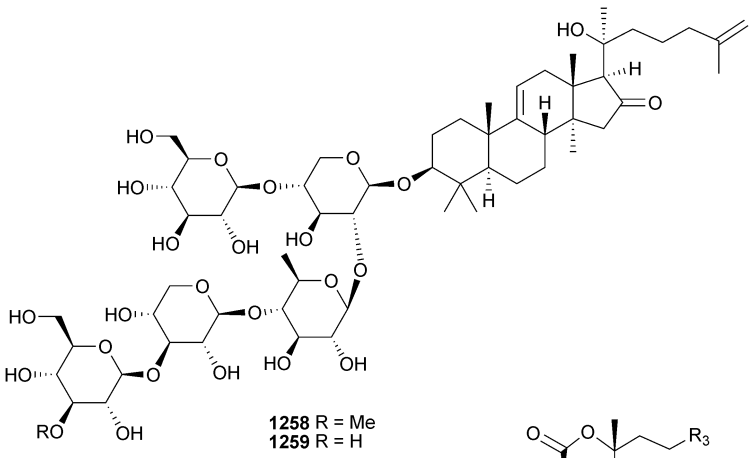
1253

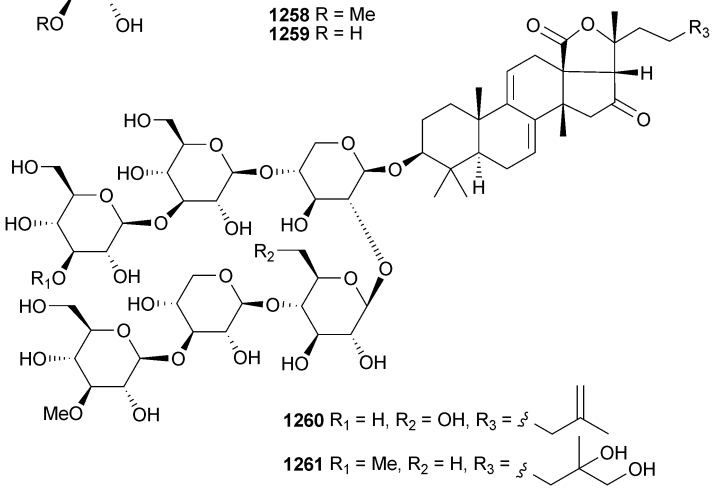


1255 X = O, R = H
1256 X = CH_2, R = OH



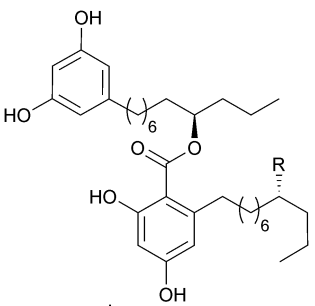
1257



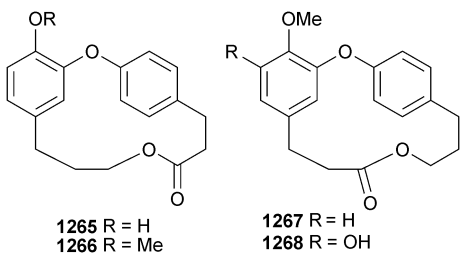


13 Mangroves

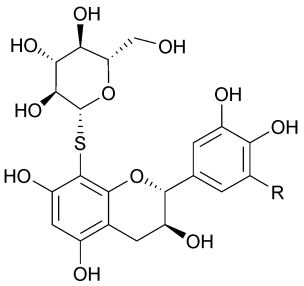
Three known dimeric alkyl aromatics integracin A **1262**, B **1263** and dehydroxy-B **1264** were isolated from *Sonneratia hainanensis* (Hainan Province, China), and absolute configurations assigned to **1262** (degradation and Mosher), **1263** (degradation and optical rotation) and **1264** (loosely on biogenetic grounds).[1023]



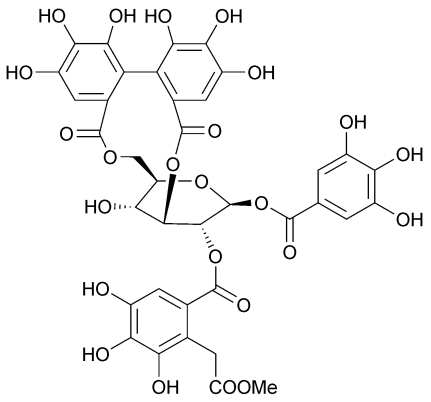
Investigation of the chemistry of the bark of *Aegiceras corniculatum* (Nizampatnam coast, India) yielded corniculatolide macrolides **1265–1268**.[1024]



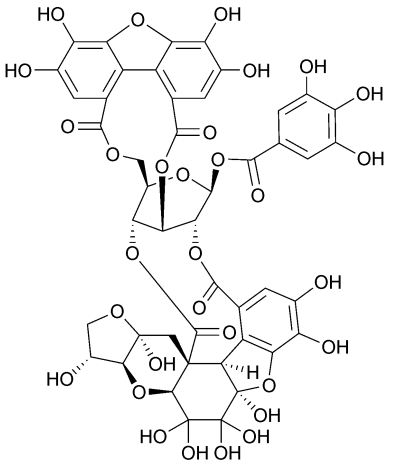
Four polyphenols excoecariphenol A–D **1269–1272**, including two unusual thioglycosides, were reported from *Excoecaria agallocha* (China).[1025] Excoecariphenol D inhibited NS3-4A protease and exhibited anti-hepatitis C virus (HCV) activity in two assays.



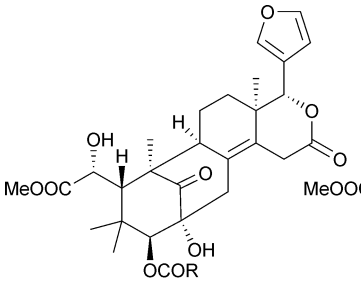
1269 R = H
1270 R = OH



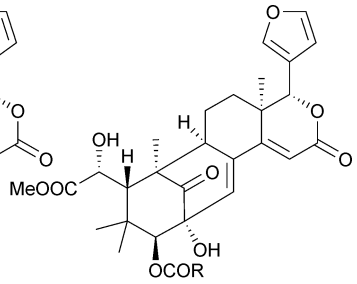
1271



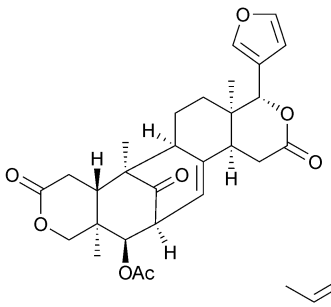
1272



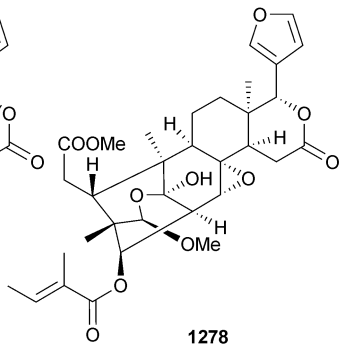
1273 R = *i*Pr
1274 R = *s*Bu



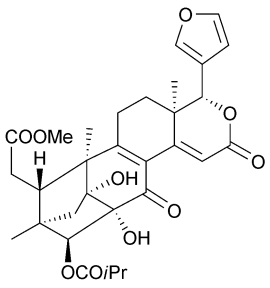
1275 R = *i*Pr
1276 R = *s*Bu



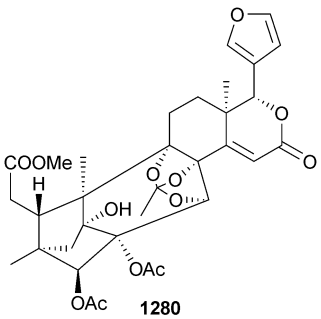
†**1277**



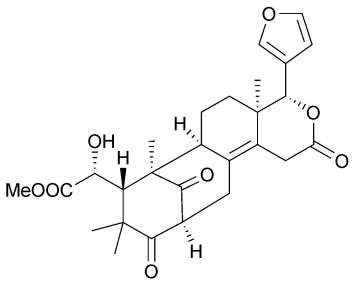
1278



1279



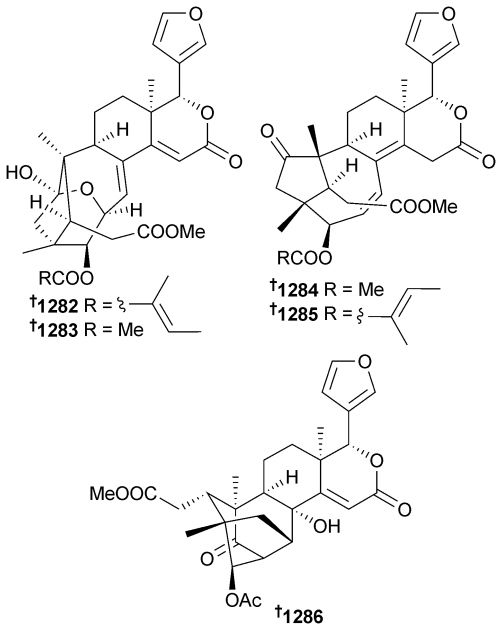
1280



†**1281**

Extracts of seeds of *Xylocarpus moluccensis* collected at two sites (Godavari and Krishna estuaries, Andhra Pradesh, India) yielded new limonoids **1273–1280** in addition to several known congeners[1026] including **1281**.[1027] Absolute configuration was assigned to both **1277** and **1281**. The known 2-hydroxyfissinolide and **1273**, **1274** and **1281** exhibited antifeedant activity towards third-instar larvae of *Brontispa longissima*, with 2-hydroxyfissinolide being the most active.

The structurally rare or unique limonoids andhraxylocarpin A–E **1282–1286** were isolated from seeds of *X. moluccensis* and *X. granatum* (Godavari and Krishna estuaries, Andhra Pradesh, India) with relative configurations of **1282** and **1284** established by X-ray analysis and absolute configurations assigned to all metabolites *via* quantum chemical calculations of CD or optical rotation properties.[1028] A bioinspired [4 + 2] dimerisation of a 4-hydroxybutenolide precursor has been used to confirm the structure of paracaseolide A,[1029] recently reported from stem bark extract of *Sonneratia paracaseolaris*.[1030]



14 Miscellaneous

The cyanobacterial neurotoxin β-*N*-methylamino-L-alanine has been detected in fins of seven species of sharks in South Florida, raising the possibility of human exposure through consumption.[1031] Using a previously reported cuttlefish (*Sepia officinalis*) neuropeptide[1032] as a biologically inactive starting point, substitution of aza-β^3-amino acids led to the discovery of analogues with increased potency.[1033] The data suggested that a peptide helical structure was not necessary for biological activity and that structural flexibility was important.

15 Conclusion

MNP research can be conveniently divided into two areas; the discovery of new compounds from macro and micro marine sources, and all other aspects including those involved with syntheses of newly discovered compounds, corrections of structure and/or stereochemistry, assignment of stereochemistry, reviews, bioactivity and biosynthetic studies along with ecological and general surveys of marine species. All but the ecological and survey aspects are normally covered each year in this annual review. Just how many corresponding authors are involved worldwide in this effort? This information is shown in Table 1 below. A survey of the literature from 2007 to 2012 was undertaken to identify those corresponding authors (hereinafter referred to as 'authors') involved in these two broad areas as well as the distribution of effort by country. Interrogation of the marine literature database MarinLit[1034] identified all papers reporting new compounds published over that period, the year of publication and the author responsible (**Compounds**) as well establishing a comparable set of results for papers reporting syntheses, corrections of structure, stereochemistry, reviews, ecological studies, surveys, bioactivities *etc* (**Other Aspects**). After compilation by author the results were assessed and placed into one of three categories, **A**, **B** or **C**. The placement was based on the numbers of papers published by each author over the six-year period and the frequency at which they were published. For the **Compounds** group the numbers of papers published by an individual author ranged down from 65 to just one and the frequency from every year to one year out of the six. Typically for an **A** placement in **Compounds** the authors needed to have published ≥10 papers and published in at least three of the years between 2007–2012. As the numbers and/or frequency diminished the rankings decreased. A comparable system based on ≥7 papers was used for **Other Aspects** where the range of papers from one author was from 19 downwards. While varying the ranking system might change the relative populations of the **A**, **B** and **C** categories, the totals remain the same. A comparable system based on ≥7 papers was used for **Other Aspects** where the range of papers from one author was from 19 downwards. While varying the ranking system might change the relative populations of the **A**, **B** and **C** categories, the totals remain the same. That is, 668 authors contributed papers on isolation only, while 286 of these authors, along with a further 1842 authors, published in the **Other Aspects** area. The crossover was usually in the direction of specialist isolation chemists also undertaking the likes of synthetic/stereochemical work. The countries that were dominant (>15 authors) in the **Compounds** area are (in alphabetical order): Australia, China, Egypt, France, Germany, India, Italy, Japan, Russia, South Korea, Spain, Taiwan and the USA. For **Other Aspects** it is a

Table 1 Worldwide distribution of corresponding authors for MNP publications

	Compounds				Other Aspects			
	A	B	C		A	B	C	
Australia	5	5	5	**15**	2	8	50	**60**
Brazil		2	5	**7**	4	8	73	**85**
Canada	2	1	6	**9**	2		46	**48**
China	23	23	134	**180**	5	17	190	**212**
Colombia		1	3	**4**	1	1	3	**5**
Egypt	1	2	14	**17**	1		13	**14**
France	3	2	20	**25**	3	9	109	**121**
Germany	4	5	22	**31**	5	14	101	**120**
India			17	**17**	6	11	105	**122**
Italy	6	4	11	**21**	1	7	50	**58**
Japan	9	20	68	**97**	12	35	188	**235**
Malaysia	1		4	**5**		2	9	**11**
New Zealand	1	1	6	**8**	4	2	15	**21**
Norway		1	3	**4**	1	1	13	**15**
Russia	8	4	4	**16**	1	5	46	**52**
South Korea	6	5	17	**28**	2	7	67	**76**
Saudi Arabia		1	3	**4**			5	**5**
Spain	2	2	12	**16**	4	6	94	**104**
Taiwan	4	5	7	**16**		3	25	**28**
Thailand	2	3	5	**10**			12	**12**
UK	1	1	7	**9**	4	10	75	**89**
USA	15	13	67	**95**	29	51	341	**421**
Other countries[a]	3	7	24	**34**	3	16	195	**214**
	96	**108**	**464**	**668**	**90**	**213**	**1825**	**2128**

[a] There were 40 countries that each had fewer than 4 corresponding authors in the **Compounds** section.

comparable list with the addition of Brazil, Canada, New Zealand, Norway, and the UK.

The 96 **A**-ranked authors in **Compounds** reported 4033 compounds in 1234 papers, those in **B** (108) were responsible for 1264 compounds in 435 papers and for **C** (464) a total of 1282 compounds in 549 papers. In **Other Aspects** the **A**-ranked authors (90) published 712 papers, those in **B** (213) 772 papers while the 1825 authors in **C** published 2142 papers. Of the overall 2510 corresponding authors across the 2007–2012 period, 499 authors published more than two papers. Possible trends across this publication period were evaluated based on the numbers of publications and the years in which they were published: *Constant* if publications for 2007–2009 = 2010–2012; *Upward* if numbers for 2007–2009 < 2010–2012; *Downward* if numbers for 2007–2009 > 2010–2012. These data were included as it was felt that the method of assessment used could have disadvantaged younger, emerging scientists who only started to publish in the 2010–2012 period. It was found that the *Upward*/*Downward* trend for the two broad areas of research across all scientists was relatively constant, but at the country level there was an *Upward* trend in **Compounds** for China and Taiwan. The crossover between the two areas is interesting. Of the 93 **A**-ranked authors in **Compounds**, 12 were also **A** in **Other Aspects** and 24 were ranked **B**. If the rankings for **Compounds** and **Other Aspects** are combined the top 50 ranked authors are almost all well-known isolation chemists confirming the breadth of interests of the marine natural product community.

The marine natural product database MarinLit[1034] has been an essential tool for the authors in assembling all aspects of this review. The ownership of MarinLit has now been transferred from the University of Canterbury, New Zealand to the Royal Society of Chemistry, London.[1035] The database was maintained by the University of Canterbury until the end of 2013. In 2014 a web-based version of MarinLit will become available.

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