

Marine natural products

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John W. Blunt,^{*a} Brent R. Copp,^b Robert A. Keyzers,^c Murray H. G. Munro^a
and Michèle R. Prinsep^d

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

^aDepartment of Chemistry, University of Canterbury, Christchurch, New Zealand.
E-mail: john.blunt@canterbury.ac.nz

^bSchool of Chemical Sciences, University of Auckland, Auckland, New Zealand

^cCentre for Biodiscovery, and School of Chemical and Physical Sciences, Victoria University of Wellington, Wellington, New Zealand

^dDepartment of Chemistry, University of Waikato, Hamilton, New Zealand

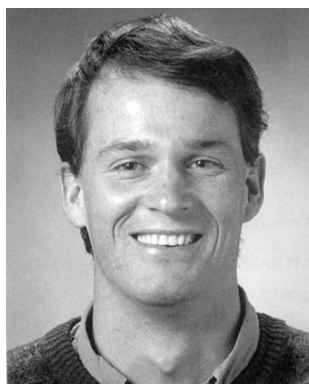


reviews of general classes of compounds that included reference to marine compounds – sesquiterpenoids,²⁶ cembrane diterpenes,²⁷ and diketopiperazines.²⁸ Reviews of natural products from various marine sources include those from



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.

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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.

*cyanobacteria,^{29,30} microalgae,^{31,32} actinomycetes,³³ gorgonians,³⁴ ascidians,^{35,36} sea cucumbers,³⁷ sponges,^{38–40} seaweeds⁴¹ 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 microorganisms⁵⁴ and marine bioactives against inflammatory diseases.⁵⁵ Topics in chemical ecology of cyanobacteria⁵⁶ and sponges⁵⁷ 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*



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.

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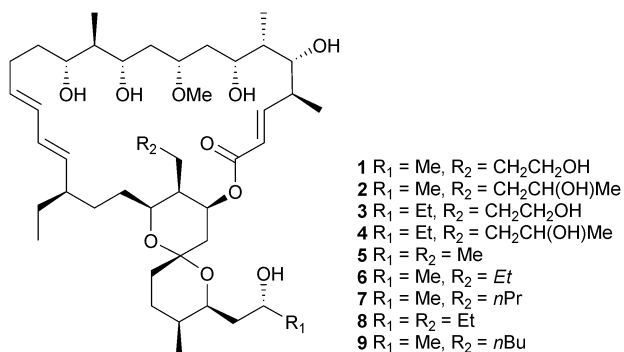
discovery,⁶⁴ mass spectrometry-based metabolomics,⁶⁵ techniques for bioactives discovery from marine fungi⁶⁶ and a commentary on past and future aspects of MNP drug discovery.⁶⁷

3 Marine microorganisms and phytoplankton

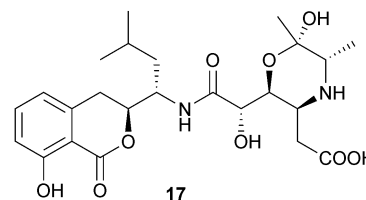
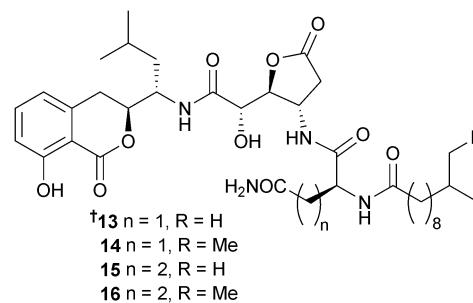
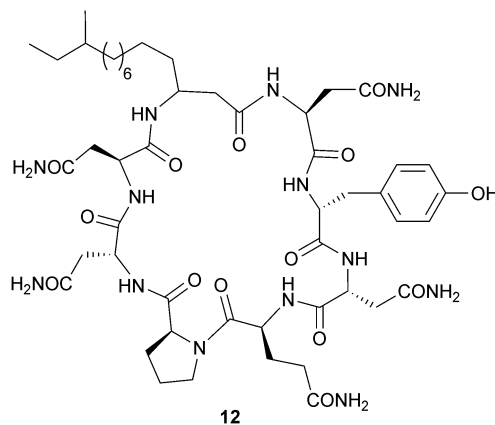
As a rich source of novel and bioactive marine microorganisms continue to be a major focus of many natural products research efforts, with a 10% increase in the number of compounds reported from the previous year following a 30% increase from 2010 to 2011. Unless otherwise stated, compounds described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

3.1 Marine-sourced bacteria (excluding from mangroves)

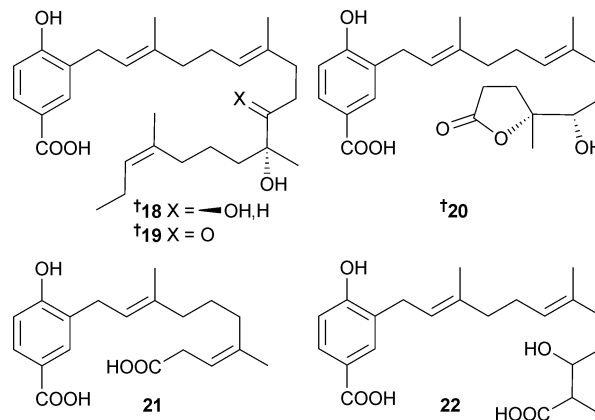
Actinoalloteichus sp. (sediment, Usa Bay, Kochi Prefecture, Japan) was the source of neomaclafungins A-I 1–9, 26-membered macrolides of the oligomycin subfamily, which all displayed significant activity against *Trichophyton mentagrophytes* (*T. mentagrophytes*).⁶⁸ Glycolipopeptides eodoglucomide A 10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



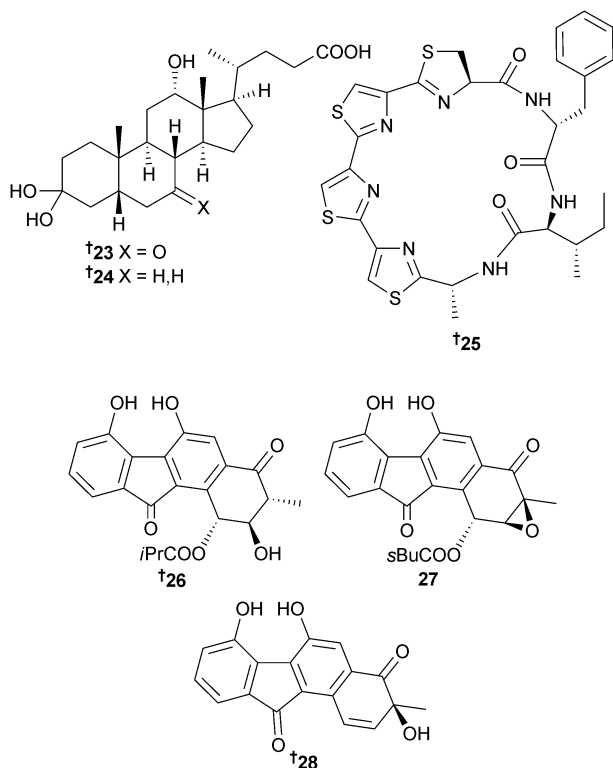
Bacillus mojavensis (pearl oyster *Pinctada martensii*, Weizhou Is., South China Sea) provided the antifungal iturinic lipopeptide mojavensin A 12,⁷⁰ while the amicoumacin analogues lipomicoumacin A–D 13–16 and a bacilosarcin analogue, bacisarcin C 17, were isolated from *Bacillus subtilis* (*B. subtilis*) (sediment, Red Sea) together with several known amicoumacins. Bacilosarcin B⁷¹ and amicoumacin A⁷² were cytotoxic to HeLa cells and are strongly antibacterial.⁷³



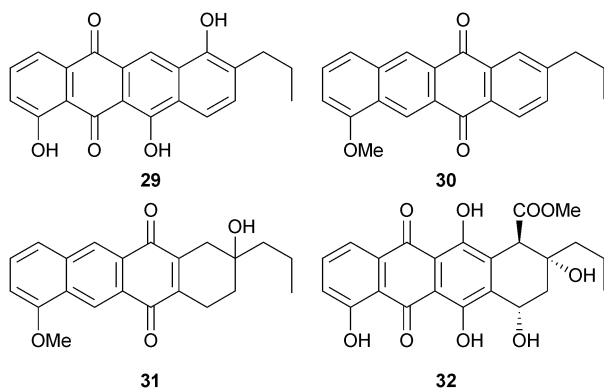
The known synthetic toluhydroquinone derivatives, 5-bromo-toluhydroquinone⁷⁴ and 4-*O*-methyltoluhydroquinone⁷⁵ were obtained for the first time from a natural source from *Dothideomyces* sp. (red alga *Chondria crassicalis*, Yokiji Is., S. Korea). Both compounds were moderate 1,1-diphenyl-2-picrylhydrazyl (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



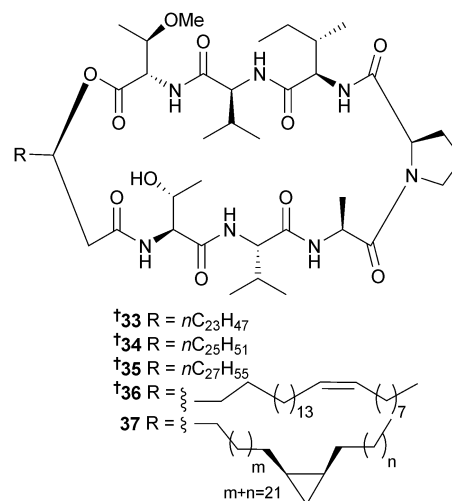
The cholic acid derivatives **23** and **24** were obtained from endophytic *Hasllibacter halocynthiae* (ascidian *Halocynthia roretzi*, Kyung-Po Beach, S. Korea)⁷⁸ and *Marinactinospora thermotolerans* (deep sea sediment, South China Sea) was the source of the sequential trithiazole-thiazoline-containing 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 fluostatin I-K **26–28** were isolated.



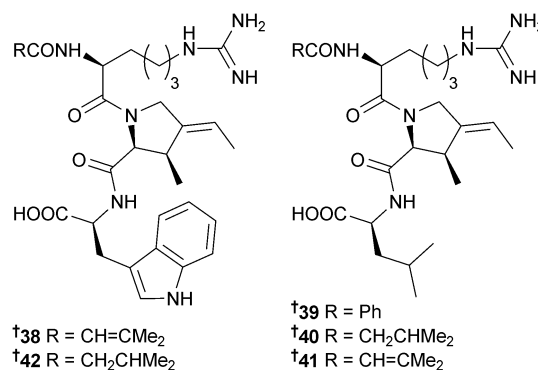
The antibiotic A201A, previously isolated from terrestrial *Streptomyces capreolus*,⁸⁰ was obtained from the marine environment for the first time from *M. thermotolerans* (deep sea sediment, South China Sea), and the gene cluster responsible for biosynthesis identified.⁸¹ The known metabolites of terrestrial *Streptomyces* species, fluostatin C–F,^{82,83} and phenanthroviridone,⁸⁴ were also obtained (first time from the marine environment).⁸⁵ The anthracynones **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



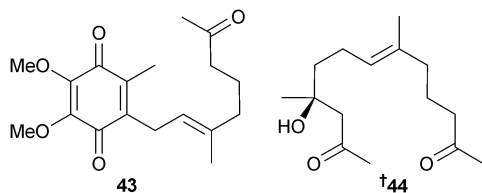
Upon assignment of the structure of the new lucentamycin analogue lucentamycin E **38** (*Nocardioopsis lucentensis*, sediment, Little San Salvador, Bahamas), the olefin geometries of the 3-methyl-4-ethylideneproline residues of lucentamycins A–D **39–42**, other tripeptides isolated from the same organism,⁸⁸ 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 indigoidine⁹² which inhibited growth of *Vibrio fischeri* and was isolated from the “marine” environment for the first time.⁹³



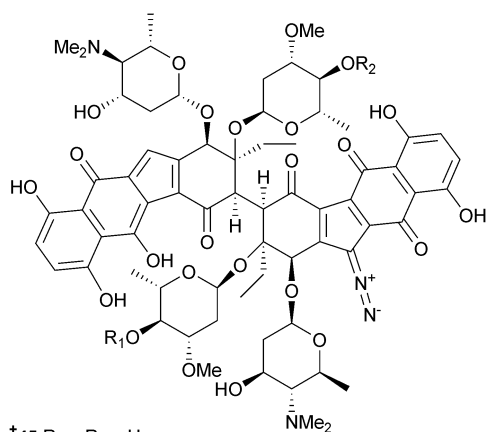
Pseudoalteromonas A **43** and B **44** were obtained from *Pseudoalteromonas* sp. (cultured-type octocoral *Lobophytum crassum*,



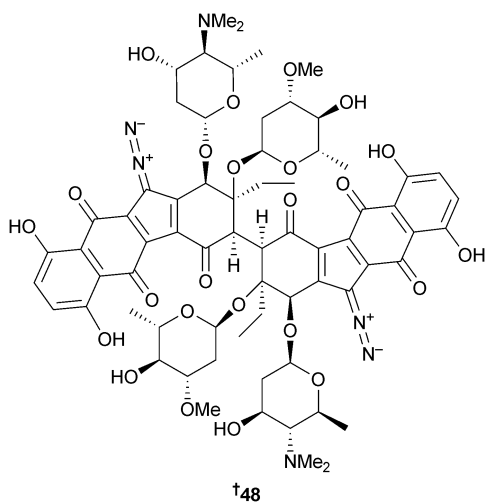
Taiwan).^{94,95} The ubiquinone derivative pseudoalteromone A possessed a 9C nor-monoterpenoid moiety, was cytotoxic to MOLT-4 (human acute lymphoblastic leukaemia) cells and inhibited release of elastase by human neutrophils.



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

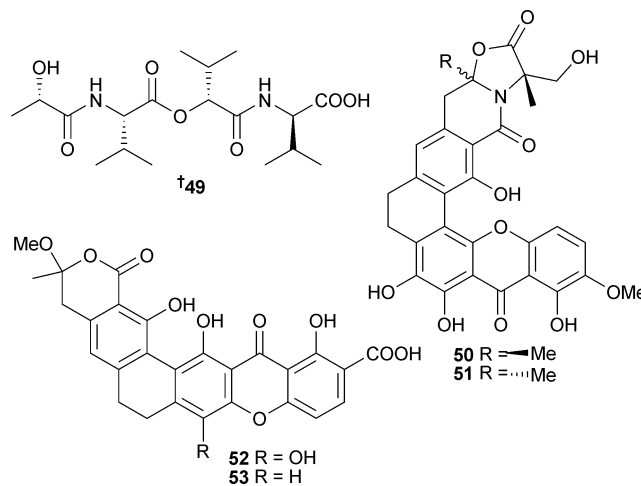


†45 $R_1 = R_2 = H$
 †46 $R_1 = Me, R_2 = H$ and $R_1 = H, R_2 = Me$
 †47 $R_1 = R_2 = Me$

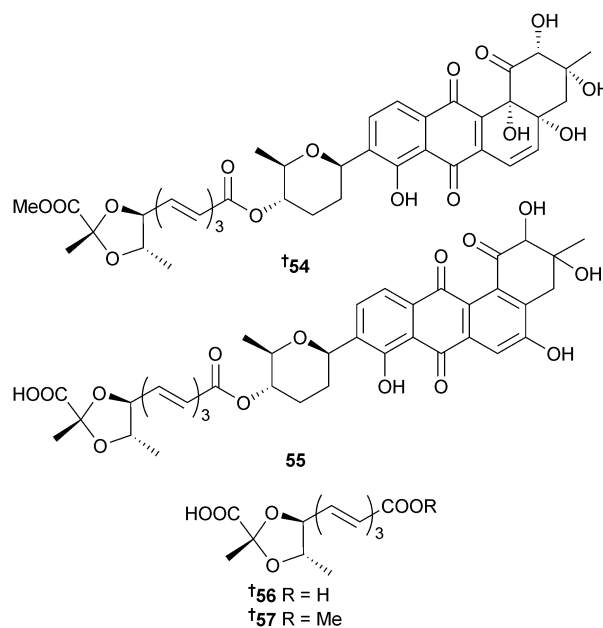


†48

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

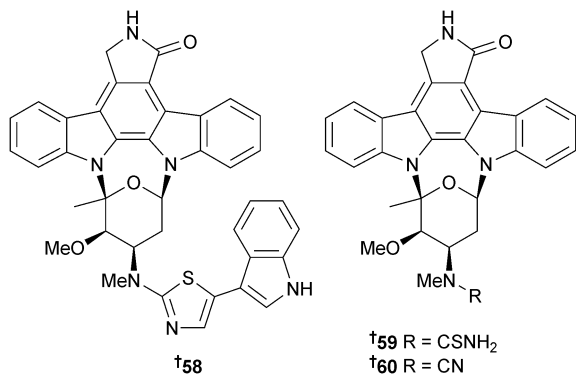


S. fradiae (sediment, source unspecified) yielded several capoamycin-type antibiotics, fradimycin A 54 and B 55 and fradic acid A 56 and B 57, of which fradimycins A and B inhibited *Staphylococcus aureus* (*S. aureus*) growth and both, as well as the known anthraquinone MK844-mF10,¹⁰³ significantly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



Fradcarbazoles A–C 58–60, indolcarbazoles 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

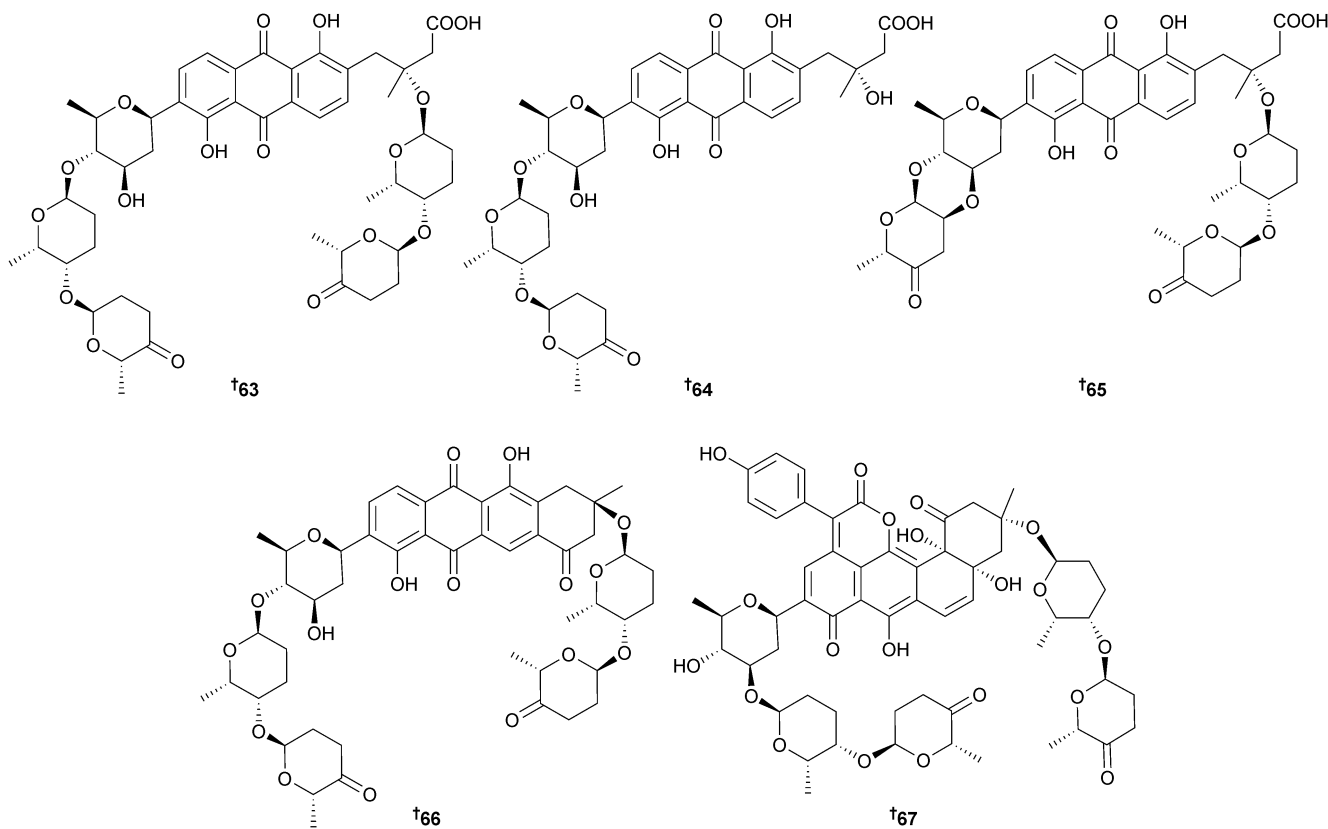
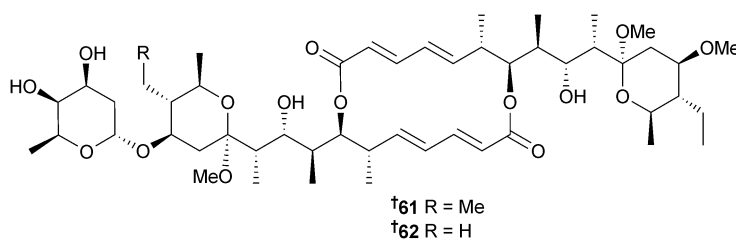
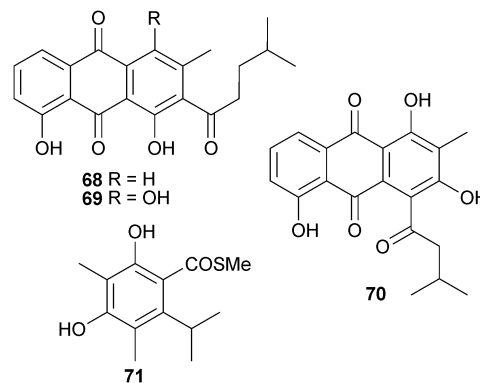




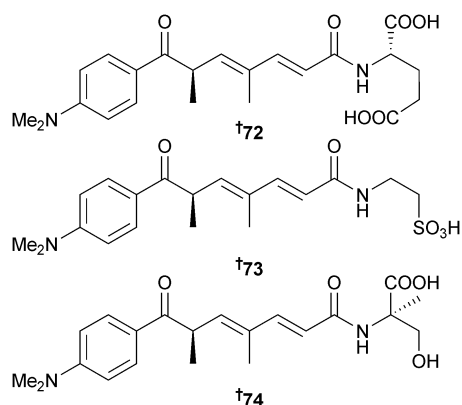
Culture of *S. hygroscopicus* (fish *Halichoeres bleekeri*¹⁰⁶) led to the isolation of macrolides halichoblelide B **61** and C **62**,¹⁰⁷ both significantly cytotoxic to a panel of HTCLs.¹⁰⁸ The C-glycoside angucyclines grincamycin B–F **63–67** were obtained from *Streptomyces lusitanus* (deep sea 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**.

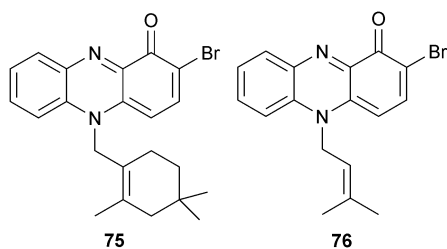
Galvaquinone B possessed epigenetic modulatory activity and moderate cytotoxicity against non-small-cell lung cancer (NSCLC) cells Calu-3 and H2887.¹¹⁰ S-Methyl-2,4-dihydroxy-6-isopropyl-3,5-dimethylbenzothioate **71** was isolated from *Streptomyces* sp. (unidentified tunicate, Lyttelton Harbour, New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



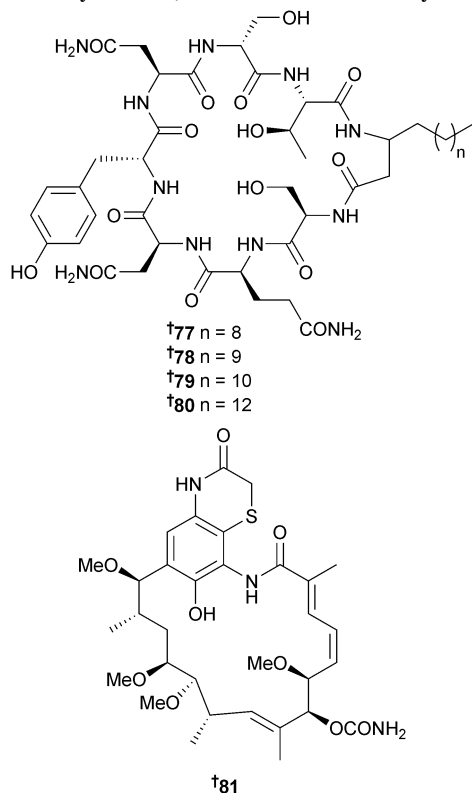
JBIR-109–111 72–74 are trichostatin analogues isolated from a *Streptomyces* strain (unidentified sponge, Takara Is., Kagoshima, Japan).¹¹²



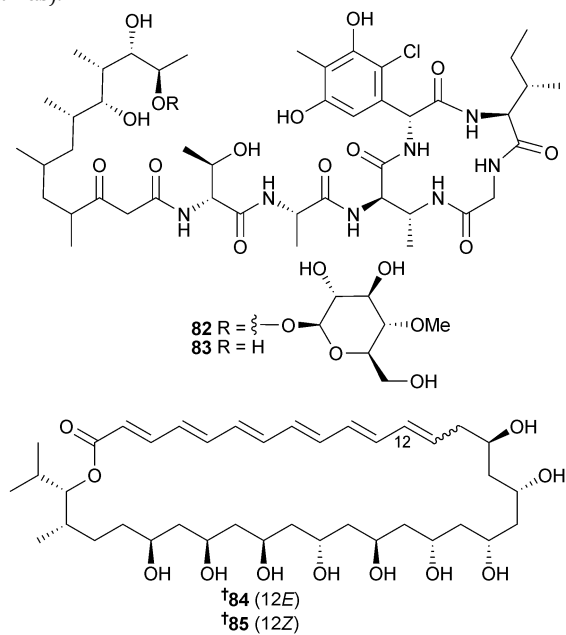
The phenazine derivatives 75 and 76 and lavanducyanin¹¹³ were isolated from a marine-derived *Streptomyces* sp. (source unspecified). All three compounds inhibited TNF- α -induced NF κ B activity and LPS-induced nitric oxide (NO) production.¹¹⁴



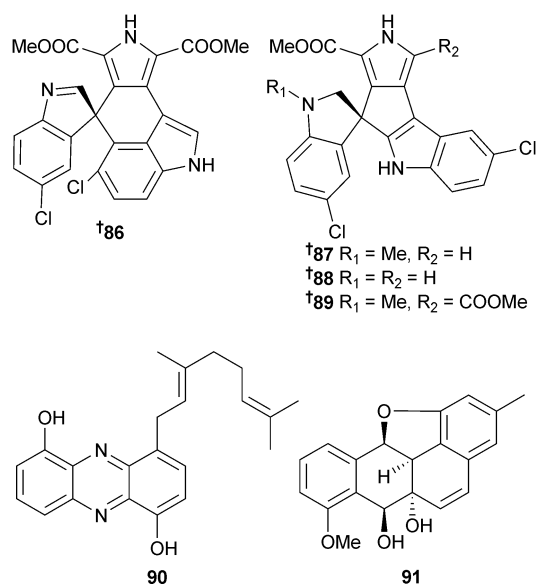
A *Streptomyces* strain (sponge *Dysidea tupa*, Rovinj, Croatia) produced the lipopeptides cyclodysidin A–D 77–80¹¹⁵ while another *Streptomyces* sp. (sediment, Heron Is., Queensland, Australia) yielded heronamycin A 81, a benzothiazine ansamycin.¹¹⁶



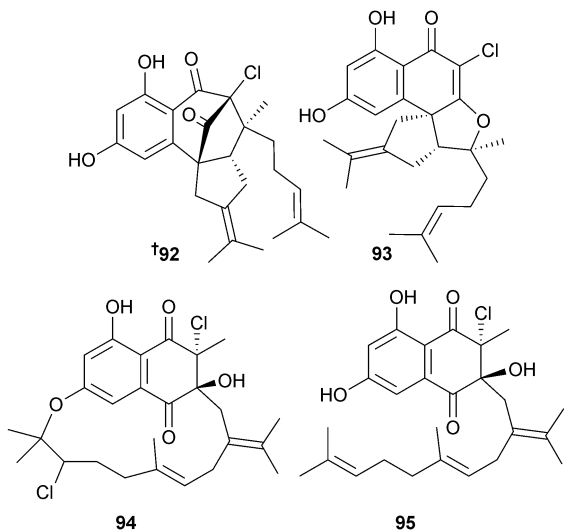
Noteworthy in the totopotensamide A 82 and the aglycone totopotensamide B 83 structures [*Streptomyces* sp. (gastropod mollusk *Lienardia totopotens*, Mactan Is., Cebu, Philippines)] are the previously undescribed 2,3-diaminobutyric acid-containing macrolactam and 4-chloro-5,7-dihydroxy-6-methylphenylglycine 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



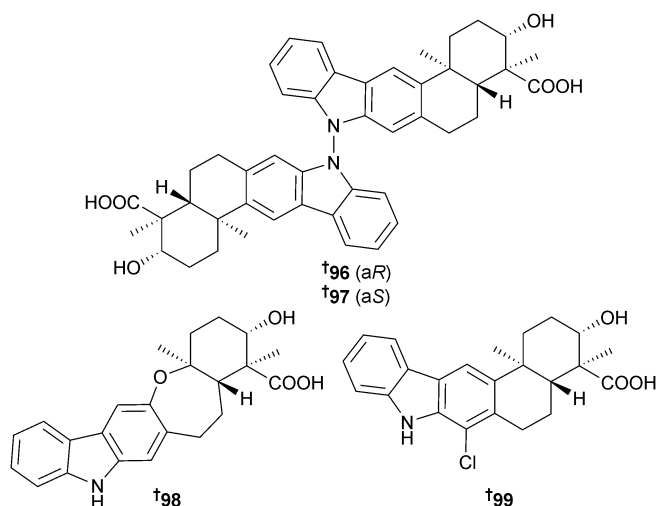
Spiroindimicins A–D 86–89 are *spiro*-bisindole alkaloids from a *Streptomyces* sp. (sediment, Bay of Bengal) obtained *via* a PCR-based screening approach. Spiroindimicins B–D displayed moderate cytotoxicity to a number of cancer cell lines.¹¹⁹ The phenazine geranylphenazinediol 90 isolated from a *Streptomyces* 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 A¹²² and B¹²³ 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}

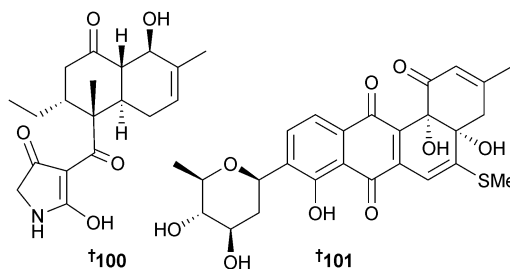


The antibacterial indolosesquiterpenes dixiamycin A **96** and B **97**, oxiamycin **98** and chloroxiamycin **99** were isolated from a *Streptomyces* sp. (sediment, South China Sea) along with the previously isolated xiamycin A.¹²⁴ Dixiamycins A and B are the first examples of naturally occurring *N-N*-coupled *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

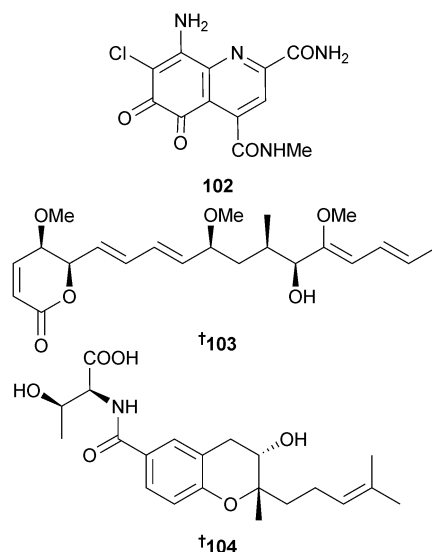


A histone deacetylase (HDAC)-based yeast assay employing a URA3 reporter gene was utilised in the isolation of streptosetin A **100** from a *Streptomyces* sp. (sediment, San Francisco Bay).¹²⁷ The *C*-glycosylated benz[*a*]anthraquinone derivatives, urdamycinone

E,¹²⁸ urdamycinone G **101** and dehydroxyaquayamycin¹²⁹ were obtained from a *Streptomyces* sp. (sponge *Xestospongia* sp., Sichang Is., Chonburi, Thailand) and along with urdamycin E¹²⁸ were potent inhibitors of the *P. falciparum* K1 strain and inhibitors of *Mycobacterium tuberculosis*.¹³⁰ Urdamycinone E¹²⁸ and dehydroxyaquayamycin¹²⁹ were obtained for the first time as natural products.¹³⁰

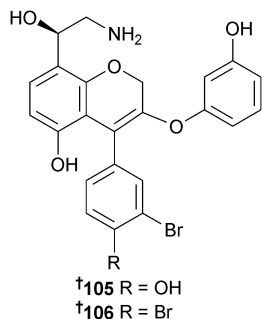


Streptomyces variabilis (sediment, Sweetings Cay, Bahamas) was the source of ammosamide D **102** (modest cytotoxicity to the MIA PaCa-2 pancreatic cancer cell line).¹³¹ The cytotoxic linear polyketide pterocidin was originally obtained from endophytic *S. hygrosopicus* associated with the bracken *Pteridium 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

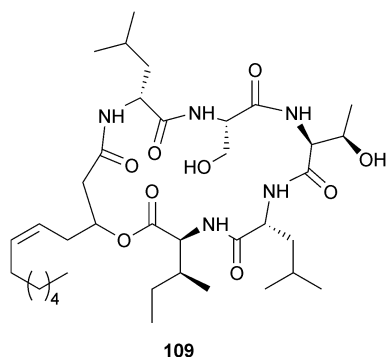
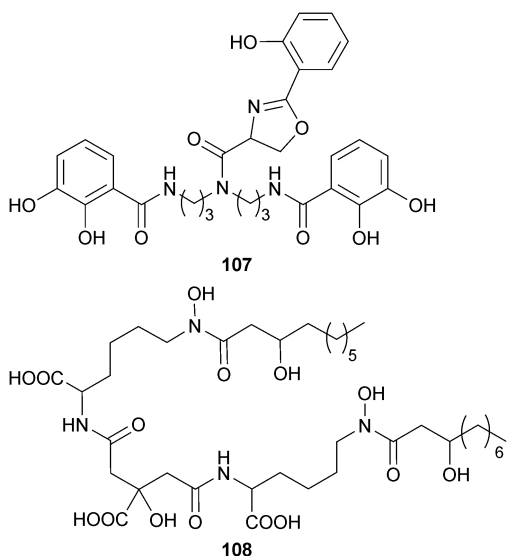


The hydroxyethylamine chromene derivatives ammonificin C **105** and D **106** were obtained from *Thermovibrio ammonificans* (hydrothermal vent, East Pacific Rise) and induced apoptosis in a cell-based screen.¹³⁶



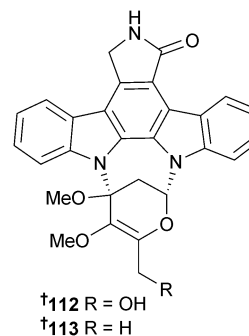
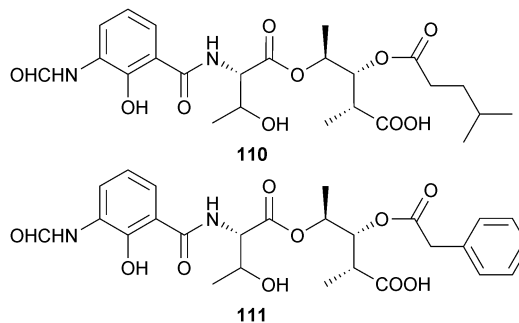


Vibrio nigripulchritudo (global marine Galathea 3 expedition)¹³⁷ produced the siderophore nigribactin **107**, a modulator of *S. aureus* virulence gene expression,¹³⁸ while another *Vibrio* species (Gulf of Mexico) was the source of the amphiphilic siderophores ochrobactin-OH A-C, but only ochrobactin-OH 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 B¹⁴⁰ and E¹⁴¹ of which kailuin B displayed strong activity against the dinoflagellate *Prorocentrum micans*.¹⁴²

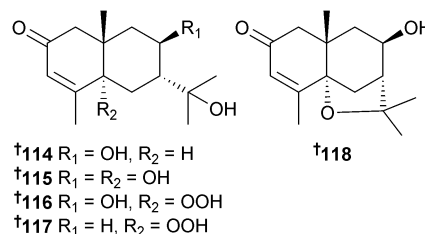


3.2 Bacteria from mangroves

Of the two antimycins, B1 **110** and B2 **111** from *Streptomyces lusitanus* (mangrove sediment, *Avicennia maritima*, 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



The eudesmene-type sesquiterpenes kandelol 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

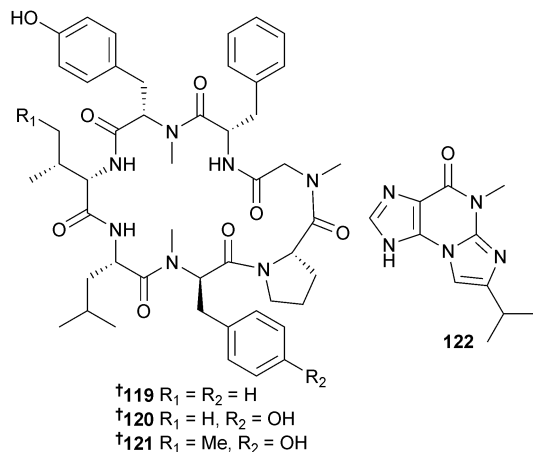


3.3 Marine-sourced fungi (excluding from mangroves)

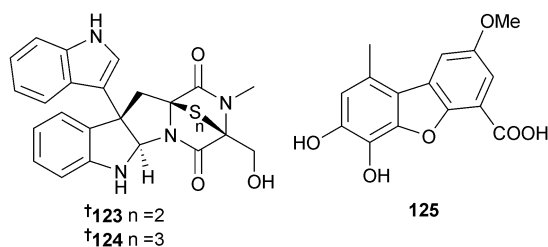
Cordyheptapeptides C-E **119–121** were isolated from *Acremonium persicinum* (sediment, South China Sea) with cytotoxicity against HTCLs noted for cordyheptapeptides C and E.¹⁴⁶ Acremolin was isolated from *Acremonium strictum* (unidentified Choristida sponge, S. Korea) with the original structure incorporating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



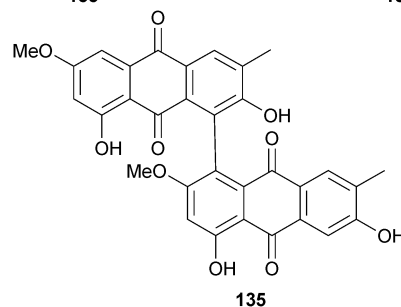
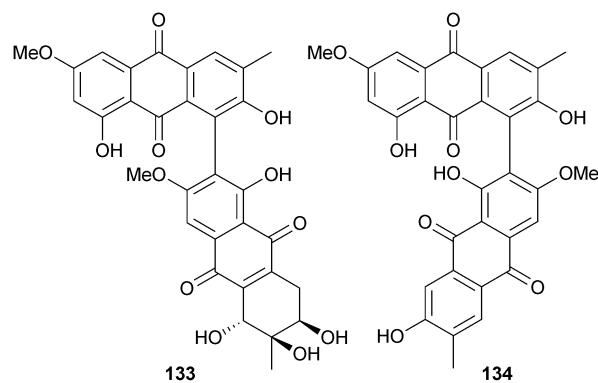
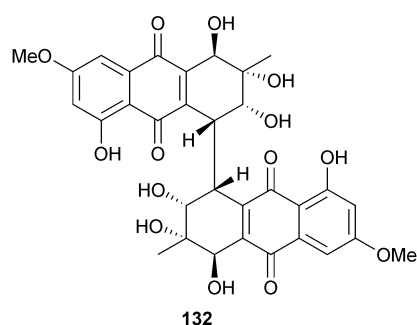
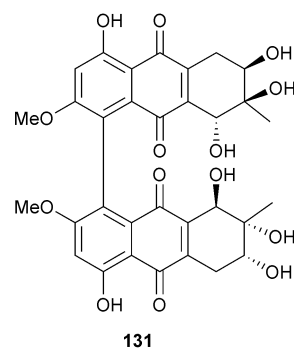
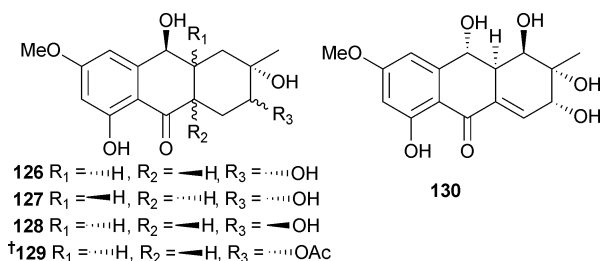
that the reported NMR spectroscopic data were incompatible with the proposed antiaromatic heterocycle, which would have been an extremely unstable compound. A plausible alternative structure, an isomeric substituted $N^2,3$ -ethenoguanine **122** has been suggested, which is consistent with all spectroscopic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



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

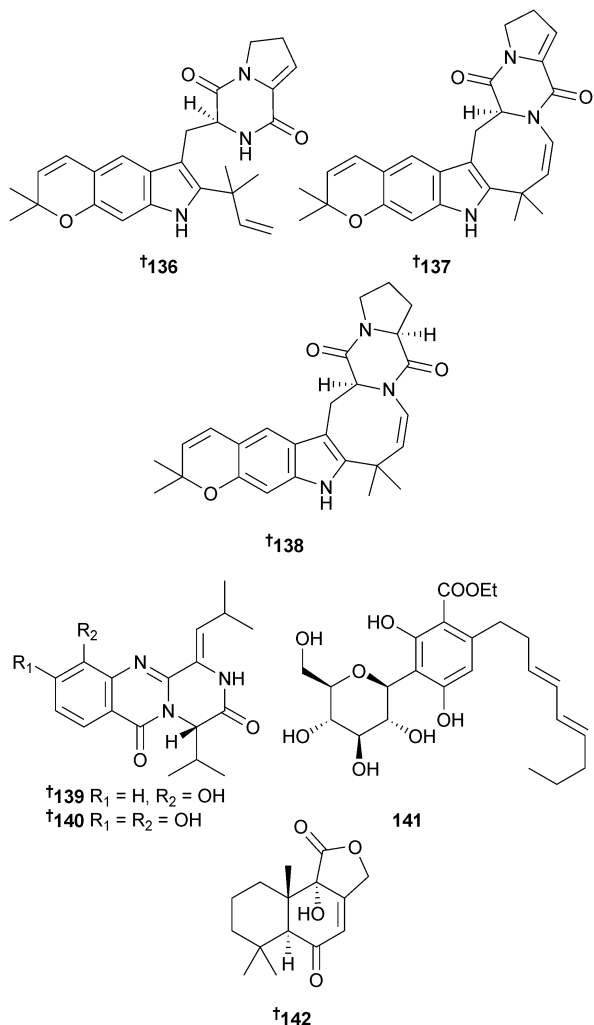


The hydroanthraquinone-derived tetrahydroaltersolanols C–F **126–129** and dihydroaltersolanol A **130**, in addition to the alterporriol-type anthranoid dimers alterporriols N–R **131–135**, were obtained from *Alternaria* sp. (soft coral *Sarcophyton* sp., Weizhou coral reef, South China Sea). Tetrahydroaltersolanol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

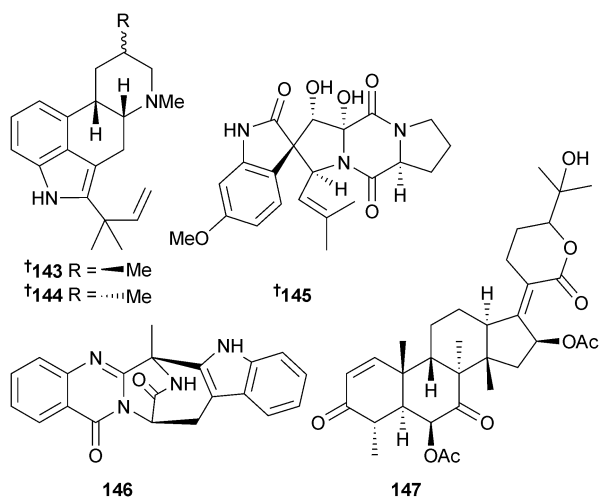


Aspergillus carneus (brown alga *Laminaria sachalinensis*, Kunachir Is., Russia) was the source of the prenylated indole alkaloids carneamide A–C **136–138**, the quinazolinone derivatives carnequinazoline B **139** and C **140**, the aryl *C*-glycoside carnemycin A **141** and a drimane sesquiterpenoid **142**. New to the marine area was a synthetic compound¹⁵² (isolated as carnequinazoline A) and a known derivative of stromemycin^{153,154} (isolated as carnemycin B).¹⁵⁵

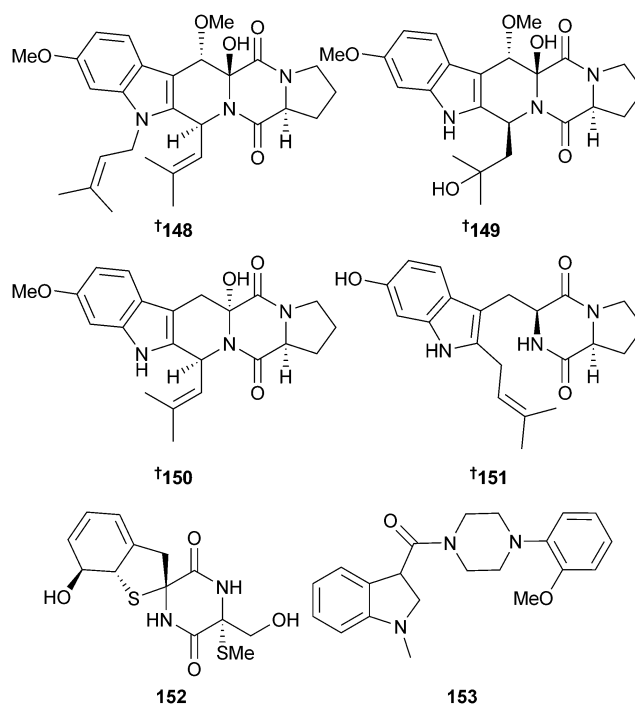




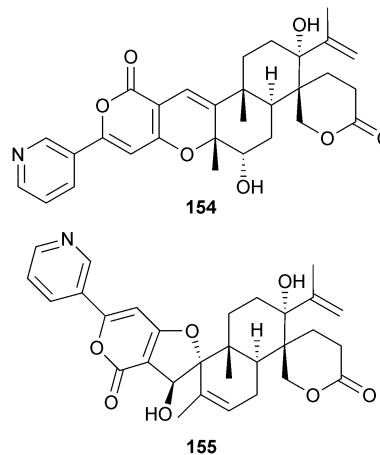
Two costaclavine alkaloids **143** and **144** were obtained from *Aspergillus fumigatus* (zoanthid *Zoanthus* sp., Amami Is., Kagoshima, Japan),¹⁵⁶ while *A. fumigatus* (soft coral *Sinularia* sp., Kunashir Is., Kuril Islands) produced the spirocyclic diketopiperazine alkaloid spirotryprostatin F **145** which had stimulatory phyto regulatory activity.¹⁵⁷ The same fungal strain was the source of the alkaloid fumiquinazoline K **146** and a nor-dammarane triterpenoid **147**.¹⁵⁸



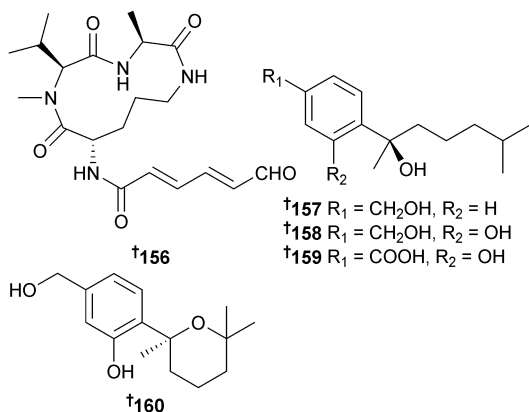
From *A. fumigatus* (intertidal mud, Yingkou, China) several diketopiperazines were isolated: prenylcyclotryprostatin B **148**, 20-hydroxycyclotryprostatin B **149**, 9-hydroxyfumitremorgin C **150**, 6-hydroxytryprostatin B **151** and spirogliotoxin **152**. Prenylcyclotryprostatin B and 9-hydroxyfumitremorgin 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 E¹⁶⁰ and secondly, from a terrestrial *A. fumigatus* as 12 β -hydroxy-13 α -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



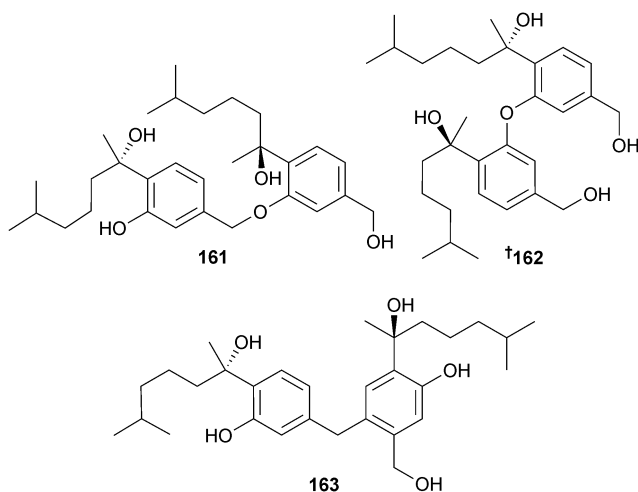
The sesquiterpene pileotin A **154** was isolated from *A. fumigatus* (sea urchin *Toxopneustes pileolus*, source unspecified) along with oxalicine B **155**, previously reported as a metabolite of *Penicillium oxalicum* in a PhD thesis¹⁶² but now reported in the literature. Oxalicine B displayed moderate cytotoxicity to P388 cells.¹⁶³



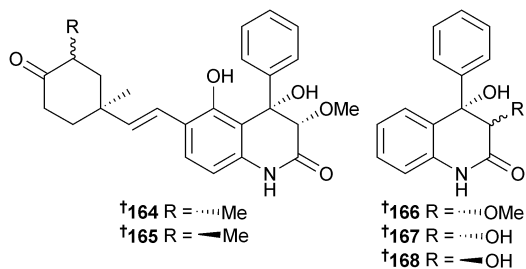
Aspergillus insulicola (sediment, Hawaii) produced the tripeptide pre-sclerotiotide **F 156**¹⁶⁴ and *Aspergillus* sp. (sponge *Xestospongia testudinaria*, Weizhou coral reef, South China Sea) the four bisabolane-type sesquiterpenoids, aspergiterpenoid **A 157**, (–)-sydonol **158**, (–)-sydonic acid **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}



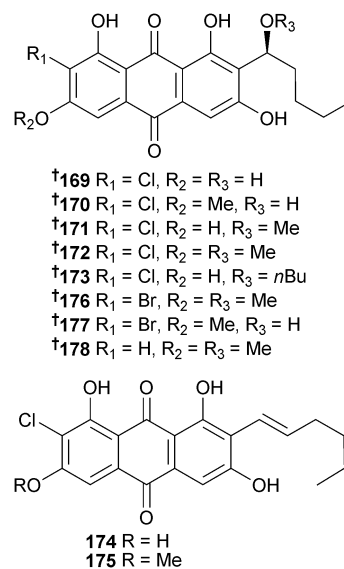
An endophytic *Aspergillus* sp. (sponge *Xestospongia testudinaria*, Weizhou Is., South China Sea) produced the phenolic bisabolane sesquiterpenoid dimers disydonol A–C **161–163**. Only disydonols A and C were cytotoxic to HTCLs.¹⁶⁸



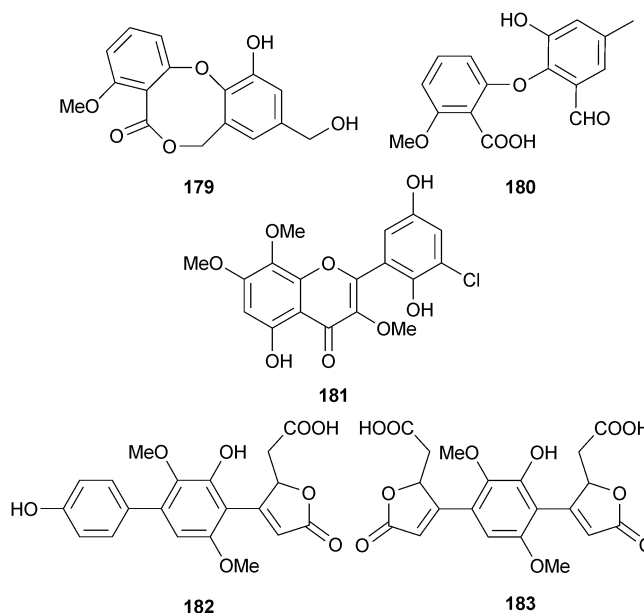
Aflaquinolones C–G **164–168** were obtained from an *Aspergillus* sp. (Dadaepo Beach, Busan, S. Korea); the same report also detailed the isolation of the related aflaquinolones A and B from a terrestrial *Aspergillus* sp.¹⁶⁹



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



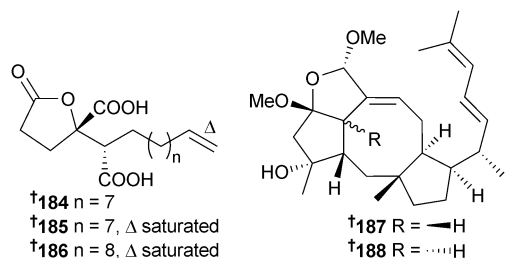
Aspergillus sp. (soil, Xiamen Beach, China) yielded barceloneic lactone **B 179**, barceloneic acid **C 180** and 5'-hydroxy-chlorflavonin **181**,¹⁷¹ in addition to two *p*-terphenyl derivatives, terphyl acid **182** and terphyl diacid **183**.¹⁷²



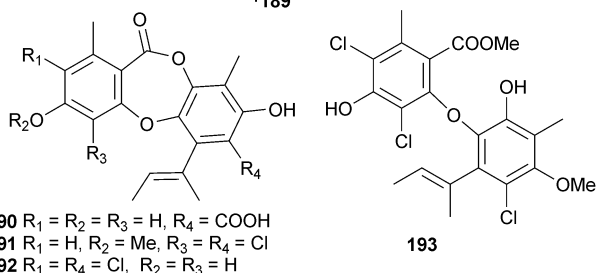
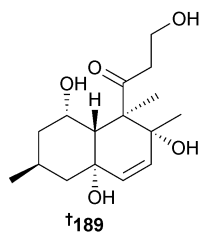
Three γ -butenolide derivatives spiculisporic acid B–D **184–186** were isolated from an endophytic *Aspergillus* sp. (sea urchin *Anthocardia crassispina*, Qionghai, Hainan, China),¹⁷³ while the sesterterpenes ophiobolin O **187** and 6-*epi*-ophiobolin O **188**



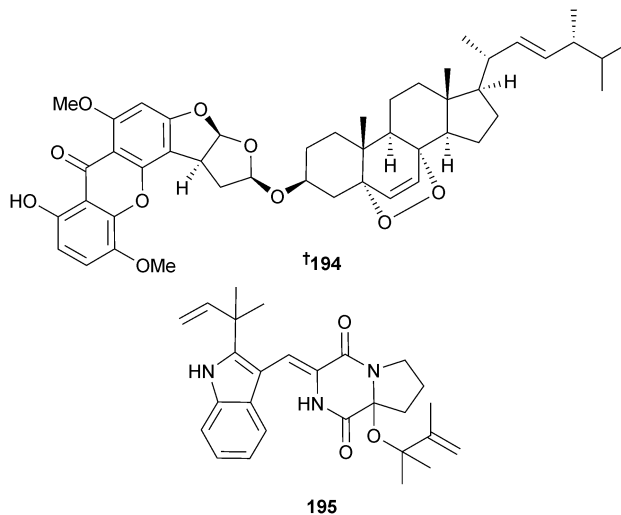
were obtained from endophytic *Aspergillus* sp. (zoanthid *Zoanthus* sp., Ayamaru Cape, Amami Is., Japan) as moderate cytotoxins to P388 cells,¹⁷⁴ with ophiobolin O also inducing apoptosis and cell cycle arrest of MCF-7 cells through activation of MAPK signaling pathways.¹⁷⁵



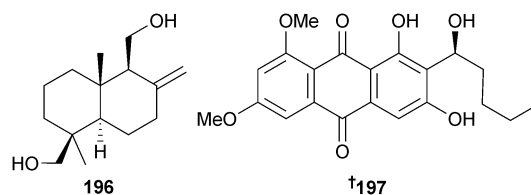
Decalin derivative decumbenone C **189** was isolated from *Aspergillus sulphureus* (sediment, location unspecified) as a potent cytotoxin against SK-MEL-5 human melanoma cells.¹⁷⁶ Coincidentally, decumbenone C was also isolated from the terrestrial basidiomycete *Craterellus odoratus* and named craterellone 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)-2H-pyran-2-one¹⁷⁸ (first isolation from a natural source). The fungal metabolites, nidulin,¹⁷⁹ nornidulin¹⁸⁰ and 2-chlorounguinol¹⁸¹ 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



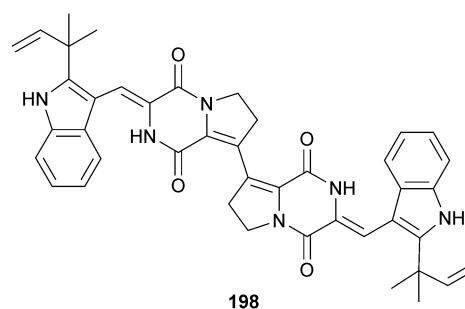
Asperserin A **194** and 9ξ-O-2(2,3-dimethylbut-3-enyl)brevianamide Q **195** were isolated from endophytic *Aspergillus versicolor* (brown alga *Sargassum thunbergii*, Pingtan Is., China), along with the known fungal metabolites brevianamide M,¹⁸³ 6,8-di-O-methylaverufin¹⁸⁴ and 6-O-methylaverufin.¹⁸⁵ Both brevianamide M¹⁸³ and 6-O-methylaverufin¹⁸⁵ were first time marine isolates.¹⁸⁶

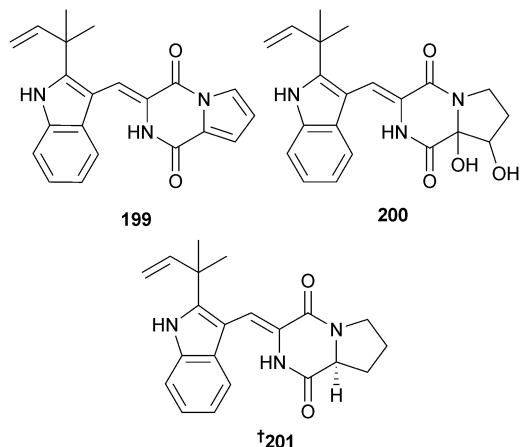


Endophytic *A. versicolor* (green alga *Codium fragile*, Dalian, China) produced the sesquiterpene albican-11,14-diol **196**, potently toxic to brine shrimp and a strong inhibitor of *E. coli* and *S. aureus*.¹⁸⁷ From another endophytic *A. versicolor* (brown alga *Sargassum thunbergii*, Qingdao, Shandong, China) the anthraquinone compound 6,8-di-O-methylaverantin **197** was obtained¹⁸⁸ together with the known anthraquinones 6,8-di-O-methylversiconol¹⁸⁹ and 6,8-di-O-methylnidurufin.¹⁹⁰

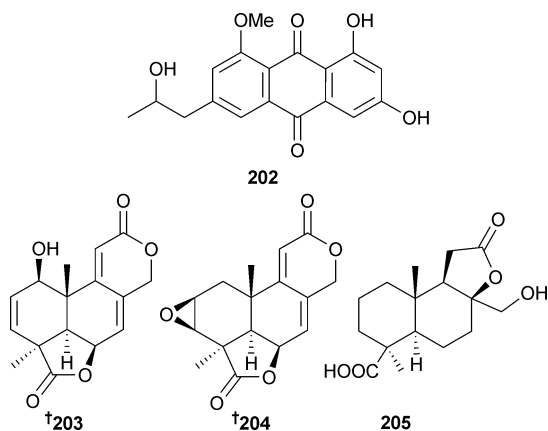


A. versicolor (sediment, Bohai Sea, China) was the source of the dimeric diketopiperazine brevianamide S **198** and the monomeric brevianamides T–V **199–201**. Brevianamide S showed selective activity against the Bacille Calmette-Guérin (BCG) strain of *Mycobacterium bovis* suggestive of a new mechanism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

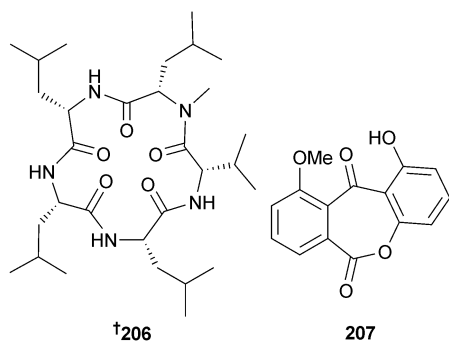




The anthraquinone isorhodoptilometrin-1-methyl ether **202** was isolated from endophytic *A. versicolor* (green alga *Halimeda opuntia*, Rass Mohamed, south Sinai, Egypt) and displayed moderate activity against *B. subtilis*, *B. cereus* and *S. aureus*.¹⁹² Examination of the endophytic *A. wentii* 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

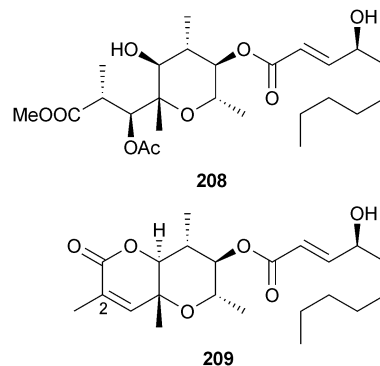


Application of OSMAC (one strain-many compounds) methodology to *Asteromyces cruciatus* (unidentified decaying green alga, La Jolla, USA) identified the pentapeptide lajollamide A **206** (absolute configuration determined by total synthesis).¹⁹⁷

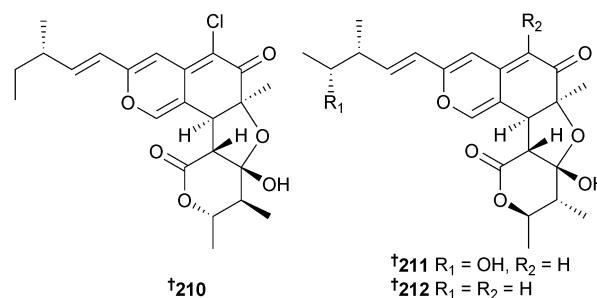


Beauveria bassiana (unidentified sponge, Iriomote Is., Okinawa) produced 1-hydroxy-10-methoxy-dibenz[*b,e*]oxepin-6,11-dione **207**,¹⁹⁸ in addition to the known terrestrial metabolites chrysozin¹⁹⁹ and globosuxanthone A,²⁰⁰ both first time marine isolates.

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}



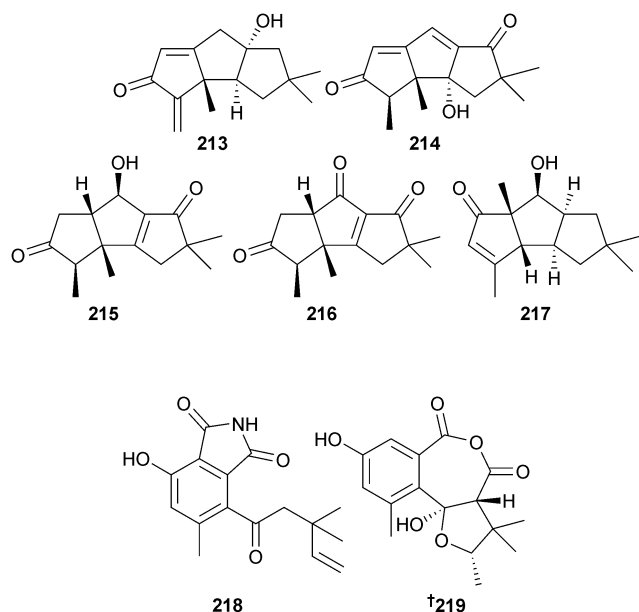
A strain of *Chaetomium globosum* (fish *Mugil cephalus*, Katsuura Bay, Japan), which has already yielded many chaetomugilin metabolites,^{205–208} was the source of three further analogues: chaetomugilins S **210**, T **211** and U **212**. Chaetomugilin S was a moderate growth inhibitor of HTCLs and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



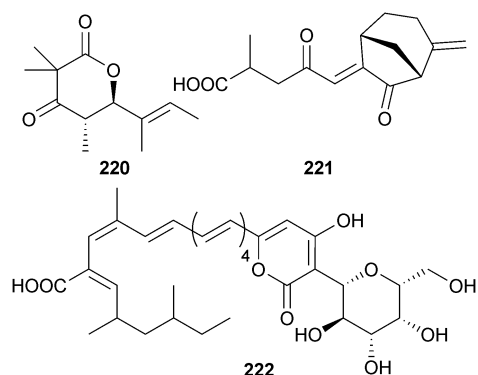
Chondrostereum sp. (soft coral *Sarcophyton tortuosum*, Hainan, South China Sea) yielded triquinane-type sesquiterpenoids chondrosterin A–E **213–217**, of which chondrosterin A was cytotoxic to several cancer cell lines.^{210,211} Endophytic *Coniothyrium cereale* (green alga *Enteromorpha* sp., Fehmarn, 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 ¹³C-labelled acetate proved that the major and



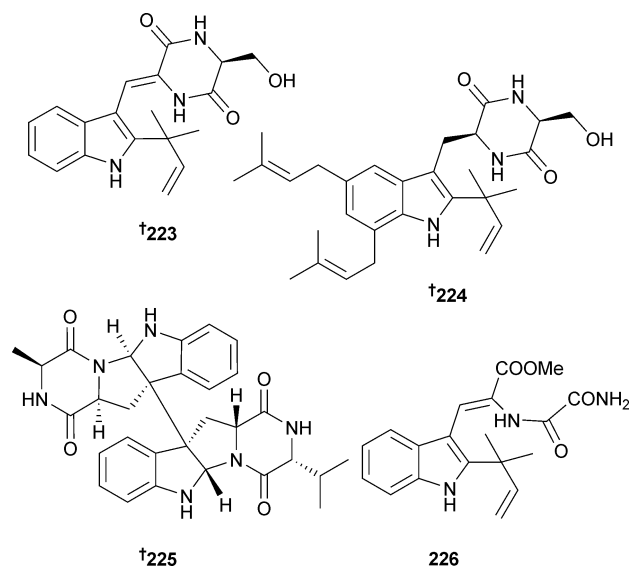
known *C. cereale* metabolite (–)-tryptelone²¹² was polyketide-derived and it is proposed as the precursor of cereoanhydride.²¹³



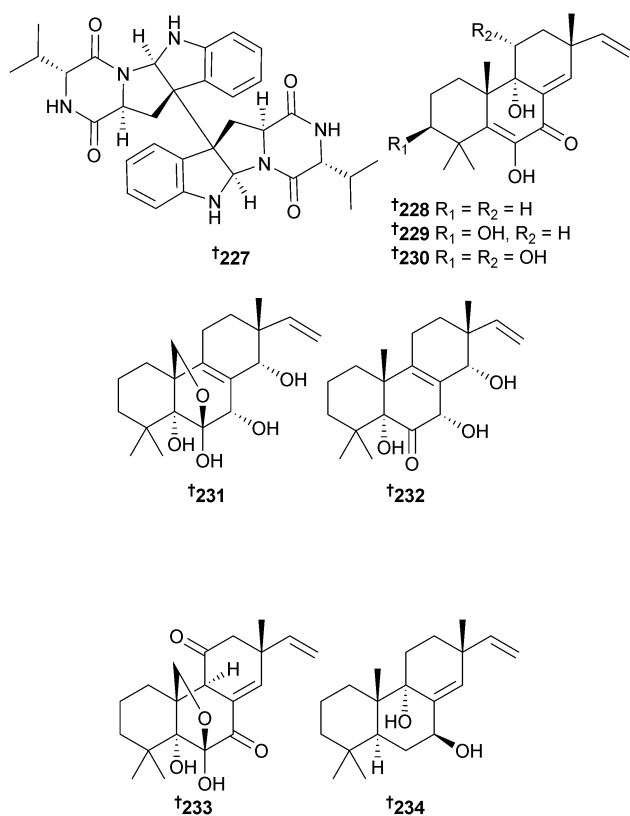
The lactone helicascalide C 220 was isolated from endophytic *Daldinia eschscholzii* (red alga *Gracilaria* sp., South Sulawesi coast, Indonesia) and was fungistatic against the phytopathogenic fungus *Cladosporium cucumerinum*.²¹⁴ Both helicascalide C and helicascalide A,²¹⁵ previously isolated from 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 *Calyspongia* 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- κ B inhibition.²¹⁹



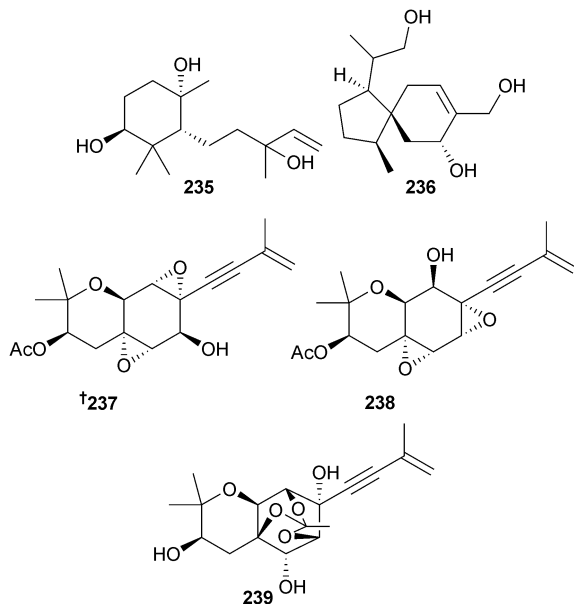
Endophytic *Eurotium cristatum* (brown alga *Sargassum thunbergii*, location unspecified) was the source of the indole alkaloids cristatumin A–D 223–226, of which cristatumin A and the co-isolated known fungal metabolite tardioxopiperazine A²²⁰ were active against *E. coli* and *S. aureus*, respectively, while cristatumin B and the co-isolated known fungal metabolite isoechinulin A²²¹ were moderately toxic to brine shrimp.²²²



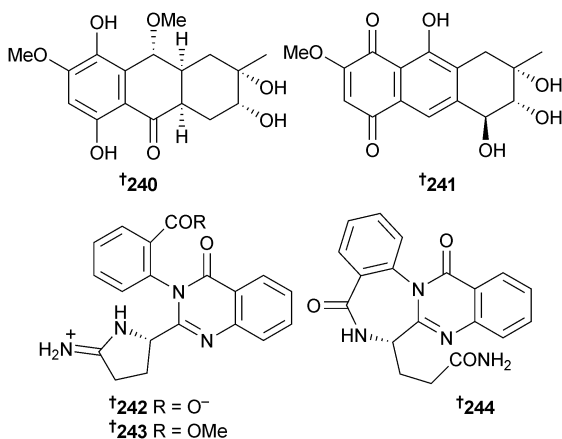
The diketopiperazine dimer eurocristatine 227 was isolated from endophytic *Eurotium cristatum* (sponge *Mycale* sp., Wonnapa Beach, Bangsaen, Thailand),^{223,224} while scopararanes C–G 228–232 are oxygenated pimarane diterpenes obtained from *Eutypella scoparia* (sediment, South China Sea). Scopararane C was moderately cytotoxic to MCF-7 cells, while scopararane D was moderately cytotoxic to both SF-268 and MCF-7 cells²²⁵ 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



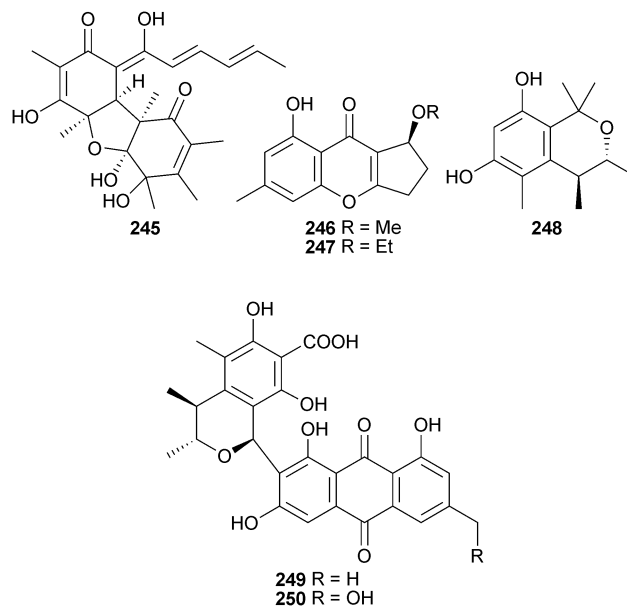
A monocyclofarnesane sesquiterpene **235** and an acorane sesquiterpene **236** were obtained from *Eutypella scoparia* (sediment, South China Sea),²²⁷ while *Isaria felina* (sediment, South China Sea, Vietnam) was the source of the chromene derivatives oxirapentyn B–D **237–239**, in addition to oxirapentyn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



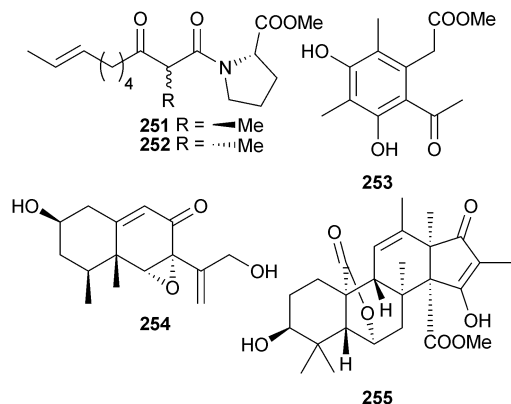
Two hydroanthraquinone analogues 4a-*epi*-9 α -methoxydihydrodeoxybostrycin **240** and 10-deoxybostrycin **241** were isolated from endophytic *Nigrospora* sp. (unidentified sea anemone, Weizhou, South China Sea). 10-Deoxybostrycin was strongly active against *B. cereus* and A549 cells.²³⁰ An OSMAC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



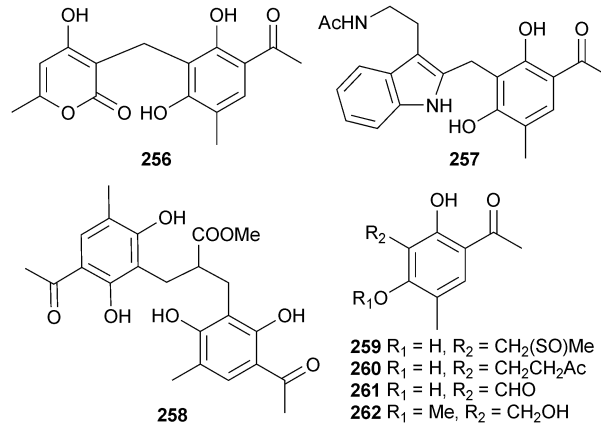
P. citrinum (unidentified sponge, Ishigaki Is., Okinawa, Japan) was the source of JBIR-124 **245**, a DPPH radical scavenger,²³² while *P. citrinum* (gorgonian sea fan *Annella* sp., Similan Islands, Thailand) yielded several polyketides including the benzopyranones coniochaetone C **246** and D **247**, 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



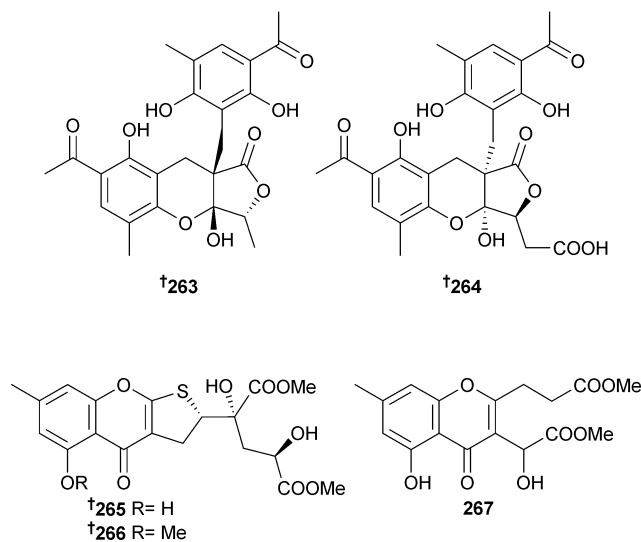
P. citrinum (sediment, Lanqi Is., Fujian, China) provided the epimeric tumonoic acids K **251** and L **252** along with methyl 2-(2-acetyl-3,5-dihydroxy-4,6-dimethylphenyl)acetate **253**,²³⁴ while isophomenone **254** and 3-deacetylcitreohybridinol **255** were obtained from *P. commune* (sediment,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



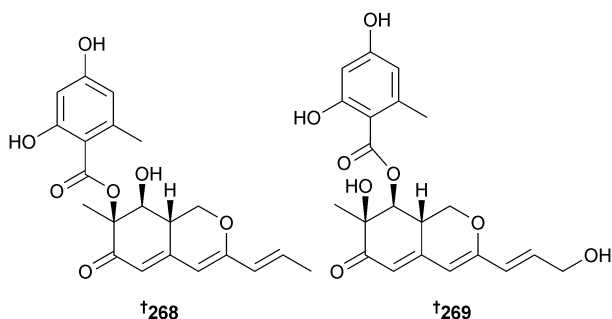
Communols A–G **256–262** are aromatic polyketides isolated from *P. commune* (gorgonian *Muricella abnormalis*, Danzhou, Hainan, China), of which communols A, F and G were moderately active against *E. coli* and *Enterobacter aerogenes* (*E. aerogenes*).^{236,237}



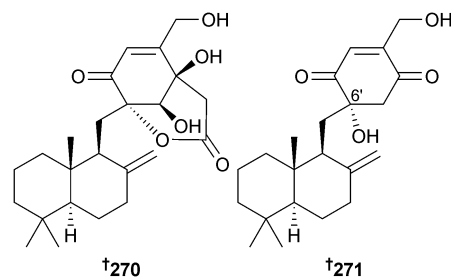
Penilactones A **263** and B **264** are highly oxygenated polyketides from *P. crustosum* (deep sea sediment, Prydz Bay, Antarctica).²³⁸ The dihydrothiophene-condensed chromones oxalicumone A **265** and B **266** and the chromone, oxalicumone C,²³⁹ were isolated from *P. oxalicum* (gorgonian *Dichotella 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



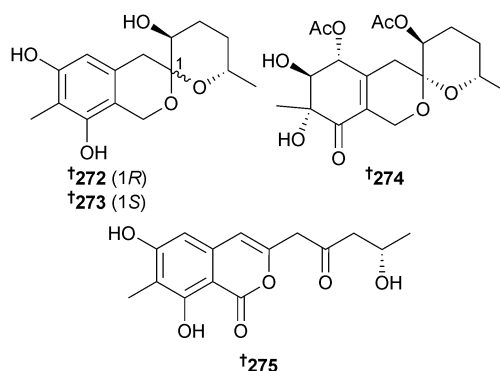
Pinophilins A **268** and B **269**, hydrogenated azaphilones from *P. pinophilum* (seaweed *Ulva fasciata*, Kasai, Tokyo, Japan), along with the co-isolated metabolite Sch 725680,²⁴¹ selectively inhibited the activities of mammalian DNA polymerases (pols), A (pol γ), B (pols α , δ , and ϵ), and Y (pols 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



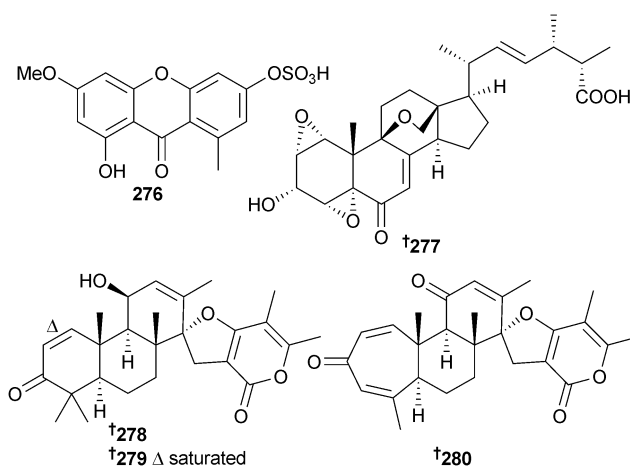
Random diethyl sulfate mutagenesis of *P. purpurogenum* (sediment, Bohai Bay, Tianjin, China) gave a mutant producing the drimenyl cyclohexenone derivatives purpurogemutantidin **270** and purpurogemutantidin **271**.²⁴⁵ From another *Penicillium* strain (deep sea sediment, northern South China Sea) 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



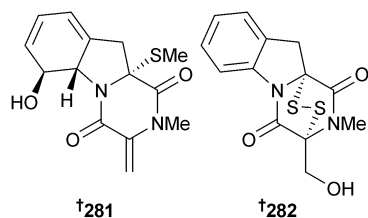
Peneciraistins A–D **272–275** were isolated from *P. raistrickii* (saline soil, Bohai Bay, Shandong, China). Peneciraistin C was moderately cytotoxic to A549 and MCF-7 cells whilst peneciraistins A, B and D exhibited radical scavenging activities against DPPH.²⁴⁷ Two further compounds were isolated 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 rings²⁴⁸ both of which are known compounds.^{249,250}



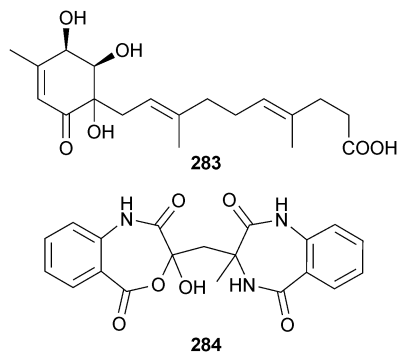
1-Hydroxy-3-methoxy-6-sulfo-8-methylxanthone **276** was isolated from *P. sacculum* (saltbush *Atriplex* sp., Dongying city, Shandong, China),²⁵¹ whilst *Penicillium* sp. (deep sea sediment, East Pacific Ocean) provided the polyoxygenated sterol, sterolic acid **277** and the spiroditerpenoids brevione I–K **278–280**. Brevione J and the known terrestrial fungal allelochemical brevione A²⁵² (obtained here for the first time from a marine source) were cytotoxic (MCF-7 cells).²⁵³



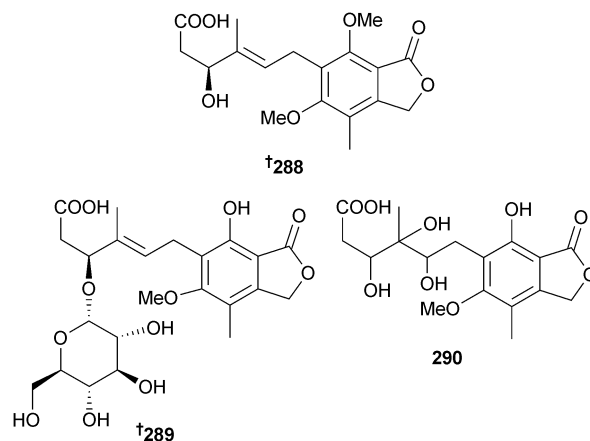
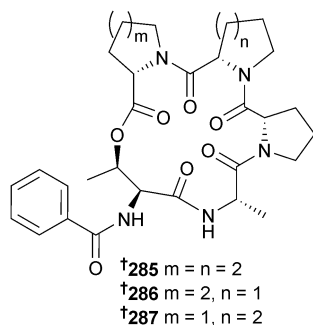
Penicillium sp. (deep sea sediment, Suruga Bay, Japan) yielded several gliotoxin-related compounds including **281** and **282**. Of the other known compounds, bisdethiobis(methylthio)gliotoxin,²⁵⁴ 5a,6-didehydrogliotoxin,²⁵⁵ gliotoxin²⁵⁶ and gliotoxin G²⁵⁷ inhibited histone methyltransferase (HMT), while **282** and gliotoxin G were cytotoxic to P388 cells.²⁵⁸



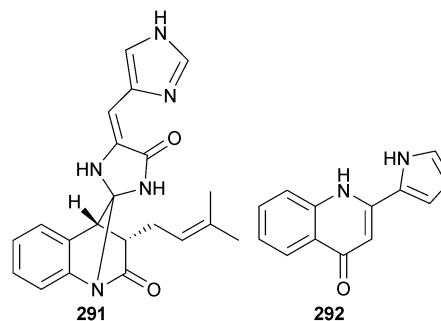
Penicillone A **283** and penicillactam **284** were isolated from a marine *Penicillium* sp. (source not given).²⁵⁹ A further compound, ethyl 2-(2,6-dihydroxybenzoyl)-3-hydroxy-5-(hydroxymethyl)benzoate,²⁶⁰ was isolated and although commercially available this was the first reported isolation as a natural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



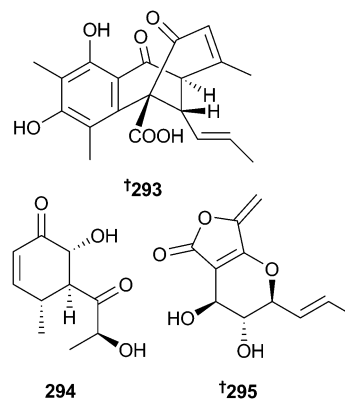
The depsipeptides JBIR-113, JBIR-114 and JBIR-115 **285–287** were obtained from *Penicillium* sp. (unidentified marine sponge, Takarajima Is., Kagoshima, Japan)²⁶¹ and another *Penicillium* sp. (sediment, South China Sea) was the source of the mycophenolic acid derivatives penicacid A–C **288–290** 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



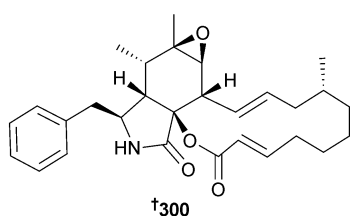
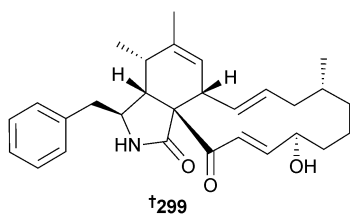
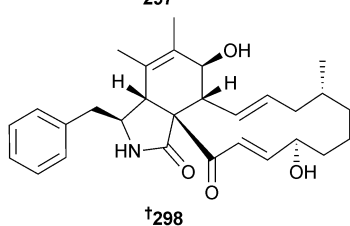
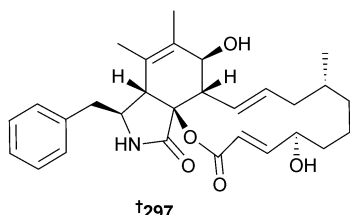
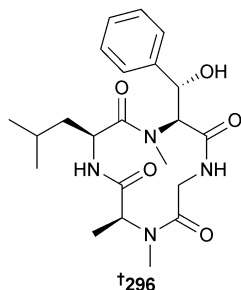
A halotolerant *Penicillium* sp. (source unspecified) yielded an alkaloid with a unique spiro-imidazolidinyl skeleton, penispirolloid A **291**, that exhibited antifouling activity toward *Bugula neritina* larvae²⁶⁴ and *Penicillium* sp. (sediment, Jiaozhou Bay, China) was the source of the pyrrolyl 4-quinolinone alkaloid penicoline E **292**.²⁶⁵



A sorbicillinoid derivative sorbiterrin A **293** with moderate acetylcholinesterase (AChE) inhibition, was obtained from *P. terrestre* (sediment, Jiaozhou Bay, China)²⁶⁶ and arthropadiol 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 C²⁶⁸ and enalin A²⁶⁹ displayed moderate neuraminidase inhibition. This was the first reported marine isolation of massarigenin C.²⁷⁰

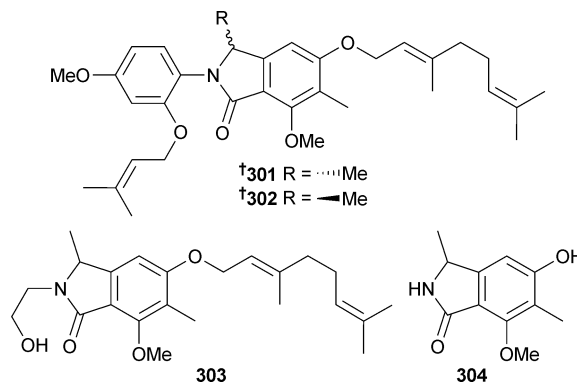


An endophytic *Phoma* sp. (giant jellyfish *Nemopilema nomurai*, southern coast, S. Korea) provided a cyclic tetrapeptide **296** which was a weak suppressor of NO production in RAW264.7 cells without notable cytotoxicity.²⁷¹ The same strain of fungus also provided four cytochalasin derivatives: cytochalasin 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}

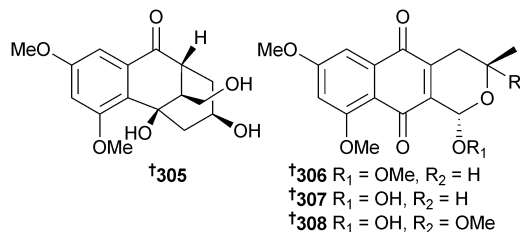


Stachylidium sp. (sponge *Callyspongia cf. flammea*, location unspecified) yielded phthalimidine derivatives, the enantiomeric marilines A1 **301** and A2 **302** and marilines

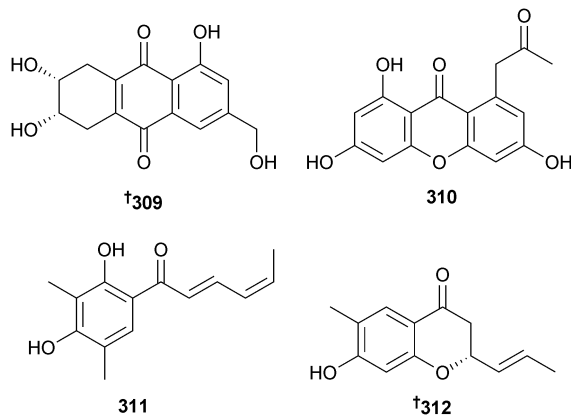
B **303** and C **304**. The various marilines were active in a wide range of bioassays.²⁷⁴



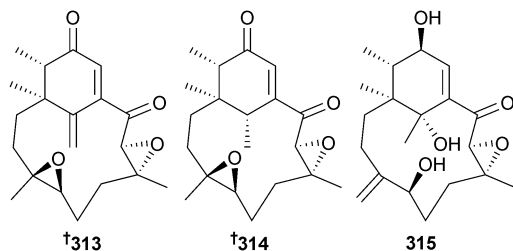
Torula herbarum (sea hare *Notarchus leachii*, Beihai, Guangxi, China) was the source of the heptaketide herbarone **305** and the *ent*-astropaquinones B **306** and C **307**. *O*-Methylherbarin, a metabolite previously reported from *T. herbarum*,²⁷⁵ was also obtained and the absolute configuration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



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

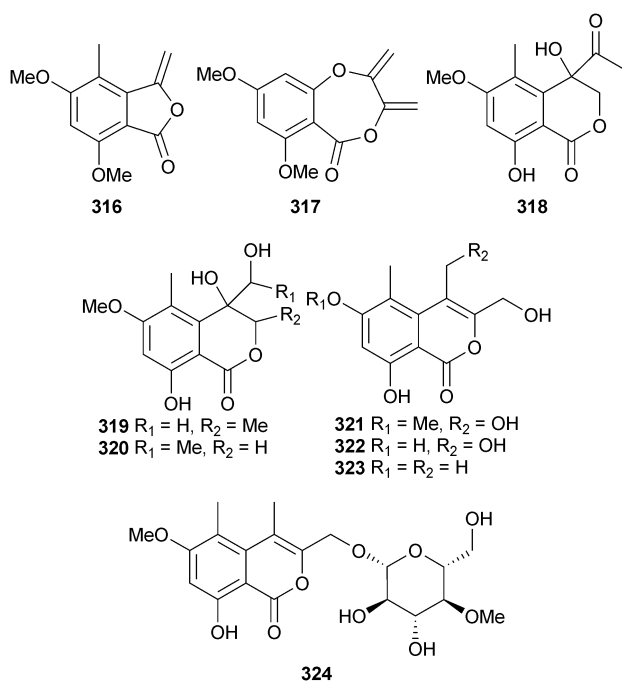


analogues (4'Z)-sorbicillin **311** and **312** (moderately cytotoxic to several HTCLs),²⁷⁸ while three diterpenes phomactin K–L **313–315** were obtained from an unidentified fungus (brown alga *Ishige okamurae*, Tateishi, Kanagawa, Japan).²⁷⁹

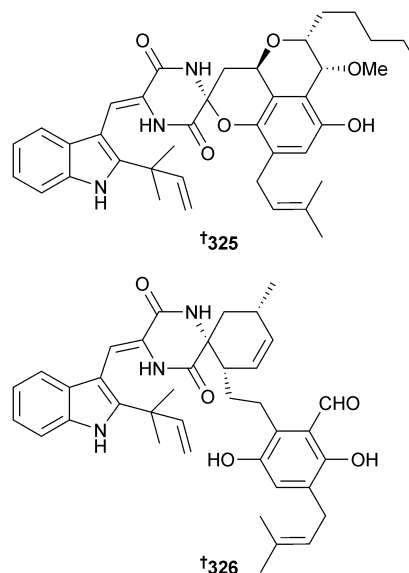


3.4 Fungi from mangroves

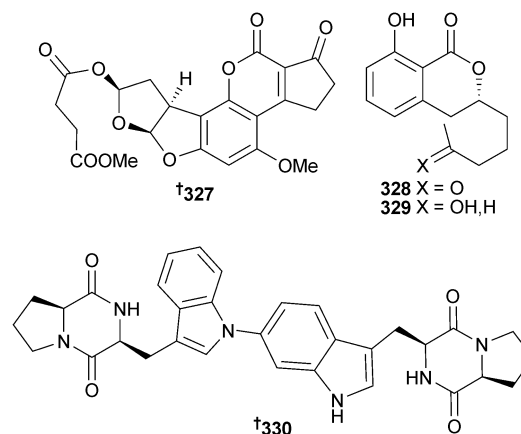
An endophytic *Acremonium* sp. (mangrove branch *Rhizophora apiculata*, Satun, Thailand) provided the phthalide derivative, acremonide **316** and the isocoumarin derivatives acremonone A–H **317–324**.²⁸⁰



The racemic spiroalkaloids effusin A and dihydro-cryptochinulin 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 dihydrocryptochinulin D inhibited growth of P388 cells and the (12*R*,28*S*,31*S*)-enantiomer **326** showed selective, moderate inhibition of topoisomerase I.²⁸¹

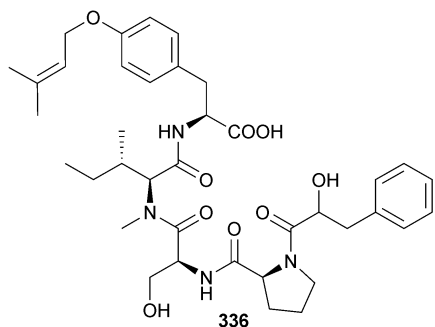
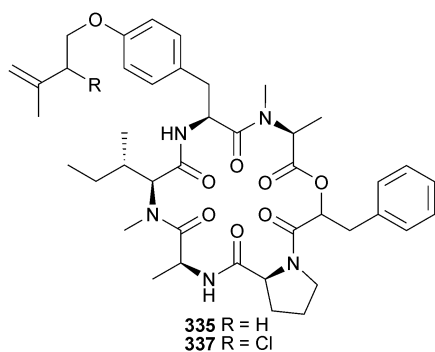
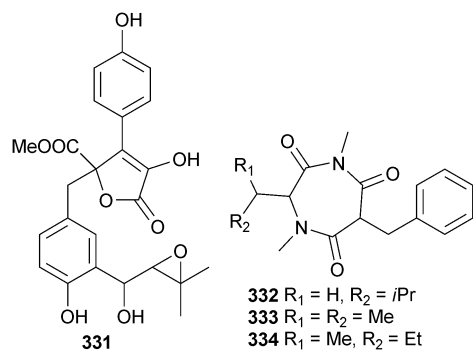


Aflatoxin B₂ **327** was obtained from endogenous *A. flavus* (mangrove root *Hibiscus tiliaceus*, Wenchang, Hainan, China) and was moderately active against *E. coli*, *B. subtilis* and *E. aerogenes*.²⁸² The dihydroisocoumarin derivatives aspergillumarin A **328** and B **329** were isolated from *Aspergillus* 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

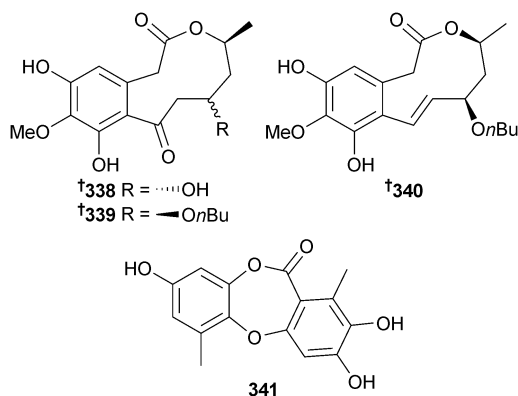


The butyrolactone 7'-hydroxybutyrolactone III **331** and terretiones A–C **332–334** were isolated from *A. terreus* (sediment, unnamed mangrove, Guangxi Zhuang, China).²⁸⁵ Along with three known terrestrial fungal metabolites, verticillin D²⁸⁶ and pullularins A and C²⁸⁷ (isolated from a marine source 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

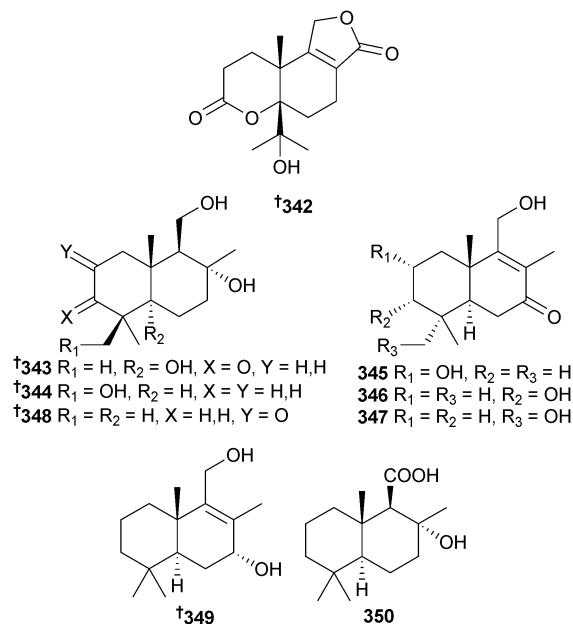




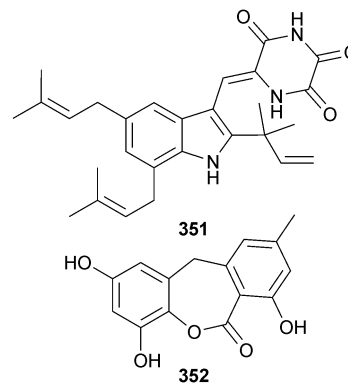
Corynespora cassicola (mangrove leaf *Laguncularia racemosa*, Hainan Is., China) yielded xestodecalactones D–F 338–340 and corynesidone C 341 as well as the known terrestrial fungal metabolites corynesidone B²⁸⁹ and 6-(3-hydroxybutyl)-7-O-methylspinochrome B,²⁹⁰ both isolated for the first time as MNPs.²⁹¹



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 349²⁹⁴ and I 350²⁹⁵ were isolated for the first time as natural products.²⁹²

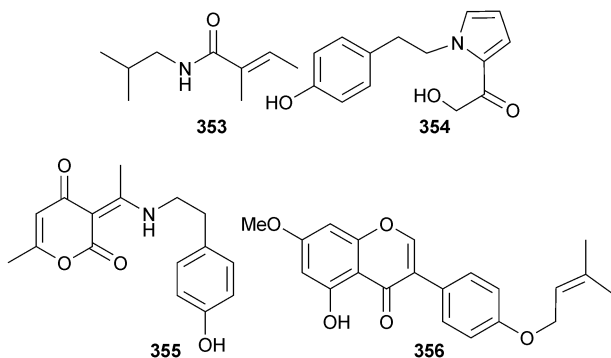


An endophytic strain of *Eurotium rubrum*, (semi-mangrove *Hibiscus tiliaceus*, Hainan Is., China) produced a diketopiperazine alkaloid 12-demethyl-12-oxo-eurotechinulin B 351 and an anthraquinone derivative 9-dehydroxyeurotinone 352,²⁹⁶ in addition to the known fungal metabolites varicolorin G²⁹⁷ and alkaloid E-7.^{297,298}

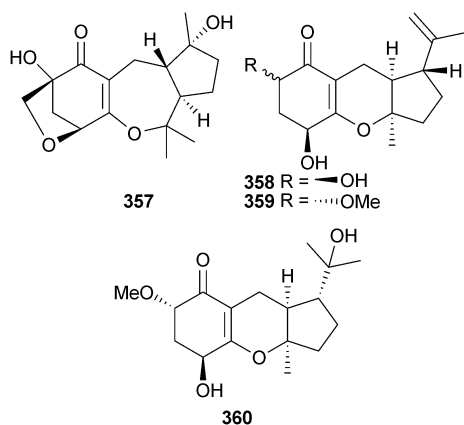


The alkaloids *N*-2-methylpropyl-2-methylbutenamide 353, fusarine 354 and fusamine 355 were discovered from endophytic *Fusarium incarnatum* (mangrove fruit *Aegiceras corniculatum*, Xiamen, Fujian, China)²⁹⁹ along with the known synthetic compounds, 2-acetyl-1,2,3,4-tetrahydro- β -carboline³⁰⁰ and 3-(1-aminoethylidene)-6-methyl-2*H*-pyran-2,4(3*H*)-dione,³⁰¹ 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

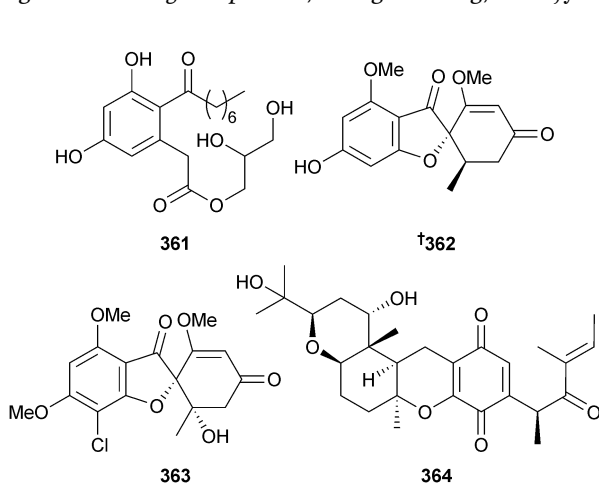




Endophytic *Guignardia* sp. (mangrove leaves *Scyphiphora hydrophyllacea*, Wenchang, Hainan, China) was the source of the meroterpenes guignardone F–I 357–360.³⁰⁴ It should be noted that the planar structure of guignardone G was the same as that of coibanol A, recently obtained from a plant endophyte, *Pycnoporus sanguineus* from Panama.³⁰⁵ The co-isolated guignardone B³⁰⁶ was obtained from a marine source for the first time.

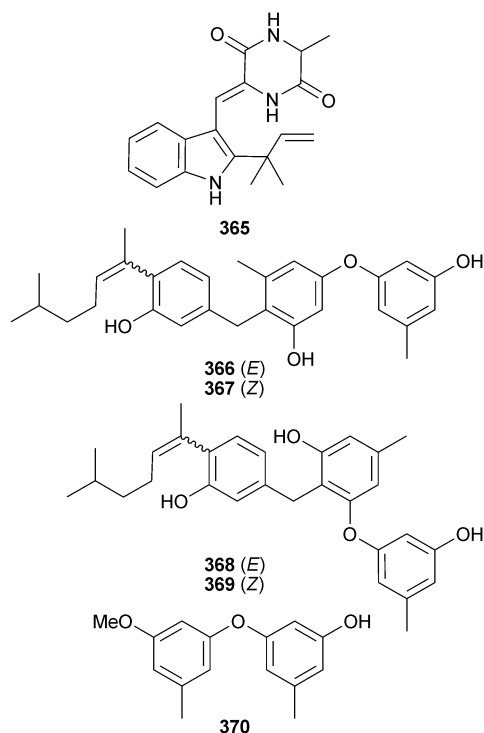


Use of epigenetic modifiers to activate secondary metabolite genes in *Leucostoma persoonii* (mangrove branch *Rhizophora mangle*, Florida Everglades) induced production of a new cytosporone analogue cytosporone R 361, in addition to known cytosporones. Of the isolated compounds, cytosporone E,³⁰⁷ a 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

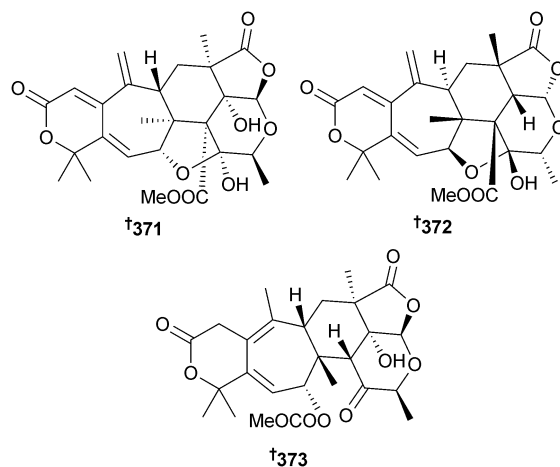


griseofulvin derivatives 362 and 363, 2,3-didehydro-19 α -hydroxy-14-epicochloquinone B 364, in addition to griseophenone C³⁰⁹ (obtained for the first time from a marine source).³¹⁰

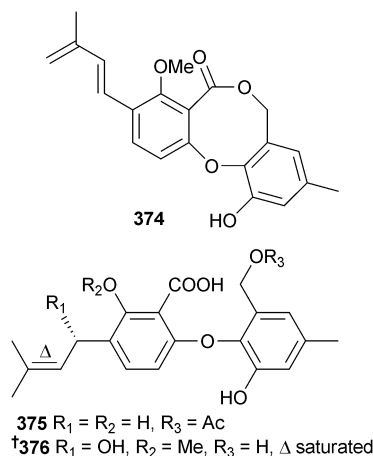
The diketopiperazine 365 (named chrysogenazine in an earlier patent application by the same authors),³¹¹ was obtained from endophytic *Penicillium chrysogenum* (mangrove leaves *Porteresia coarctata*, Choroa Is., Goa, India) and displayed antibacterial activity comparable to that of streptomycin.³¹² 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



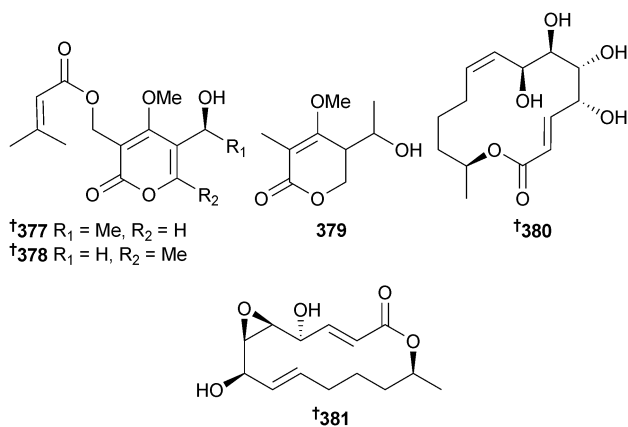
A *Penicillium* sp. (mangrove rhizospheric soil *Bruguiera gymnorhiza*, Hainan Is., China) produced meroterpenoid derivatives 4,25-dehydrominiolutelide B 371, 4,25-dehydro-22-



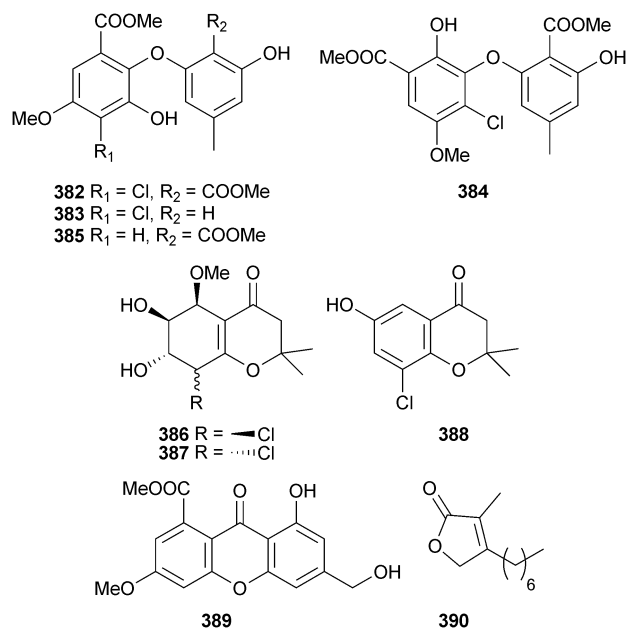
deoxyminiolutelide B 372 and isominiolutelide A 373 from static culture and diphenyl ether derivatives $\Delta^{1'3'}$ -1'-dehydroxyphenicillide 374, 7-O-acetylsecopenicillide C 375 and hydroxytenelic acid B 376 from shaken culture.³¹⁴ A number of known compounds were also isolated from the shaken culture: penicillide,³¹⁵ secopenicillide C,³¹⁶ dehydroisopenicillide³¹⁷ and 3'-O-methyldehydroisopenicillide³¹⁸ (all obtained from a marine source for the first time).



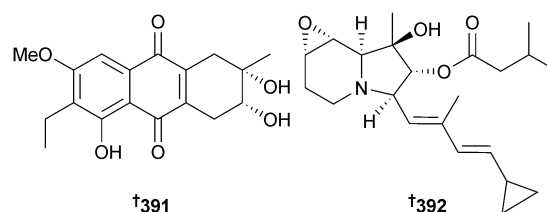
The α -pyrones pestalotiopyrone A–C 377–379 were isolated from *Pestalotiopsis* sp. (mangrove twigs *Rhizophora apiculata*, Trang province, Thailand) and the seircuprolides pestalotioprolide A 380 and B 381 (isolated as the diacetate) were obtained from *Pestalotiopsis* sp. (mangrove twigs *Rhizophora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



An endophytic *Pestalotiopsis* sp. (mangrove branch *Rhizophora 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

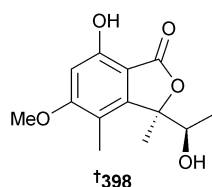
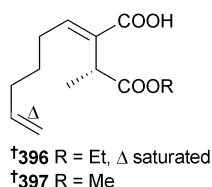
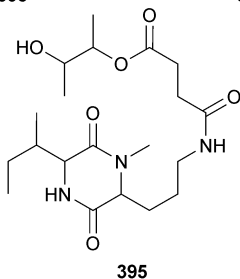
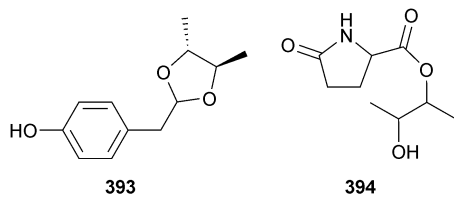


The tetrahydroanthraquinone derivative 391 was isolated from *Phomopsis* sp. (mangrove leaf *Rhizophora apiculata*, Songkhla, Thailand) and possessed weak cytotoxicity against MCF-7 cells in addition to antibacterial activity against *S. aureus* and MRSA.³²¹ *Saccharopolyspora* sp. (mangrove soil, Ishigaki Is., Japan) yielded the cyclizidine analogue JBIR-102 392, along with cyclizidine³²² itself (first time from a marine source). Both were cytotoxic to human malignant pleural mesothelioma (MPM) ACC-MESO-1 cells.³²³

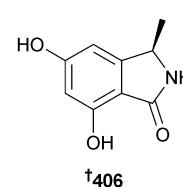
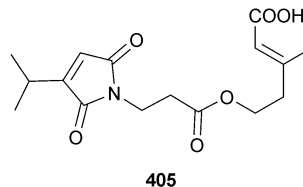
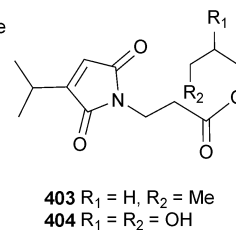
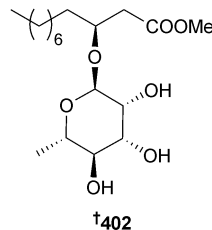
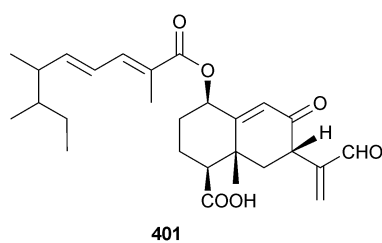
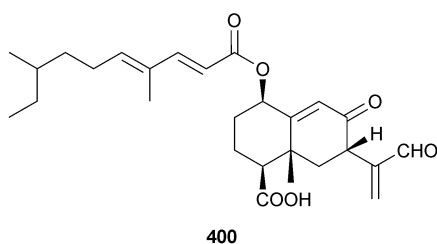
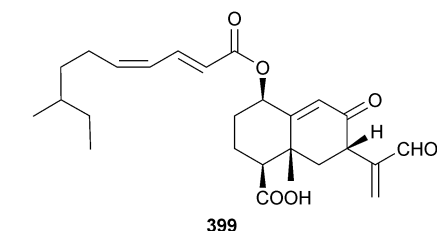


Trichoderma atroviride (mangrove root soil *Ceriops tagal*, South Sea, China) yielded three new metabolites 393, 394 and atroviridetide 395.³²⁴ The succinic acid derivatives xylacinic acid A 396 and B 397 were isolated from *Xylaria cubensis* (mangrove branch *Bruguiera parviflora*, Suratthani, Thailand),³²⁵ 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



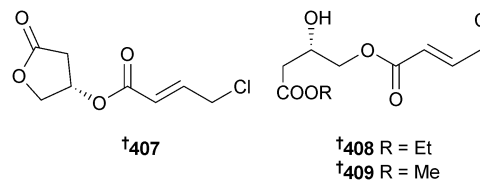


An endophytic *Xylaria* sp. (unidentified mangrove, South China Sea coast) was the source of the eremophilane sesquiterpenes **399–401**³²⁸ and the known fungal metabolite 07H239-A.³²⁹ A fatty acid glucoside **402** with moderate inhibitory properties against *S. aureus* and MRSA was obtained from an 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

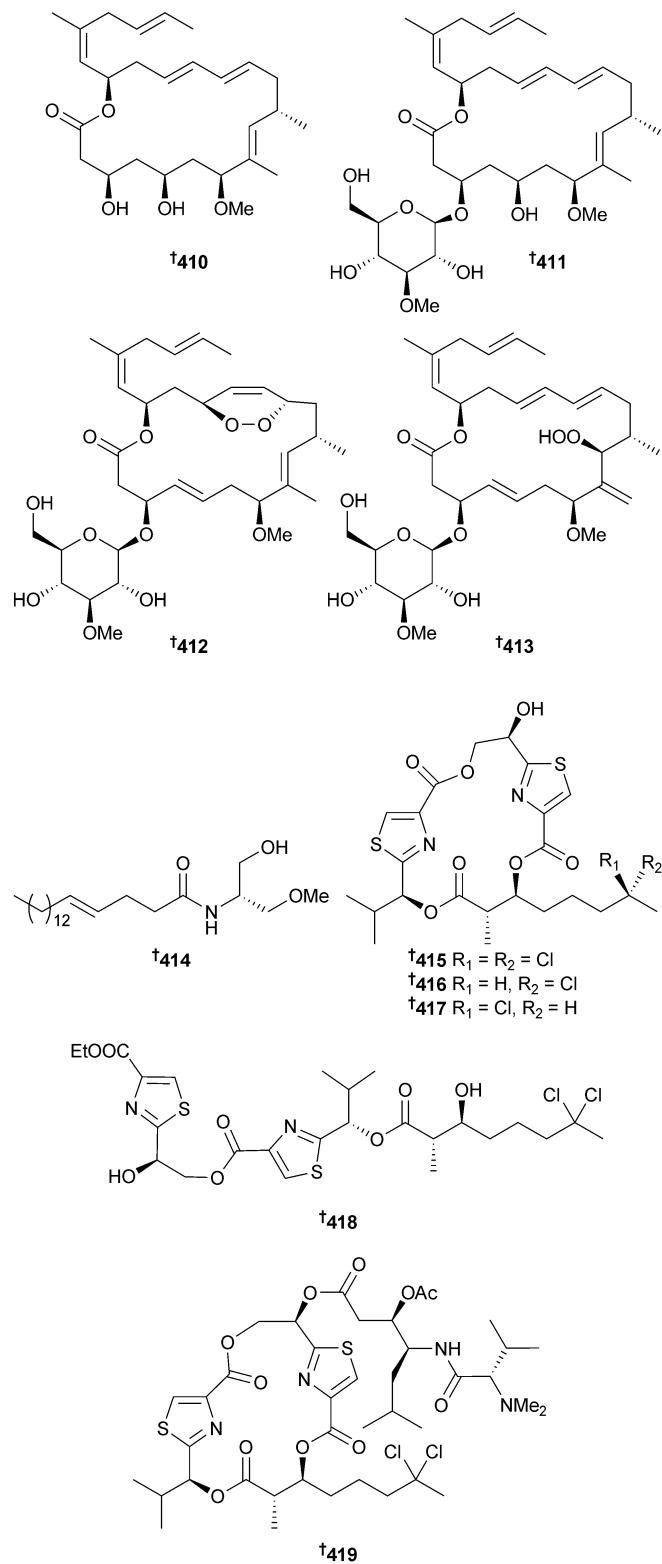
Cyanobacteria continue to be a valuable source of new compounds, although the number of new metabolites isolated in the past year is somewhat less than in 2011. *Leptolyngbya crossbyana* (Hōnaunau reef, Hawaii) was the source of honaucins A–C **407–409**, chlorinated metabolites that were potent inhibitors 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 biselyngbyaside³³⁵ and biselyngbyolide A³³⁴ were obtained from another *Lyngbya* sp. (Tokunoshima Is., Japan). Biselyngbyaside B inhibited growth and induced apoptosis in HeLa S₃ and HL-60 cells with increased cytosolic Ca²⁺ concentration in the HeLa S₃ cells.³³⁶

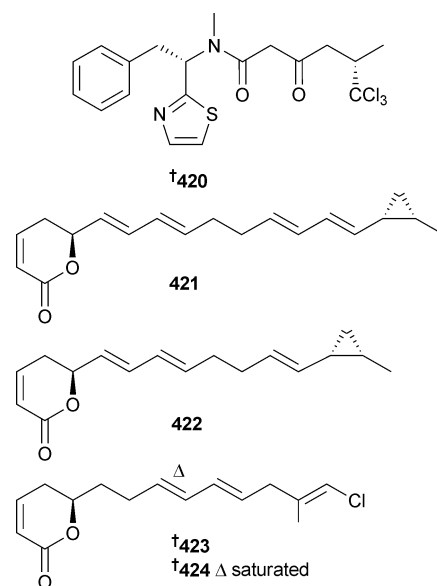
Serinolamide B **414**, a fatty acid amide obtained from a *Lyngbya* sp. (Piti Bomb Holes, Guam) along with malyngamide B³³⁷ are cannabinomimetics, decreasing forskolin-induced cAMP accumulation.³³⁸ The lipopeptides lyngbyabellin K **415** and L **416**, 7-*epi*-lyngbyabellin L **417** and lyngbyabellin 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



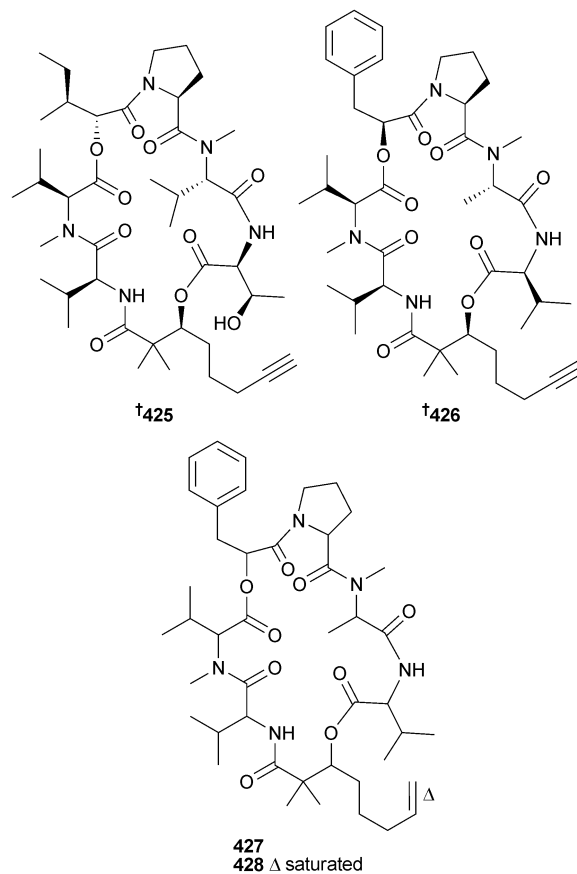


The biosynthetic gene cluster for the chlorinated molluscicide barbamide,³⁴⁰ obtained from the marine species *Moorea producens*, was heterologously expressed in the terrestrial actinobacterium *Streptomyces venezuelae* and resulted in the production of a new barbamide analogue 4-*O*-demethylbarbamide **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



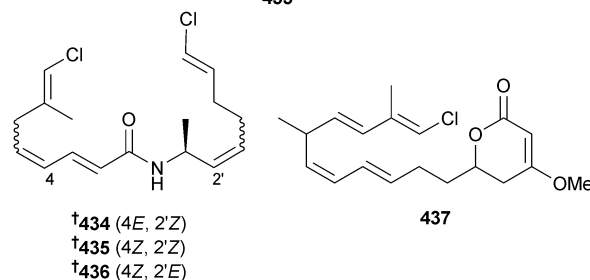
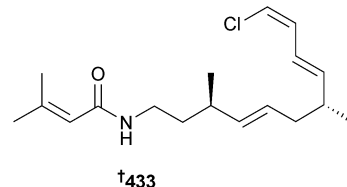
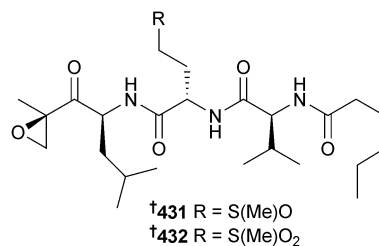
The viequeamides, 2,2-dimethyl-3-hydroxy-7-octynoic acid (Dhoya)-containing cyclic depsipeptides, were obtained from the “button” cyanobacterium *Rivularia* sp. (Playa de la Chiva, Vieques Is., Puerto Rico). Of these, viequeamide A **425** was highly toxic to



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

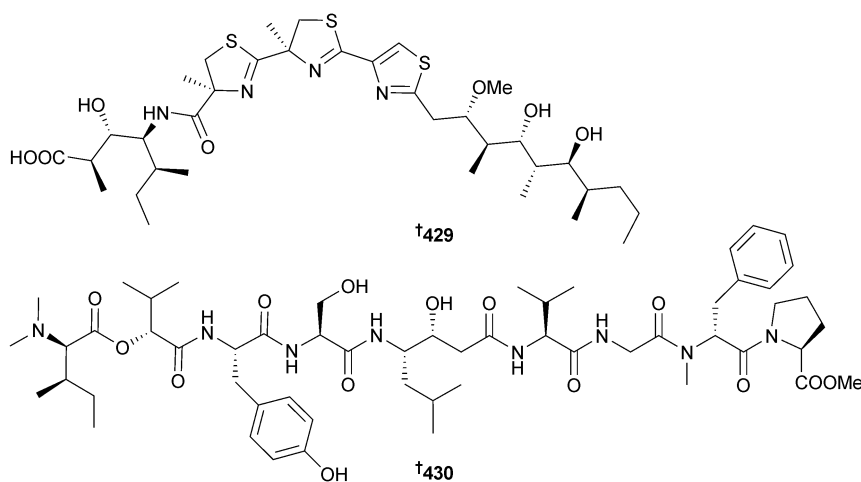
A collection of *Symploca* sp. (CARMABI, Curaçao) was the source of carmaphycins A **431** and B **432**, peptidic proteasome inhibitors containing a leucine-derived α,β -epoxyketone connected respectively to methionine sulfoxide or methionine sulfone. Convergent and flexible total syntheses of each were achieved. Both carmaphycins A and B strongly inhibited the $\beta 5$ 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 produ-cens* (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

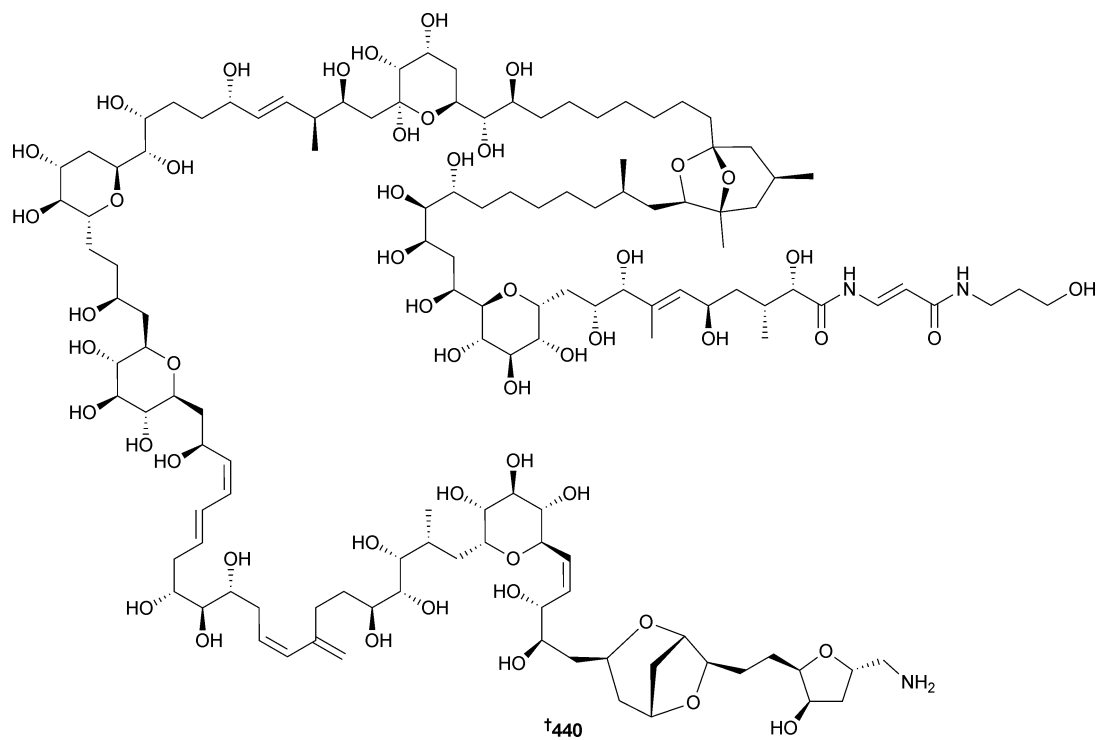
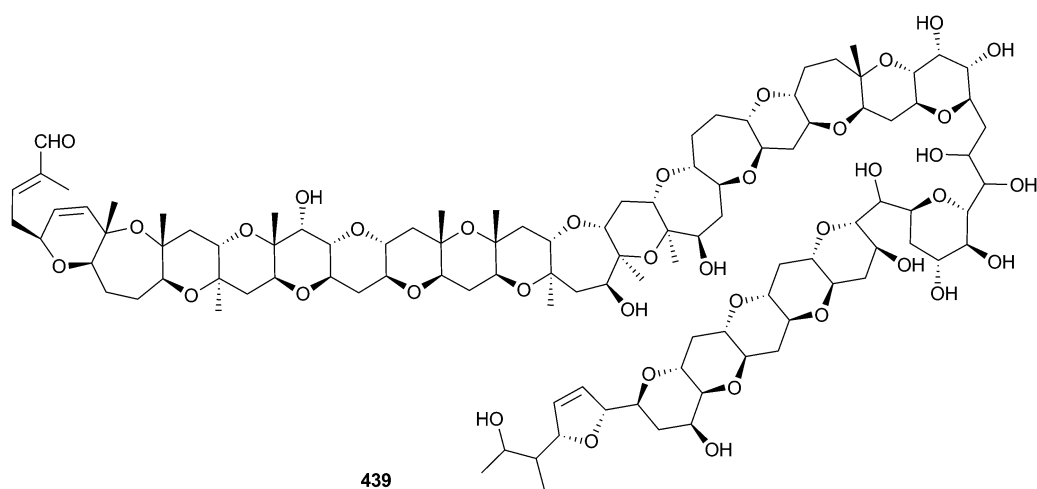
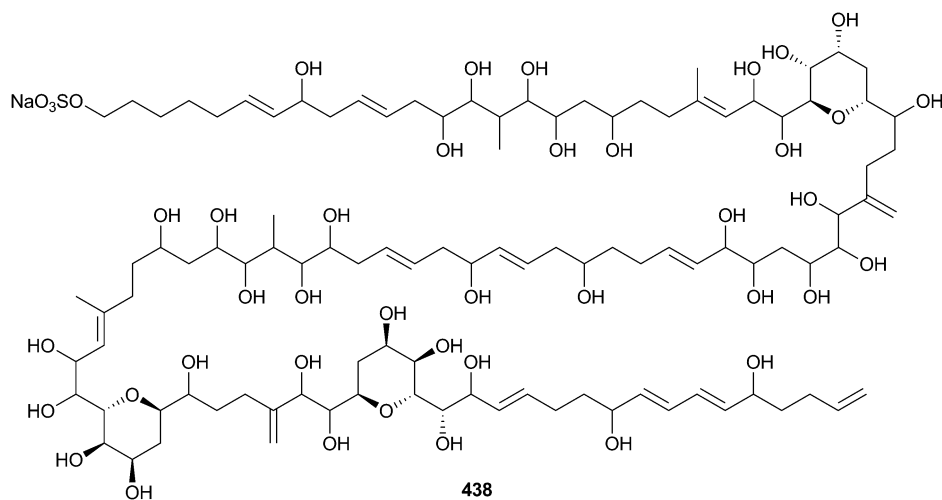


3.6 Dinoflagellates

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,

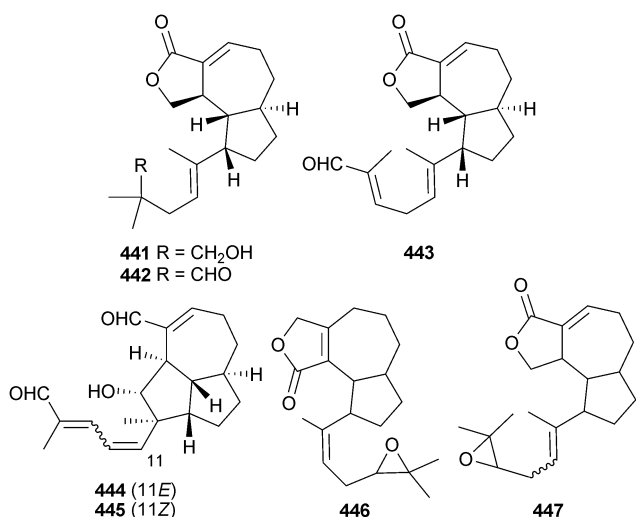




ovatoxin-f was detected in a North Western Adriatic strain of *Ostreopsis cf. ovata* (Portonovo, Italy) but was not fully characterised.³⁵⁴

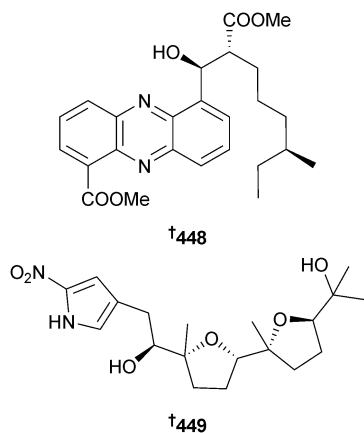
3.7 Ciliates

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 ubatubaolidenol **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



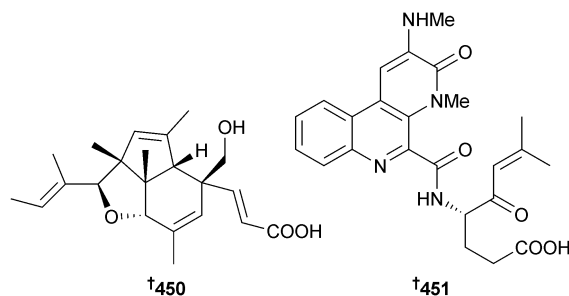
3.8 Synthetic aspects

Asymmetric synthesis of streptophenazine G³⁵⁶ 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

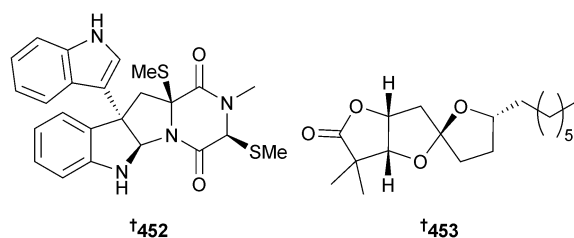


absolute configuration of naturally occurring heronapyrrole C is proposed as **449**.³⁶⁰

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 albo-griseolus*³⁶³ was synthesised and the absolute configuration determined as **451**.³⁶⁴

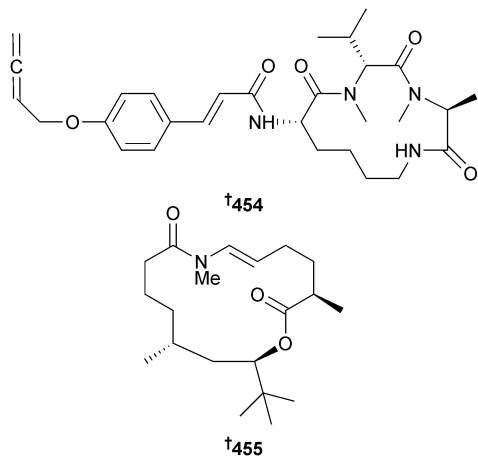


A synthesis of apiosporic acid, originally isolated from *Apiospora montagnei* (fungal endophyte of the North Sea alga *Polysiphonia violacea*),³⁶⁵ has confirmed the absolute configuration as originally drawn.³⁶⁶ (+)-Gliocladin B, a diketopiperazine metabolite of the fungus *Gliocladium* sp.,³⁶⁷ has 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-spiroketal, led to a suggested structure for cephalosporolide H as **453**. This awaits comparison with an authentic sample for confirmation.³⁷¹

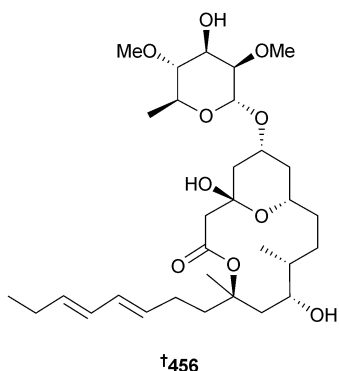


Xyloallenoide A, an *N*-cinnamoylcyclopeptide isolated from the endophytic mangrove fungus *Xylaria* sp.,³⁷² has been synthesised and the absolute configuration determined as **454**.³⁷³ Palmyrolide A is a neuroprotective macrolide obtained from an assemblage of the cyanobacteria *Leptolyngbya* and *Oscillatoria* 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





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 core³⁷⁹ and also with the stereochemistry of lyngbyalide B,³⁸⁰ a metabolite obtained from a different species of *Lyngbya*, but with the same macrocyclic core as lyngbouilloside.³⁷⁸



Veraguamide A is a cyclic hexadepsipeptide isolated from the cyanobacteria *Symploca cf. hydroides* (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 iodopyridone, 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 completed³⁹⁰ 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 Salinipyron 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 (\pm)-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, non-enolides 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-diketopiperazine⁴²³ 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-hydroxyacetylindole⁴²⁵ and *N*-acetyl- β -oxotryptamine⁴²⁶ 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-one⁴²⁹ and 6-heptyl-3-hexyl-4-hydroxyl-2*H*-pyran-2-one⁴³⁰ 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'-bipyrrrole metabolites of a *Streptomyces* sp.,^{434,435} has indicated that two flavin-dependent halogenases catalyse the unprecedented *N,C*-bipyrrrole homocoupling reaction.⁴³⁶ Haterumalides are antitumour halogenated macrolides obtained from terrestrial plant-associated bacteria,^{437,438} and subsequently from a marine sponge⁴³⁹ 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 marine⁴⁴⁵ 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,

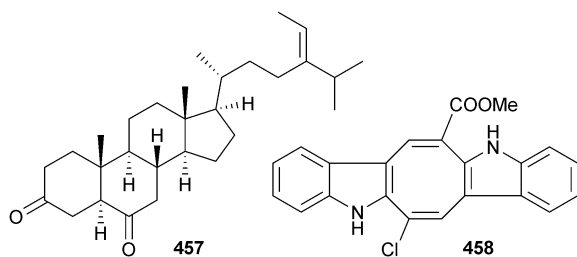
Tianjin, China) with the antibiotic gentamicin produced a mutant in which previously silent gene clusters were activated to produce antitumour compounds of four different chemical types: janthinone,⁴⁴⁷ fructigenine A,⁴⁴⁸ aspterric acid methyl ester⁴⁴⁹ and citrinin,⁴⁵⁰ demonstrating the potential of this 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 [2-¹³C]malonate and [1,2,3-¹³C₃]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 ¹³C-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 marine⁴⁵⁷ and terrestrial⁴⁵⁸ 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 marine⁴⁵⁹ and terrestrial⁴⁶⁰ fungal metabolite monodictyphenone.⁴⁶¹ NotB, the enzyme which catalyses the indole 2,3-oxidation of the *Aspergillus* metabolite notoamide E⁴⁶² to notoamides C⁴⁶² and D⁴⁶² through an apparent pinacol-like rearrangement, has been characterised *in vitro*. Precursor incorporation experiments utilising [¹³C]₂-[¹⁵N]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 ¹⁸O₂ atmosphere and with supplementation of the culture media with [¹⁸O₂]-acetate, followed by collision-induced dissociation tandem mass spectrometry (CID MS/MS) of the labelled yessotoxin, indicated that the ether oxygens were labelled from ¹⁸O₂ and the hydroxy oxygen on C-32 was derived from [¹⁸O₂]-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 DTX5c⁴⁶⁸ was investigated by addition of sodium [1-¹³C]- and



[2-¹³C]-acetate to artificial cultures of the dinoflagellate *Proocentrum 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

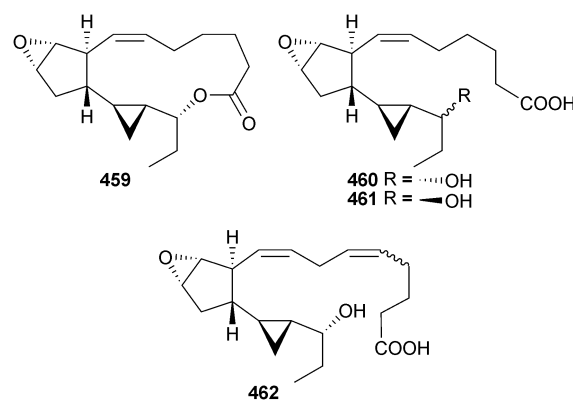


Included in the green alga literature for 2012 were a number of papers, that while not reporting new compounds, are worthy of comment. These include the finding that separate isoprenoid-24-alkyl sterol pathways have evolved in fungi and green algae which converge to yield ergosterol,⁴⁷⁴ the role of caulerpin as a potential antiviral drug against HSV Type 1,⁴⁷⁵ tetrapyrrolic pigments as photosensitisers for photodynamic therapy⁴⁷⁶ 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

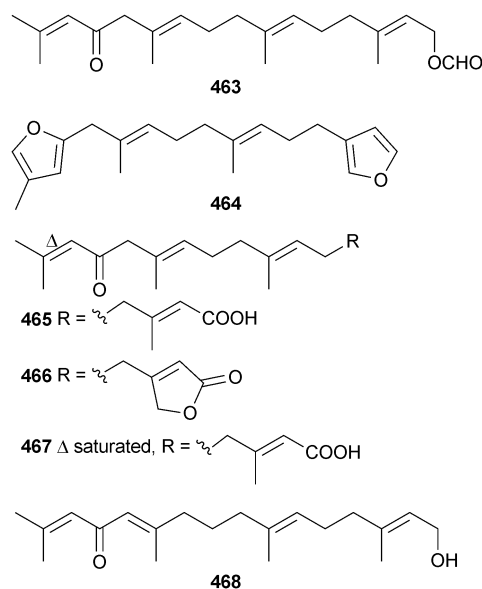
5 Brown algae

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.

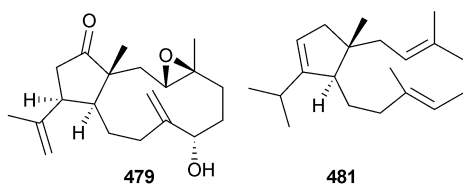
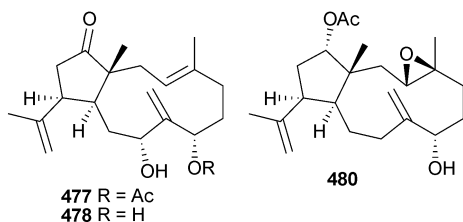
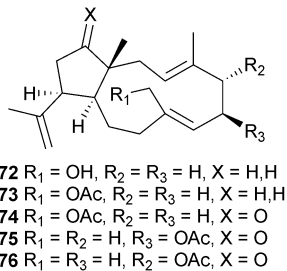
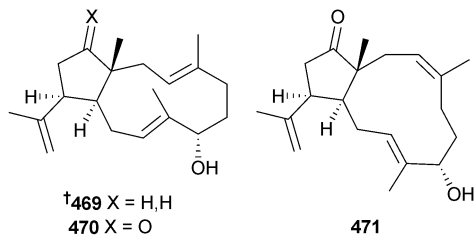


Two studies on *Bifucaria bifurcata* (Roscoff, France) defined the metabolic makeup of this alga with the isolation of the sesquiterpenoids formyleleganolone **463**, bibifuran **464** and four new eleganolone derivatives **465–468**.^{481,482} Also isolated were eleganolone,⁴⁸³ five previously described eleganolone derivatives^{484–488} and 16-hydroxygeranylgeraniol⁴⁸⁹ (isolated for the first time from this species) which collectively can be correlated in a hypothetical metabolic grid.⁴⁸²

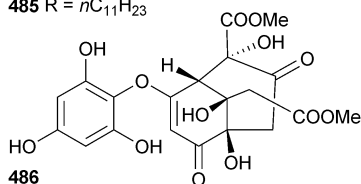
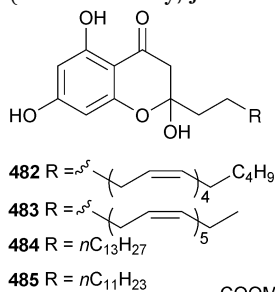


In a follow-up study the structures and relative configurations of a further 13 dolabellane diterpenoids **469–481** from the alga *Dilophus spiralis* (Elafonissos Is., Greece) were described along with the antibacterial properties of **469–477** and **481**. The absolute configuration of **469** was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



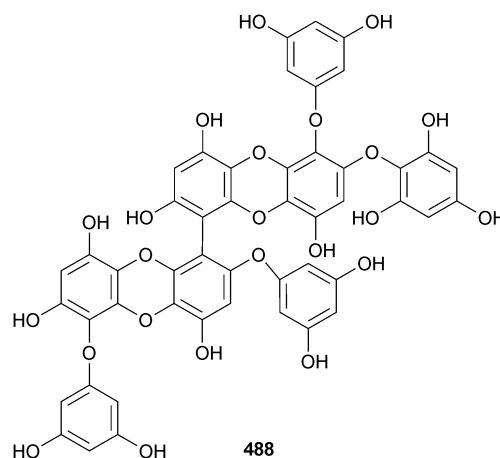
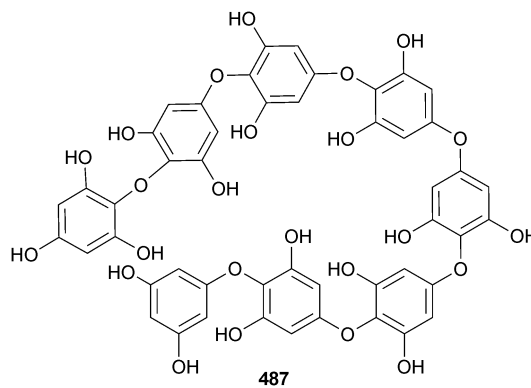


Investigation of the kinase and antibacterial activity of *Zonaria spiralis* (North Walkerville, Victoria, Australia) led to the isolation of the hemiketal spiralisones A–D, **482–485**. These are phloroglucinol-derived lipids and were isolated as racemates. The relative instability of the spiralisones, the zero optical rotation and the isolation of co-occurring 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

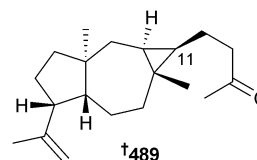


Sargussumol was the phenolic rather than the methyl ether (sargussumketone) previously isolated from *S. kjellmanianum*.⁴⁹³

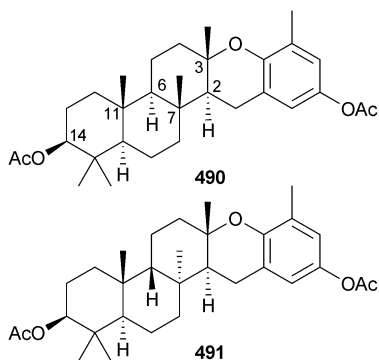
From a survey of 15 algae from the Sea of Japan for α -amylase activity, the phlorotannin DDBT was found in *Sargassum patens* (Noto Peninsula, Japan). DDBT was a potent competitive inhibitor of α -amylase and also inhibited α -glucosidase suggesting a potential role as a natural nutraceutical to prevent 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



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



In light of the confusion that has surrounded the absolute configurations of the meroditerpenoids taondiol^{500,501} and epitaondiol⁵⁰² 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.

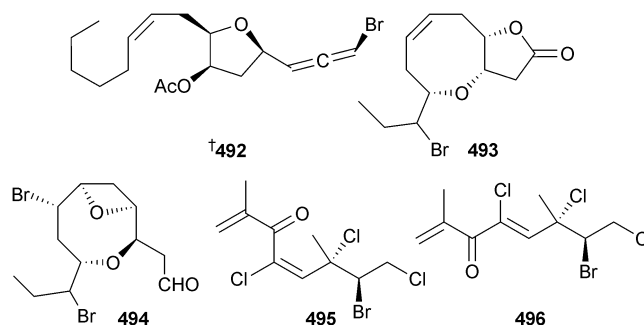


A stereoselective synthesis of the *trans*-hydrindane core of dictyoxetane⁵⁰⁴ has been reported,⁵⁰⁵ as has the development of “borono-sclareolide”, a terpenyl radical precursor that can be produced on the multi-gram scale allowing rapid access to a wide variety of meroterpenoids. This was demonstrated by the synthesis of 10 meroterpenoids, the majority being of marine origin.⁵⁰⁶ The C₄₀ allenic-carotenoid fucoxanthin has been synthesised by a stereocontrolled route that also led to a longer chain (C₄₂) 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 meroditerpenoid⁵⁰⁹ from *Cystoseira nodicaulis* (Penmarc'h, Brittany, France) were considered.⁵¹⁰ The incidence of betaines in species of the Laminariales was studied⁵¹¹ and two papers have been published on the biological properties of sargachromanol G from *Sargassum siliquastrum*⁵¹² covering anti-inflammatory properties⁵¹³ 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 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

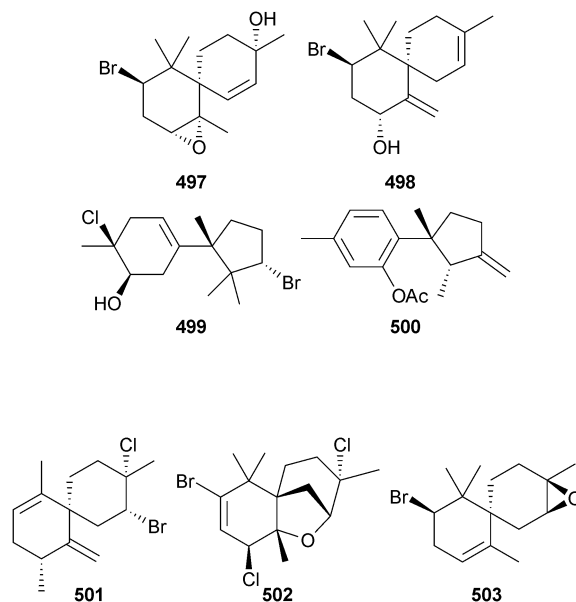
6 Red algae

The 46 new compounds reported from red algae in 2012 is similar to the number reported from the previous year (42).

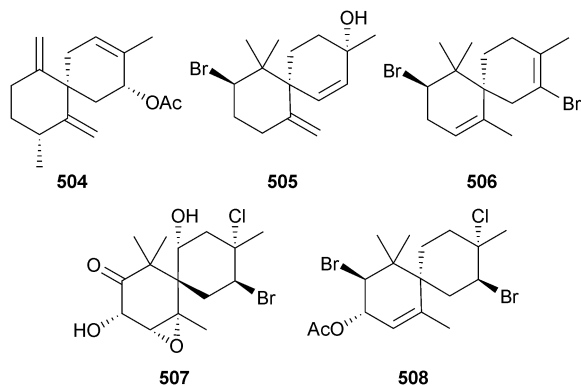
Three bromoallenes, including the new dihydroitomanallene **492**, were obtained from *Laurencia nangii* (Sabah, Malaysia).⁵¹⁸ Desepilaurallene **493** is a C₁₂-acetogenin extracted from *L. okamurai* (Rongcheng, China), along with four new sesquiterpenes described later in this section.⁵¹⁹ A different collection of *L. okamurai* (Weihai, Shandong Province, China) also contained a mixture of a C₁₂-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



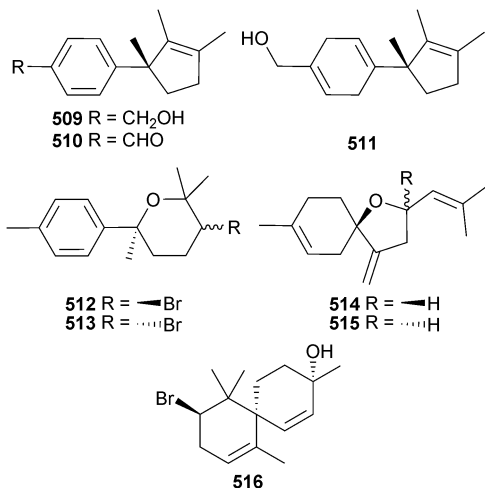
The brominated chamigrenes **497** and **498** and cuparene **499**, together with the known sesquiterpene **500**, but new as a natural product, were isolated from the same *L. okamurai* that yielded the C₁₂-acetogenin **493** described earlier. The sesquiterpene **500** had potent antibacterial activity.⁵¹⁹ 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



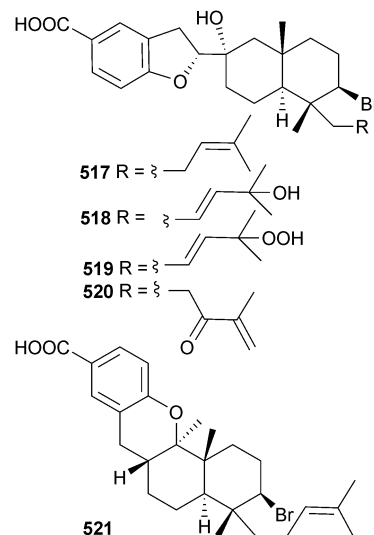
Four new chamigranes laurecomin A–D **504**–**507** and the sesquiterpene **508** were isolated from *L. composita* (Pingtan Is., China). Laurecomin B was the only compound showing anti-fungal activity.⁵²⁴



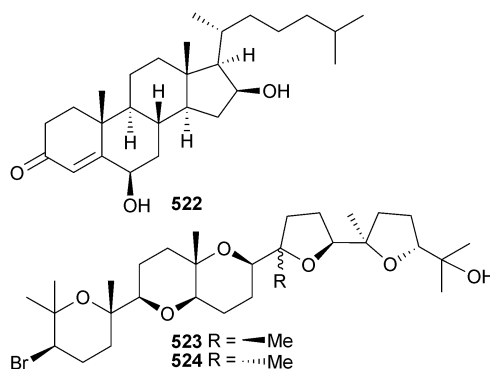
A Red Sea (Jeddah, KSA) collection of *L. obtusa* yielded three new laurene sesquiterpenes **509**–**511** all of which had strong antibacterial activity, while **510** also had significant antifungal and antitumour activities.⁵²⁵ Four new bisabolanes okamurene A–D **512**–**515** and the new chamigrane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



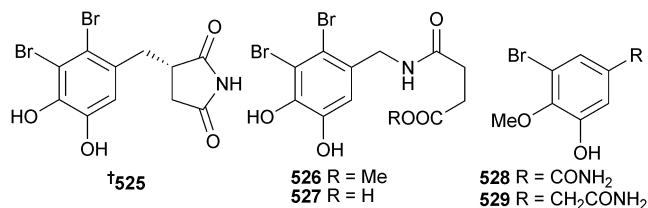
The structure proposed for the sesquiterpene aldingenin B (*L. aldingensis*)⁵²⁶ has been synthesised, but discrepancies between the spectroscopic data of the synthetic and natural material suggest that the claimed structure is incorrect.⁵²⁷ From a Fijian (Mango Bay Resort, Viti Levu) collection of *Callophycus* 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



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



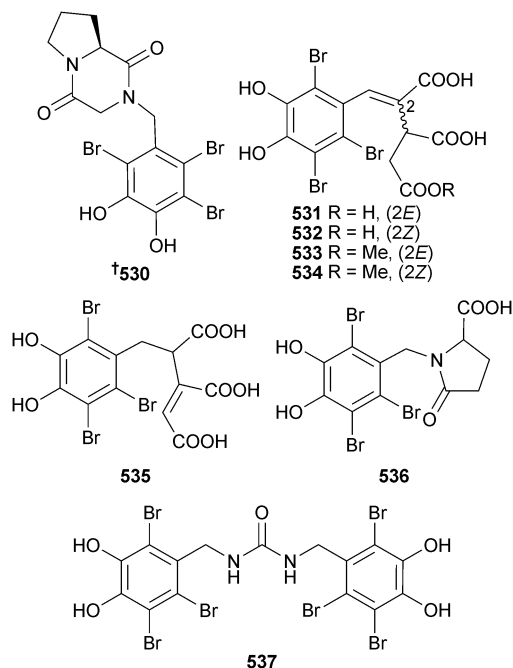
Bromophenols are frequently reported from red algae, and an additional 13 were described in 2012. The potentially radical scavenging bromophenols **525**–**529** were obtained from *Rhodomela confervoides* (Dalian, Liaoning Province, China).⁵³²



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



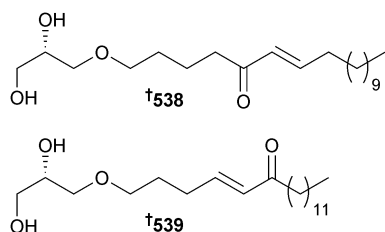
A–G 531–537. Symphyocladin G showed modest antifungal activity.⁵³⁴



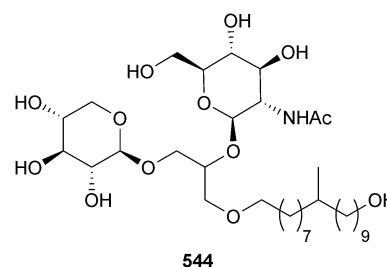
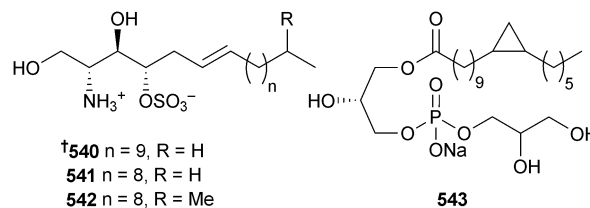
Several papers described new biological activities for red algal metabolites, including anti-HSV-1 and HSV-2 glycolipids from *Osmundaria obtusiloba*,⁵³⁵ antitumour effects of elatol from *Laurencia microcladia*,⁵³⁶ antinociceptive and anti-inflammatory extracts from *Bryothamnion triquetrum*⁵³⁷ and 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

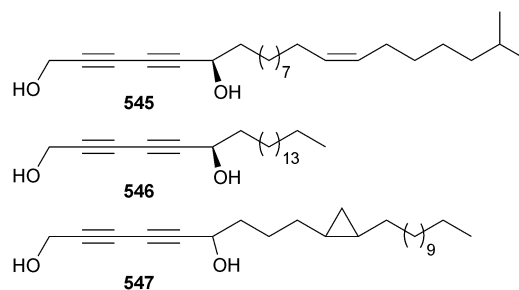
The number of new compounds reported from marine sponges in 2012 (355) has increased by approximately 20% compared with 2011.¹ Pachastrissamine (*Pachastrissa* sp.),⁵⁴⁰ also known as jaspine B, requires dual inhibition of both Forkhead box 03 (Fox03) and cyclin-dependent kinase 2 (Cdk2) to prevent melanoma 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

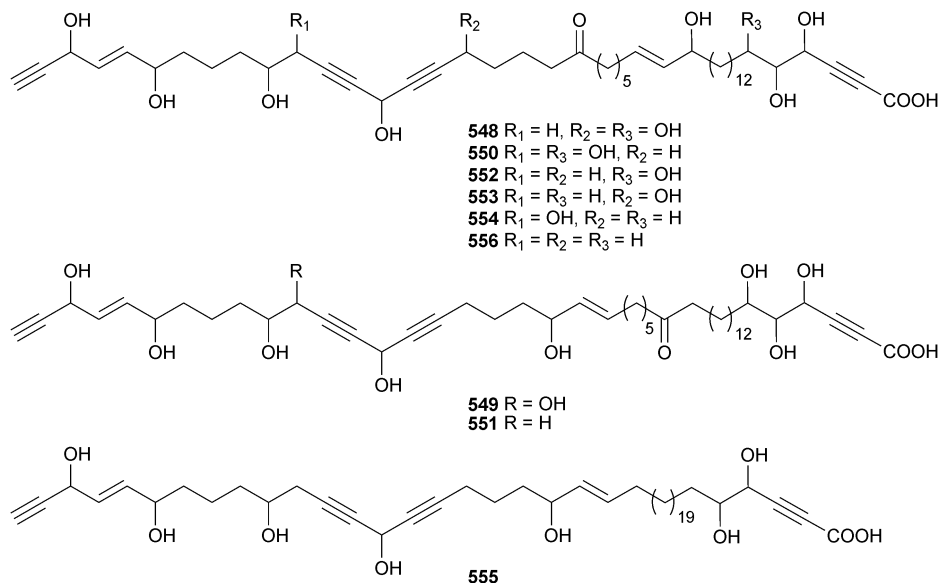


Myrmekioside E 544 is an acetylated glycolipid from *Myrmekioderma dendyi* (Epi Is., Vanuatu Archipelago) with moderate potency against lung tumour cells.⁵⁴⁶ A Micronesian *Xestospongia* cave sponge was the source of three polyacetylenes 545–547 with low μM activity against *Pseudomonas aeruginosa* (*P. aeruginosa*),⁵⁴⁷ while an extract of *Haliclona fulva* (Procida Is., Gulf of Naples, Italy) contained the nine acetylenes fulvyne A–I 548–556.⁵⁴⁸



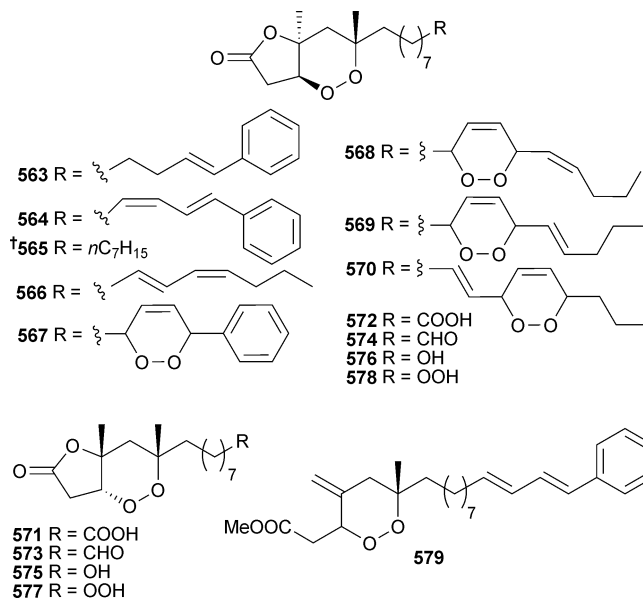
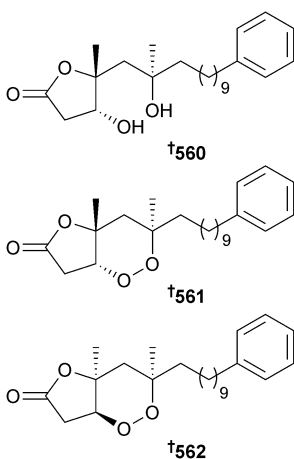
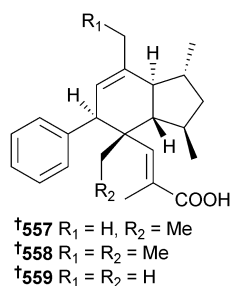
The structures of plakotenin 557 (*Plakortis* sp.),⁵⁴⁹ homoplakotenin 558 and norplakotenin 559 (*Plakortis lita*)⁵⁵⁰ have been revised following total synthesis and intensive spectroscopic characterisation.^{551,552} Two comprehensive synthetic, chemical and spectroscopic investigations of various plakortolide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





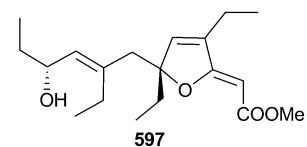
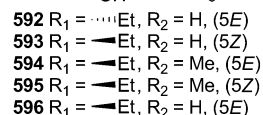
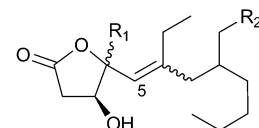
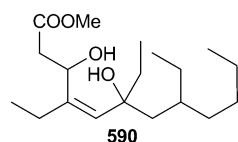
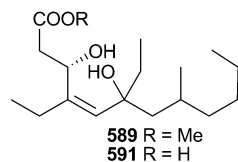
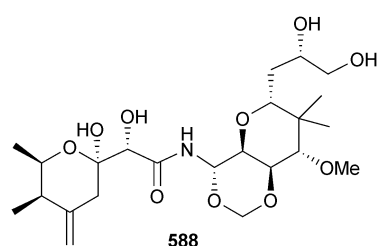
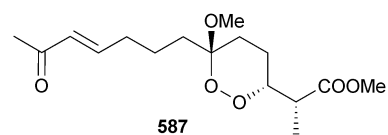
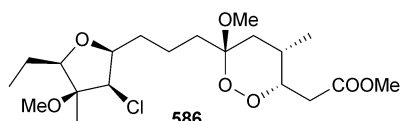
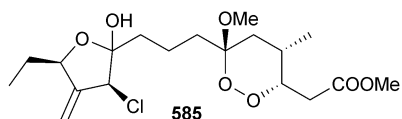
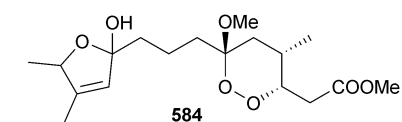
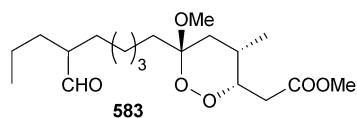
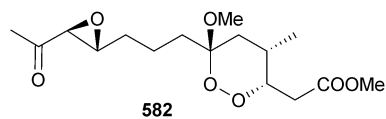
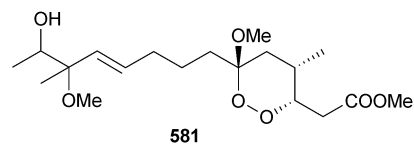
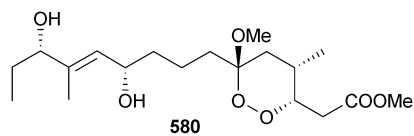
the originally reported plakortolides E (*Plakortis* sp.)⁵⁵³ and I (*Plakortis simplex*)⁵⁵⁴ are actually *seco*-plakortolide E **560** and plakortolide E **561**, respectively, and that a related but previously unnamed variant from *Plakinastrella* sp.⁵⁵⁵ is plakortolide I **562**.^{556,557} **Warning:** 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

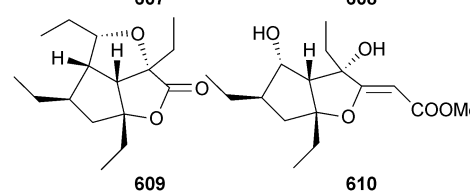
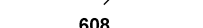
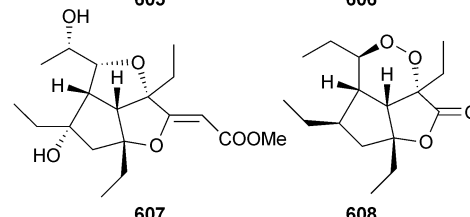
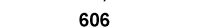
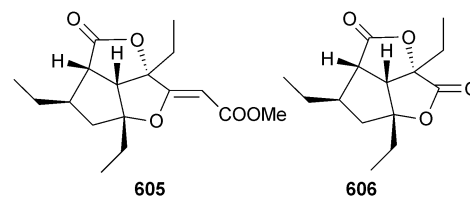
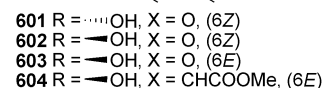
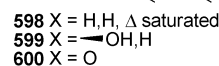
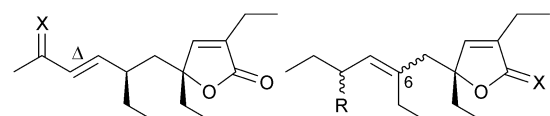


Manadoperoxides E–K **580–586** and peroxyplakoric ester C **587** are potent antiprotozoals (*Trypanosoma brucei rhodesiense*) from *Plakortis lita* (Bunaken, Sulawesi, Indonesia).⁵⁵⁹ Mycalamide E **588** and congeners (*Mycale hentscheli*, Pelorus Sound, New Zealand) are potent protein synthesis inhibitors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





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

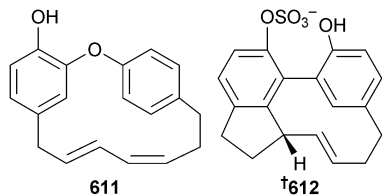


Investigations of *Plakortis simplex* (Yongxing Is., South China Sea) revealed the moderately antifungal woodylides A–C **589**–**591**,⁵⁶¹ and the less active simplexolides A–E **592**–**596** and plakorfuran A **597**.⁵⁶²

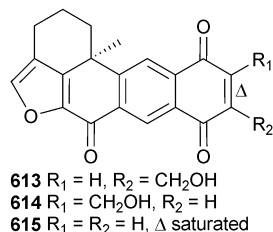
A Fijian *Plakinastrella mamillaris* contained plakilactones A–F **598**–**603** and gracilioether D **604**. Plakilactone C has potential

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

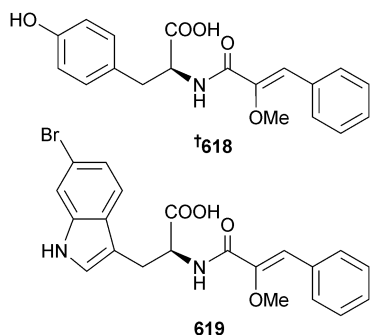
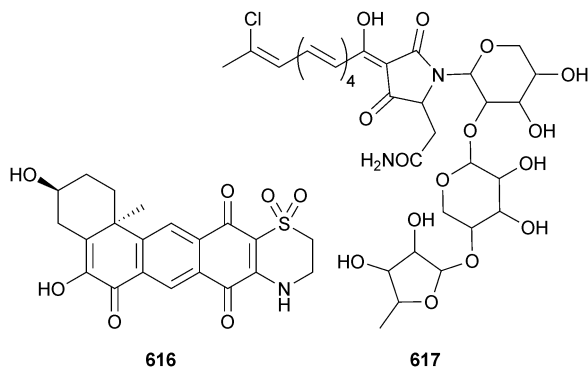




A Malaysian *Petrosia alfiani* yielded 14-hydroxymethylxestoquinone **613**, 15-hydroxymethylxestoquinone **614** and 14,15-dihydroxymethylxestoquinone **615**, all of which activated the hypoxia-inducible factor-1 (HIF-1). Moreover, **613** enhanced respiration and decreased mitochondrial membrane potential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

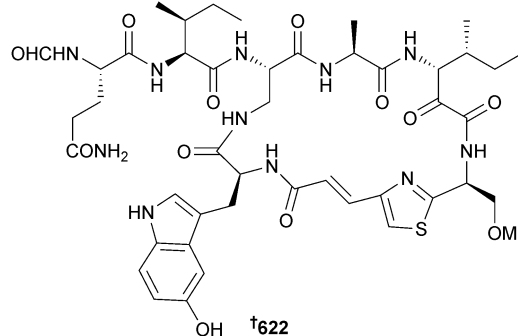
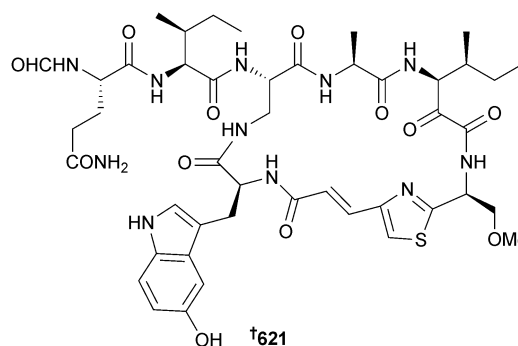
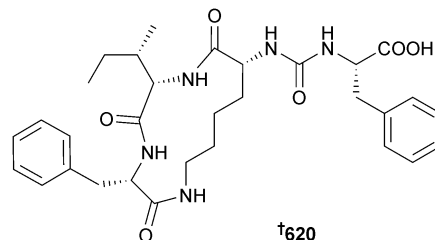


Xestosaprol N **616** has been reported from a *Xestospongia* sp. (Weno Is., Chuuk State, Federated States of Micronesia),⁵⁶⁹ while the antifungal aurantoside K **617** was isolated from a species of *Melophlus* (Cicia, Lau group of Fiji).⁵⁷⁰ Ietrochamides A **618** and B **619** (*Ietrochota* sp., Curacao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

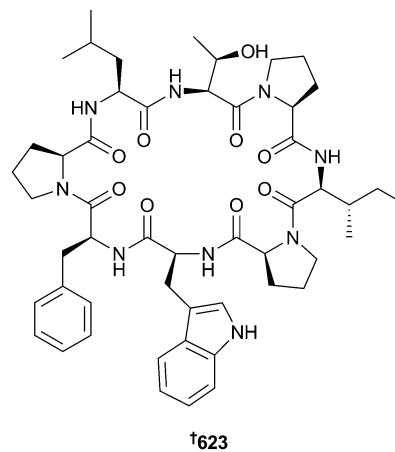


The total synthesis of (–)-irciniastatin B (*Ircinia ramosa*)⁵⁷² has been achieved.⁵⁷³ The accepted structure of cyclocinamide A (*Psammocinia* sp.), originally reported in 1997 and revised in 2008,^{574,575} has been disproven by synthesis leaving the structure of the natural product as a mystery.⁵⁷⁶ 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**.

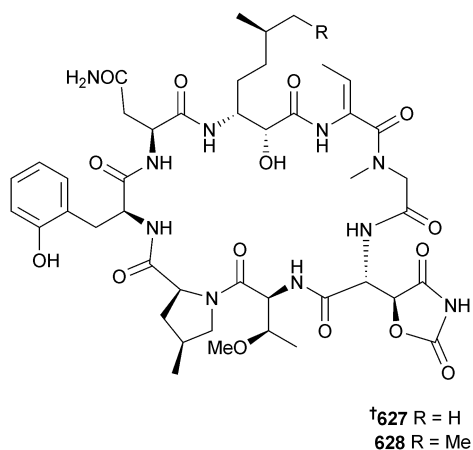
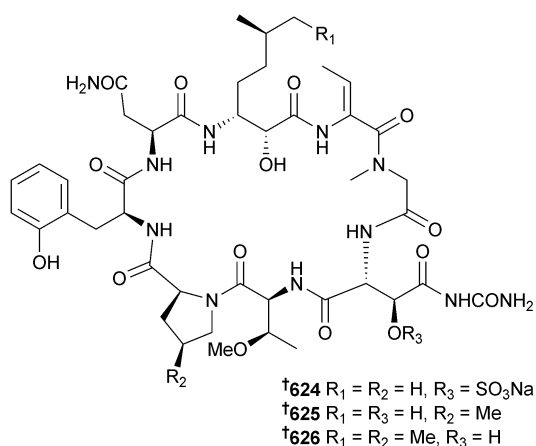


The presence of metagenomic DNA from the filamentous bacterium *Candidatus Enthothionella* sp. that produces similar

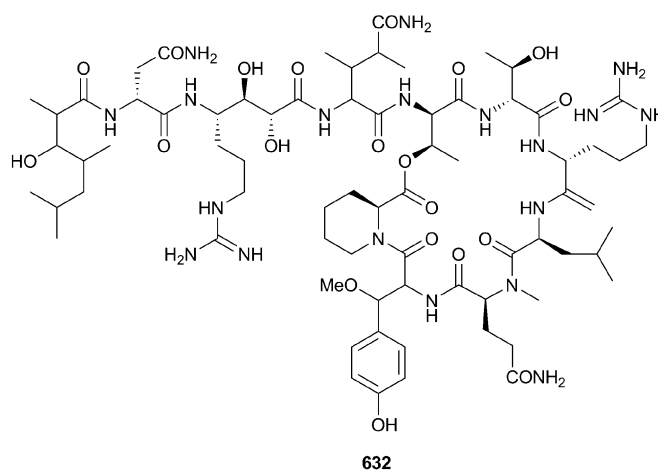
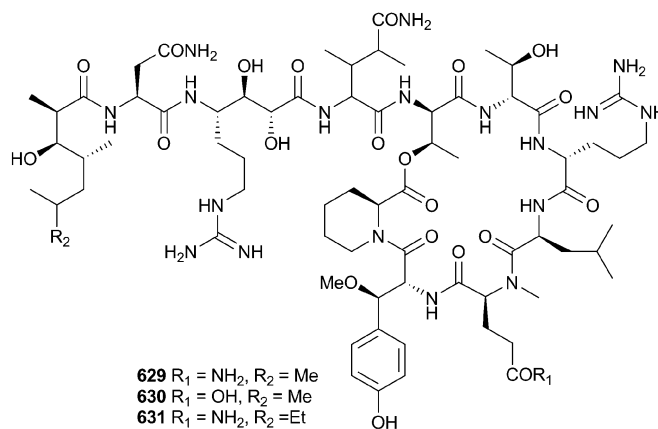


cyclopeptides in other sponges suggested that the calyxamides are produced by a symbiont.⁵⁷⁸ The proline-rich octapeptide stylissamide X **623** was reported from *Stylissa* sp. (Biak, Indonesia), and inhibited HeLa cell migration at sub-inhibitory concentrations.⁵⁷⁹

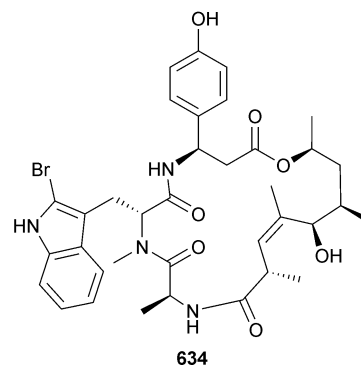
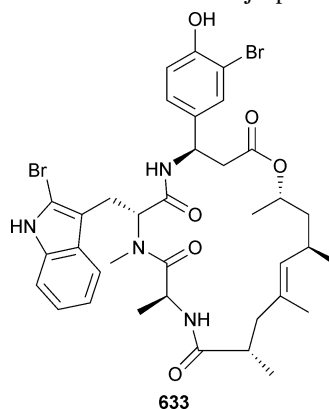
Droplet counter-current chromatography (DCCC) was used to isolate perthamides G–K **624–628** from a *Theonella swinhoei* (Solomon (Malaita) Is.). All of the perthamides isolated had some anti-inflammatory activity, suggesting structure activity relationships (SAR) were linked to the γ -methylproline,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

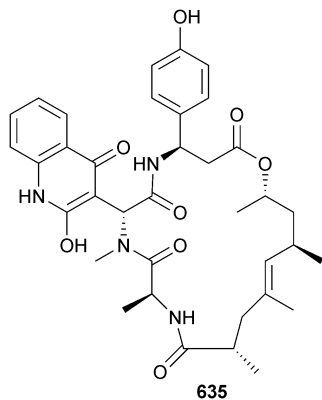


The sponge *Neamphius huxleyi* (Milln Reef, Cape Grafton, Queensland) yielded neamphamides B–D **629–631** as potent and non-selective cytotoxins.⁵⁸¹ An earlier report had used the name neamphamide B to describe **632** from *Neamphius* sp. (Okinawa, Japan), which inhibited the growth of *Mycobacterium 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.



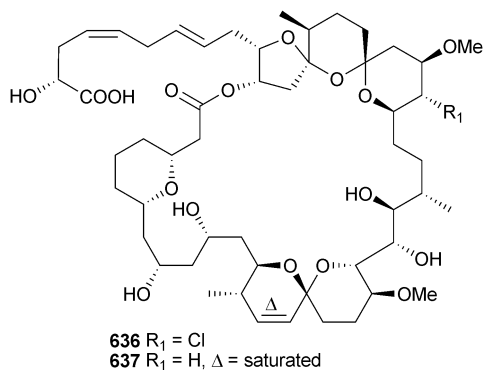
The sponge *Pipestela candelabra* (Guadalcanal, Solomon Is.) contained the mixed NRPS-PKS pipestelides A–C **633–635**, which are related to the well known jaspamides.⁵⁸³



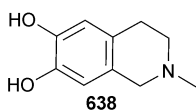


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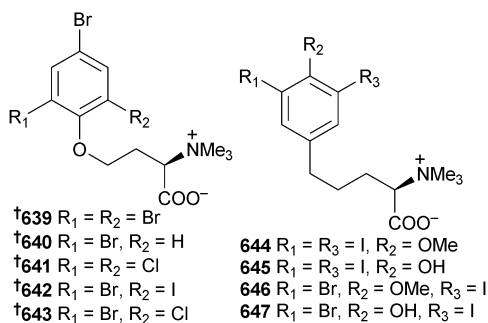
The absolute configuration of both leiodermatolide (*Leiodermatium* sp.)⁵⁸⁴ and callipeltoside B (*Callipelta* sp.)⁵⁸⁵ were confirmed as originally drawn by total synthesis,^{586,587} while salarin C (*Fascaplysinopsis* sp.)⁵⁸⁸ was a potent activator of apoptosis.⁵⁸⁹ Spirastrellolides A **636** and B **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



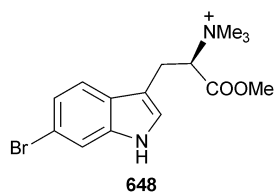
636 R₁ = Cl
637 R₁ = H, Δ = saturated



638



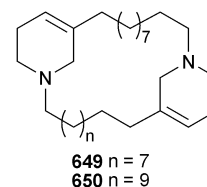
†**639** R₁ = R₂ = Br
 †**640** R₁ = Br, R₂ = H
 †**641** R₁ = R₂ = Cl
 †**642** R₁ = Br, R₂ = I
 †**643** R₁ = Br, R₂ = Cl
644 R₁ = R₃ = I, R₂ = OMe
645 R₁ = R₃ = I, R₂ = OH
646 R₁ = Br, R₂ = OMe, R₃ = I
647 R₁ = Br, R₂ = OH, R₃ = I



648

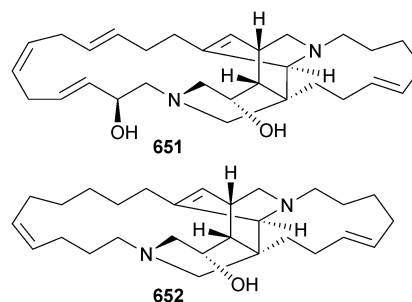
The first total synthesis of halichondrin B (*Halichondria okadae*)⁵⁹⁴ has been achieved.⁵⁹⁵ N-Methylnorsalsolinol **638** is a radical scavenging antioxidant from *Xestospongia* sp. (Bougainville Reef, Queensland),⁵⁹⁶ while purpuroines A–J **639**–**648** are halogenated zwitterionic amino acid derivatives 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-hydroxyngamine A **651** and dihydroingenamine D **652** with activities in the low ng mL⁻¹ range against various strains of *P. falciparum*.⁶⁰¹



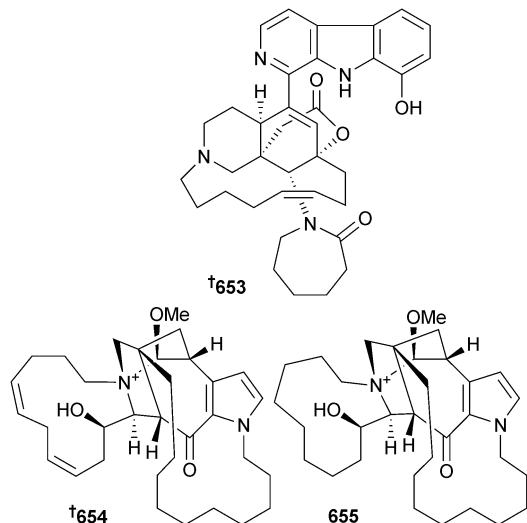
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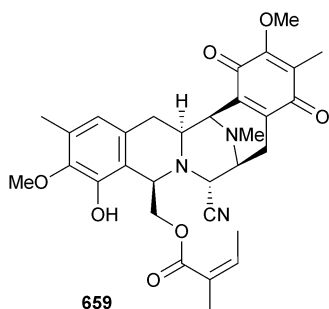
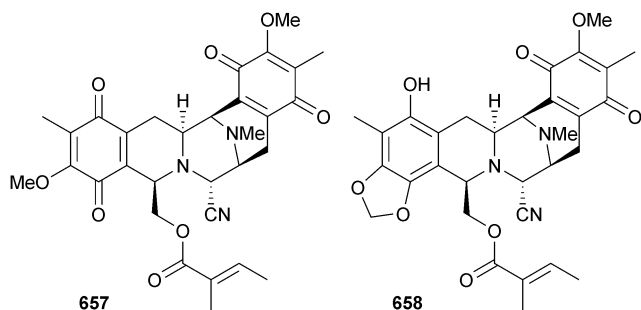
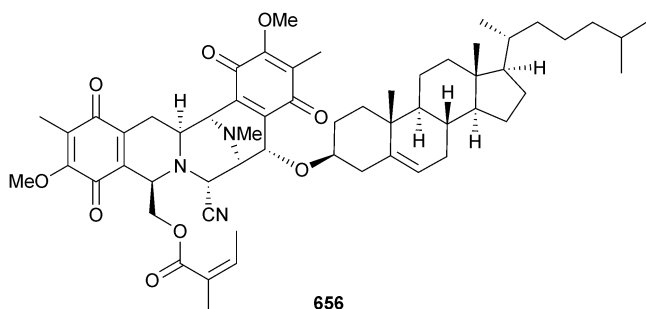
(–)-8,15-Diisocyno-11(20)-amphilectene (*Hymeniacidon amphilecta*)⁶⁰² and 7,15-diisocyno-11(20)-amphilectene⁶⁰³ (*Hymeniacidon* sp.) are potent inhibitors (nM range) of thromboxane B₂ suggesting potential as neurological anti-inflammatory agents,⁶⁰⁴ while bengamides A and B, originally isolated from 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 monogial cells.⁶⁰⁸

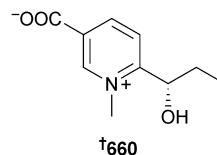




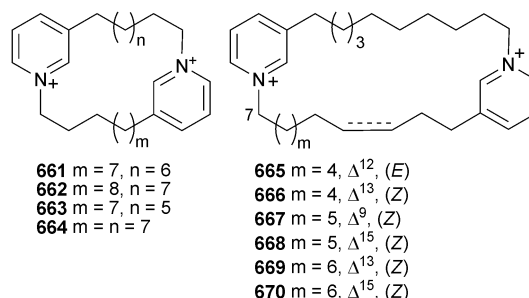
Renieramycin V **656** (*Xestospongia* sp.) is the first compound of the class to be conjugated to a sterol,⁶⁰⁹ while pre-treatment of another *Xestospongia* sp. (Puerto Galera, Philippines) with KCN unsurprisingly yielded the cyano-derivatives renieramycin W–Y **657–659**.⁶¹⁰



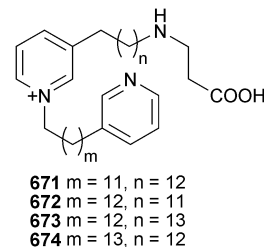
The sponge *Axinella polypoides* (Calvi, Corsica, France) was the source of a new betaine **660**.⁶¹¹ The asymmetric total synthesis of nakinadine B (*Amphimedon* sp.)⁶¹² has been accomplished, although the original report did not contain an optical rotation so the absolute configuration of the natural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



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



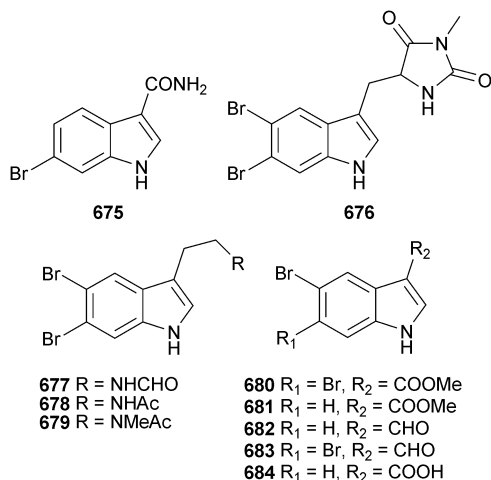
An Arctic *Haliclona viscosa* (Blomstrandhalvøya, Svalbard, Norway) yielded viscosalines B₁ **671**, B₂, **672**, E₁ **673** and E₂ **674**, with the structures established from NMR and comprehensive mass spectrometric fragmentation studies using different ionisation sources. The structures were confirmed by total synthesis.⁶¹⁷



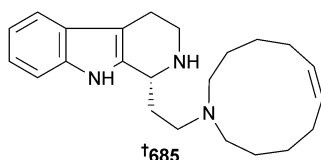
The proposed use of polymeric 3-alkylpyridinium alkaloids (*Reniera sarai*) as therapeutic adjuvants may be unwise due to their cardiotoxicity.⁶¹⁸ *Mycale fibrexilis* (Hainan Is., China) was



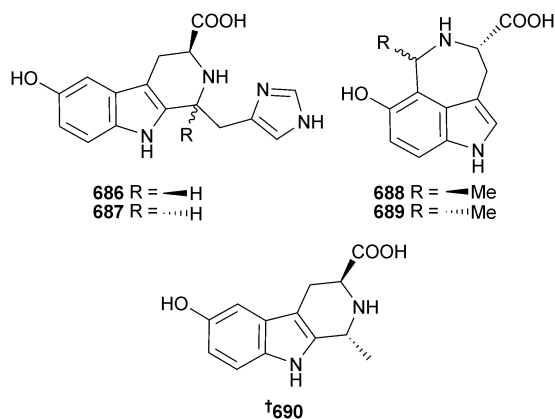
the source of the 6-bromo-1*H*-indole-3-carboxamide **675**,⁶¹⁹ while a Thai *Smenospongia* sponge (PP Is., Krabi Province) provided a series of brominated indole alkaloids **676–684**, isolated from a natural source for the first time.⁶²⁰



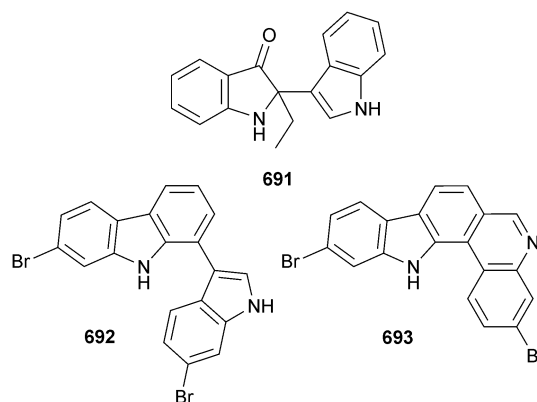
The synthesis of keramamine C **685** (*Amphimedon* sp.)⁶²¹ established the absolute configuration.⁶²²



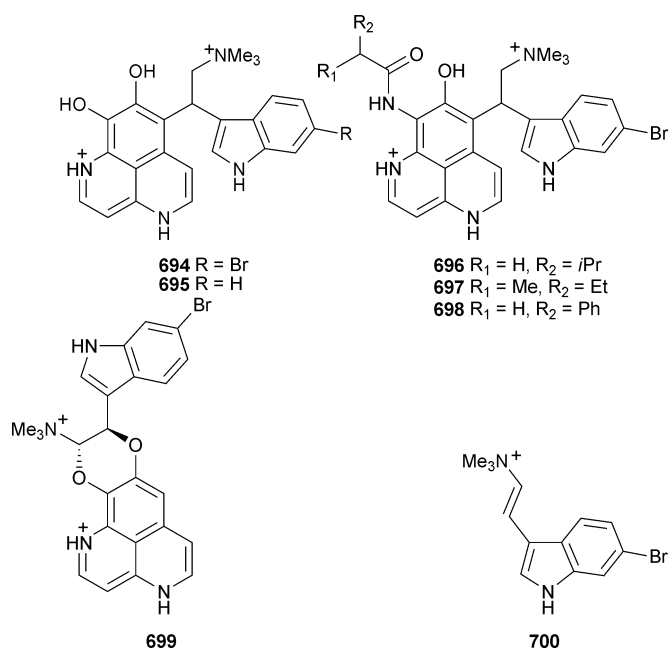
Hyrtioreticulins A–E **686–690** were reported from *Hyrtios reticulatus* (N. Sulawesi, Indonesia) with hyrtioreticulins A and B inhibiting the formation of the E1-ubiquitin-activating enzyme and having promise as anti-cancer proteasome modulators.⁶²³



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 -carboline **692** and **693** have been isolated from a species of *Penares* collected by dredging at 95 m in the South China Sea.⁶²⁵

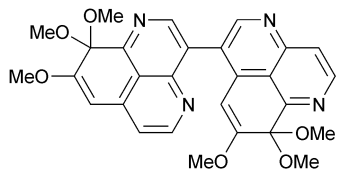


A *Suberites* sponge (Unten Port, Okinawa) was the source of nakijinamines A **694**, B **695**, F–I **696–699** and 6-bromoconicamin **700**. Nakijinamines A, B, F and I were isolated as racemates.⁶²⁶

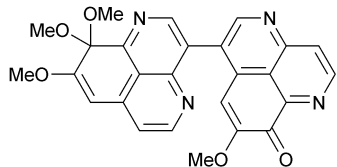


Suberitines A–D **701–704** were isolated from *Aaptos suberitoides* (Xisha Is., South China Sea), and are low micromolar inhibitors of P388 cells. They are thought to occur naturally *via* radical dimerisation.⁶²⁷

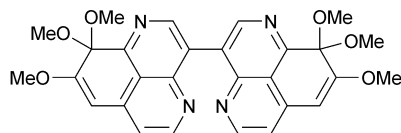




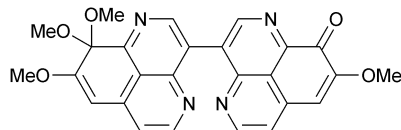
701



702

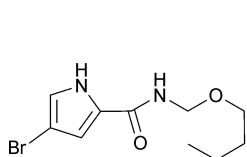


703

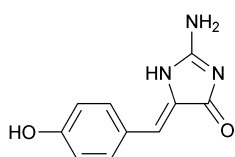


704

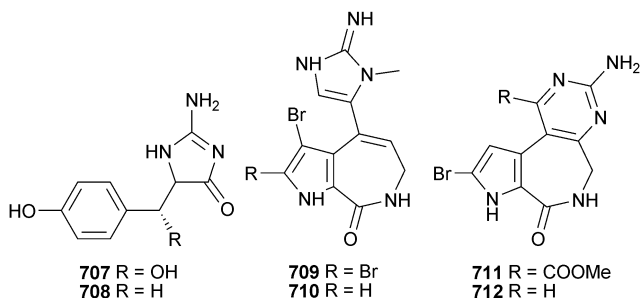
The bromopyrrole **705** was reported from *Agelas mauritiana* (Paracel (Xisha) Is.),⁶²⁸ while phorbatopsins A–C **706–708** are anti-oxidant aminoimidazolines from *Phorbas topsenti* (Marseille, France).⁶²⁹ Two new stevesines **709** and **710** and two debromatolonduines **711** and **712** have been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



705



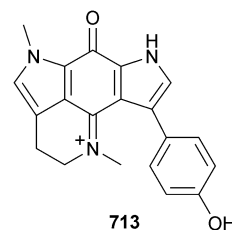
706



The original latonduines (*Stylissa carteri*)⁶³¹ are extremely potent correctors of $\Delta F508$ 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

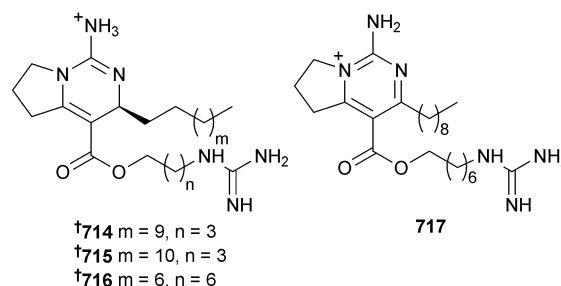
latonduines an important new lead for treatment of cystic fibrosis.⁶³² The bromopyrrole ageladine A (*Agelas nakamura*)⁶³³ has been used as an inherently fluorescent, pH-sensitive imaging molecule for transparent animals such as jellyfish.⁶³⁴

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

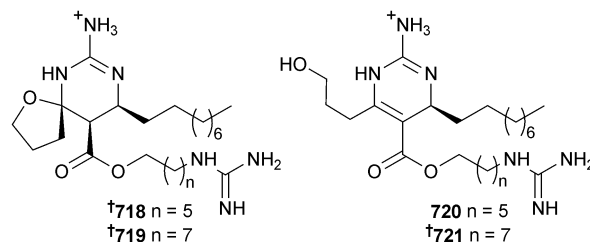


713

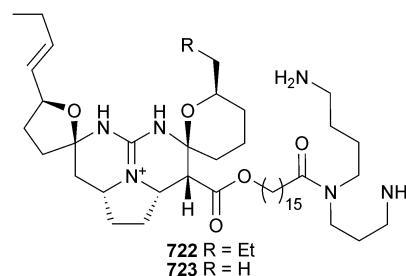
Eleven cytotoxic crambescins including the new congeners **714–721** have been reported from *Crambe crambe* (Villefranche-Sur-Mer, France).⁶³⁸



717



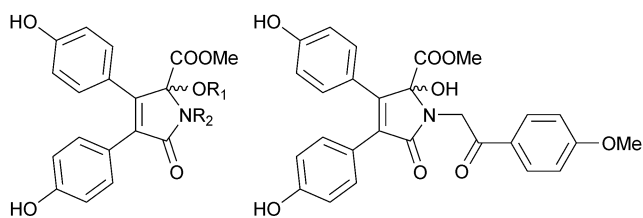
The structure of merobatzelladine B (*Monanchora* sp.)⁶³⁹ has been confirmed by synthesis,⁶⁴⁰ while the related monanchomycalins A **722** and B **723** were potent cytotoxins (low nM level) isolated from a dredged *Monanchora pulchra* (Sea of Okhotsk).⁶⁴¹



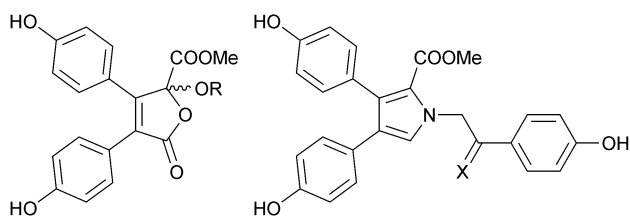
Members of the kealiinine class (*Leucetta chagosensis*)⁶⁴² have been synthesised independently by two different groups,



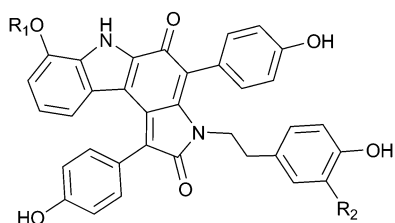
but with discrepancies in spectral data to those of the natural products noted. These discrepancies are likely due to different tautomeric forms.^{643,644} An *Ianthella* sp. collected by trawling (Bass Strait, Australia) yielded ianthellidones A–H 724–731 and lamellarins O1 732 and O2 733. The ianthellidones 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



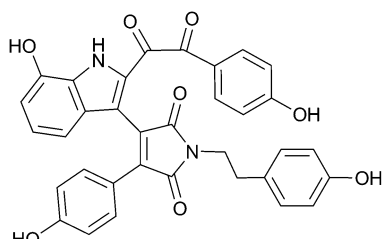
724 $R_1 = R_2 = H$
 725 $R_1 = Et, R_2 = H$
 726 $R_1 = H, R_2 = CH_2OMe$
 727 $R_1 = H, R_2 = CH_2OEt$
 728 $R_1 = H, R_2 = CH_2COOEt$



730 $R = H$
 731 $R = Me$
 732 $X = O$
 733 $X = H, OH$



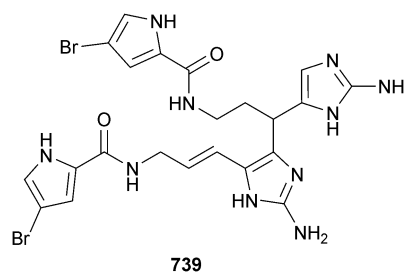
734 $R_1 = R_2 = H$
 735 $R_1 = Me, R_2 = H$
 736 $R_1 = H, R_2 = Br$
 737 $R_1 = H, R_2 = I$



738

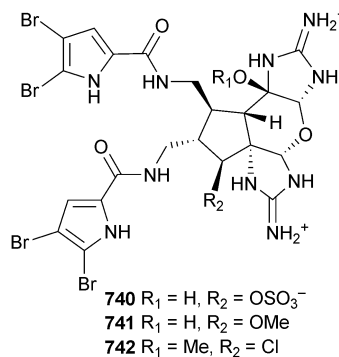
Didebromonagelamide A 739 was isolated from a Caribbean *Stylissa caribica* (Bahamas). Cell-free enzyme preparations from the same sponge and also *Agelas scep trin* were able to catalyse

the synthesis of benzoscep trin C (*Agelas* sp.)⁶⁴⁷ and nagelamide H (*Agelas* sp.)⁶⁴⁸ from oroidin (*Agelas oroides*).^{649,650}

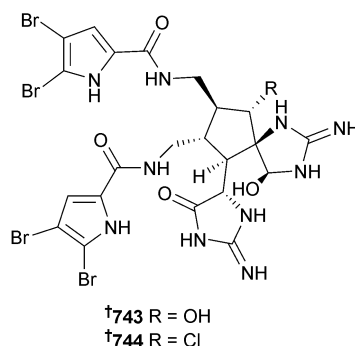


739

The “*meta*-biosynthetic” conversion of oroidin to the scep trin 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 “pre-axinellamine”, the key intermediate to all dimeric pyrrole-ami noimidazole alkaloids.⁶⁵⁵



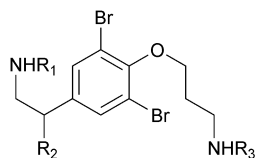
740 $R_1 = H, R_2 = OSO_3^-$
 741 $R_1 = H, R_2 = OMe$
 742 $R_1 = Me, R_2 = Cl$



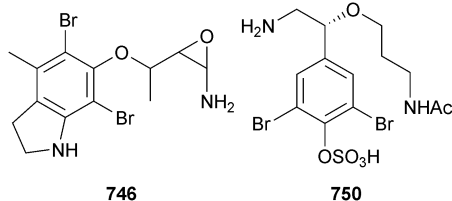
743 $R = OH$
 744 $R = Cl$

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





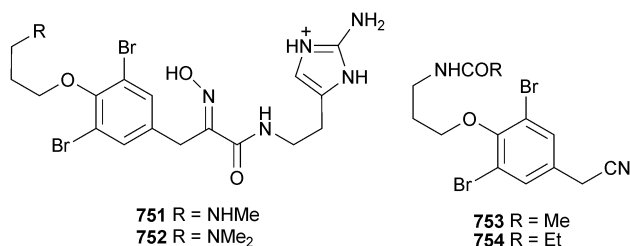
- 745 $R_1 = R_3 = \text{H}, R_2 = \text{OMe}$
 747 $R_1 = R_2 = \text{H}, R_3 = \text{CONH}_2$
 748 $R_1 = \text{CHO}, R_2 = \text{H}, R_3 = \text{COCONH}_2$
 749 $R_1 = \text{CHO}, R_2 = \text{H}, R_3 = \text{COOEt}$



746

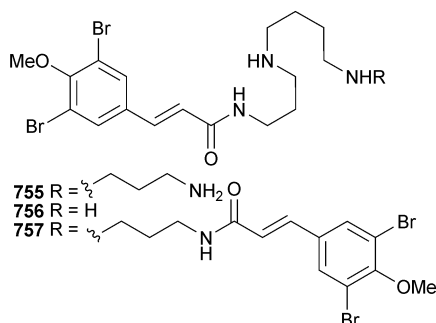
750

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 $R = \text{NHMe}$
 752 $R = \text{NMe}_2$

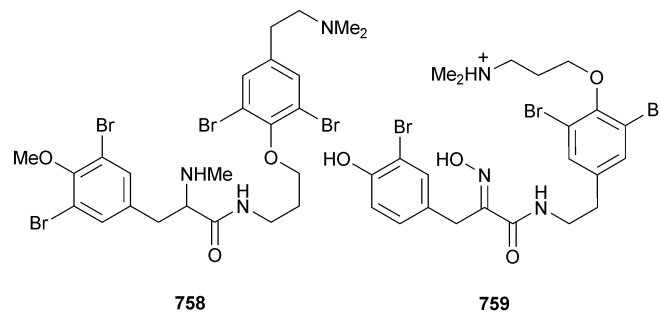
- 753 $R = \text{Me}$
 754 $R = \text{Et}$



- 755 $R = \text{-(CH}_2\text{)}_4\text{-NH}_2$
 756 $R = \text{H}$
 757 $R = \text{-(CH}_2\text{)}_4\text{-NH}$

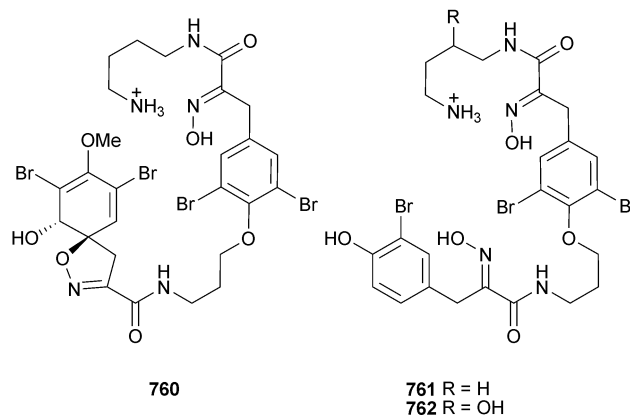
The syntheses of pseudoceramines A–D (*Pseudoceratina* sp.)⁶⁶³ have been achieved,⁶⁶⁴ as have the syntheses of psammaplin C and tokaradine A,^{665,666} both from *Psammaplysilla purpurea*.⁶⁶⁷ Aplysamine-2 (*Aplysina* sp.),⁶⁶⁸ aplyzanzine A (*Aplysina* sp.),⁶⁶⁹ anomoian A (*Anomoianthella popeae*),⁶⁷⁰ purpurcalidin 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}



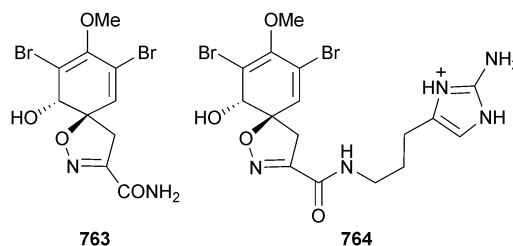
758

759



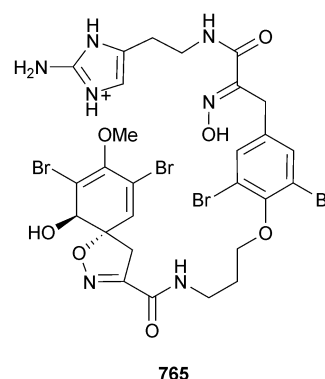
760

- 761 $R = \text{H}$
 762 $R = \text{OH}$



763

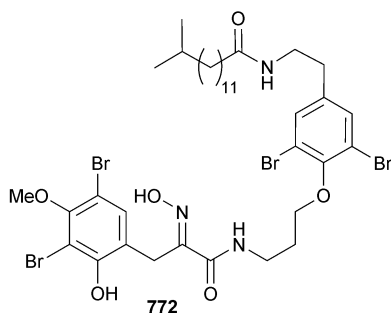
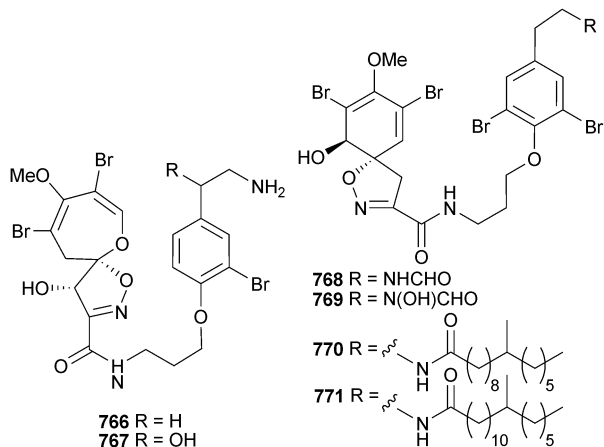
764



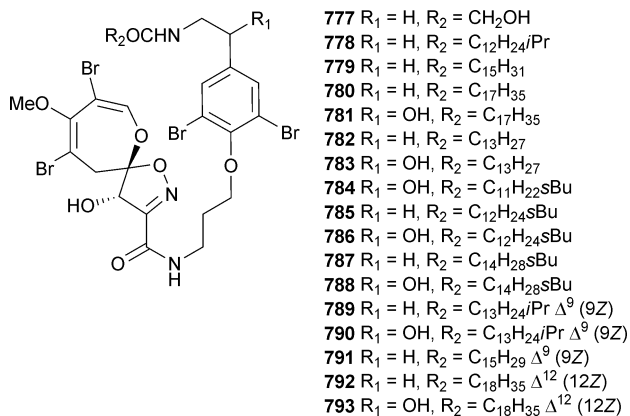
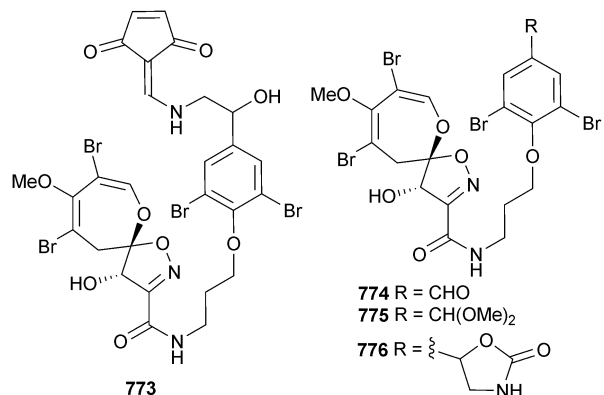
765

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 araplysellin congeners 768–772. Araplysellin N-20 formamide 768 and araplysellin N-20-hydroxyformamide 769 are moderate antimalarials.⁶⁷⁸

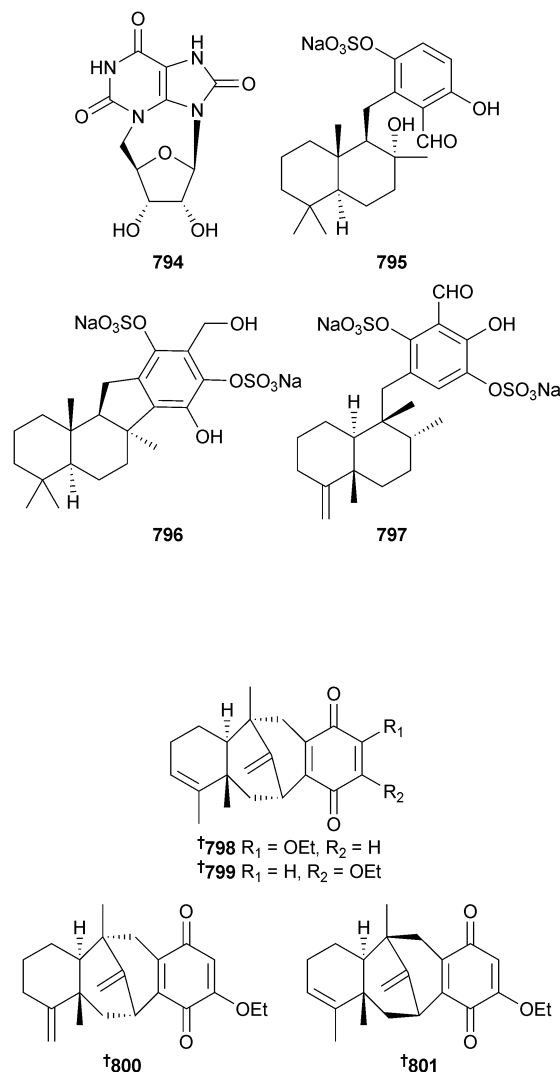




Twenty one psammaplysin variants 773–793 were isolated from *Aplysinella strongylata* (Tulamben Bay, Bali, Indonesia), although only 19-hydroxypsammaplysin E 773 showed any activity against *P. falciparum*.⁶⁷⁹

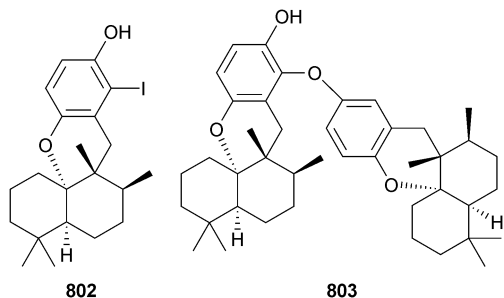


The synthesis of dioxepine bastadin-3 (*Ianthella reticulata*)⁶⁸⁰ has been achieved.⁶⁸¹ A new cyclonucleoside 794 has been reported from *Axinella polypoides* (Calvi, Corsica, France).⁶¹¹ Siphonodictyal sulfate 795 and akadisulfates A 796 and B 797 are antioxidant merosquiterpenoids from *Aka coralliphaga* (Quintana Roo, Mexico),⁶⁸² while dysideavarones A–D 798–801 are cytotoxic merosquiterpenes 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

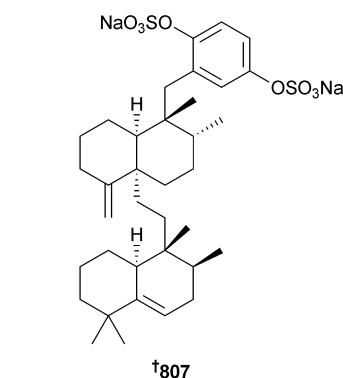
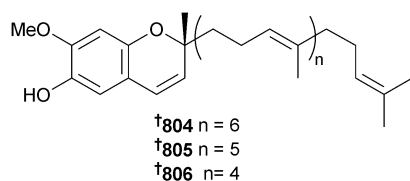


A *Smenospongia* sponge (PP Is., Thailand) was the source of the iodine-containing 6'-iodoauerol 802 and the dimeric 6'-auroxyaureol 803.⁶²⁰ The total synthesis of akaol A (*Aka* sp.)⁶⁸⁴ confirmed the absolute configuration as originally drawn.⁶⁸⁵

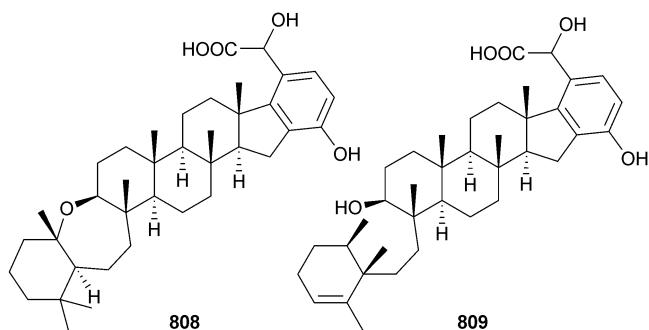




An *Ircinia* sponge (Weno Is., Chuuk State, Federated States of Micronesia) was the source of three linear polyphenyl hydroquinones **804–806**.⁶⁸⁶ The asymmetric synthesis of (+)-akaterpin **807** (*Callyspongia* sp.)⁶⁸⁷ established the absolute stereostructure as shown.⁶⁸⁸

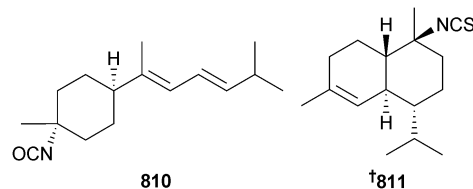


The merotriterpenoids halicloic acid A **808** and B **809** were isolated from a *Haliclona* sponge (Culasian Point, Leyte, Philippines). Both compounds inhibited indoleamine 2,3-dioxygenase, which is required for tumour immune-response escape, but were unstable in deuterated DMSO.⁶⁸⁹

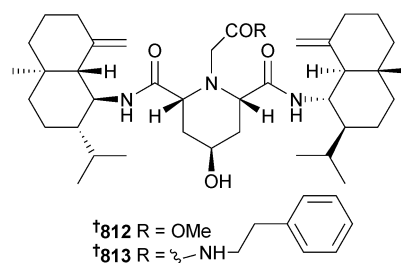


Rhaphoxya sp. (Blue Hole, Guam) provided the sesquiterpene theonellin isocyanate **810**.⁶⁷⁷ The synthesis of 10-isothiocyanato-4-cadinene (*Acanthella cavernosa*)⁶⁹⁰ established the absolute configuration, although the spectroscopic data differed

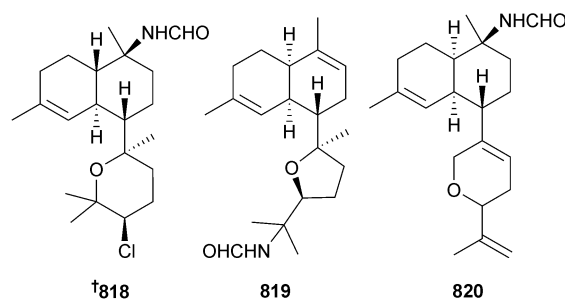
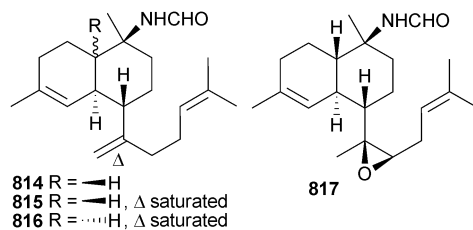
from those reported for a metabolite with the same assigned structure isolated from the nudibranch *Phyllidiella pustulosa*.⁶⁹¹ This study also synthesised the structure proposed for 10-*epi*-10-isothiocyanato-4-cadinene (*Stylissa* sp.).⁶⁹² However, discrepancies in the NMR data between the synthesised and reported compounds suggest that the natural product structure requires revision.⁶⁹³

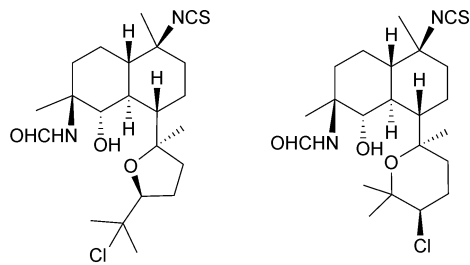


Halichonadins K **812** and L **813** are sesquiterpene dimers from a *Halichondria* sponge (Unten Port, Okinawa). The absolute configurations of the compounds were determined by X-ray crystallography and chemical interconversion.⁶⁹⁴ Racemic syntheses of luffarin X (*Luffariella geometrica*)⁶⁹⁵ and cacospongionolide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



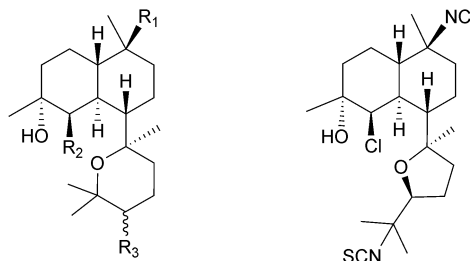
Cavernenes A–D **814–817**, kalihinenes E **818** and F **819** and kalihipyran C **820** are formamide diterpenoids from *Acanthella cavernosa* (Xisha Is., South China Sea).⁶⁹⁸ Also obtained from *A. cavernosa* (Xisha Is., South China Sea) were the antifouling compounds kalihinols M–T **821–828**.⁶⁹⁹



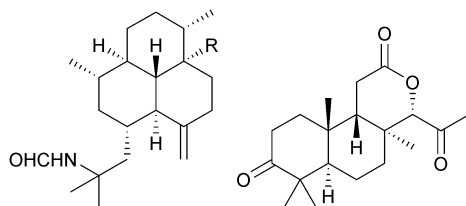


†821

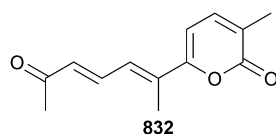
†822

†823 R₁ = NCS, R₂ = NC, R₃ = Cl†824 R₁ = NC, R₂ = NCS, R₃ = Cl†825 R₁ = NC, R₂ = NCS, R₃ = Cl†826 R₁ = R₂ = NCS, R₃ = Cl†827 R₁ = NCS, R₂ = NHCHO, R₃ = 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

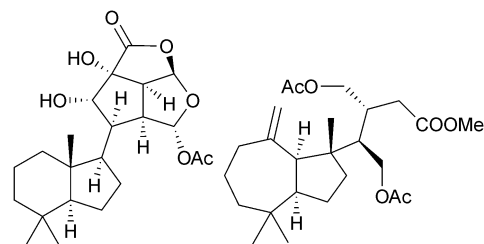
829 R = NCO
830 R = NCS

831



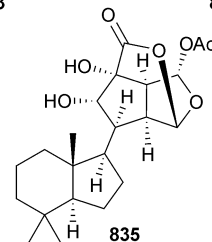
832

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.



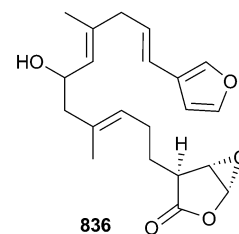
833

834

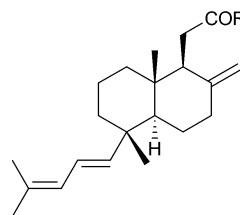


835

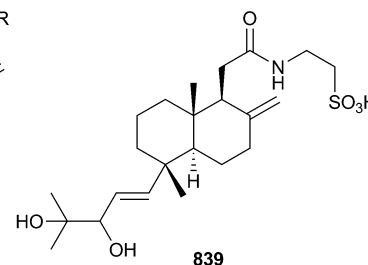
A linear C₂₁ furanoterpene **836** was reported from *Coscino-derma matthewsi* (Gneerings Reef, Mooloolaba, Australia),⁷¹⁰ while *Clathria compressa* (Panama City Beach, Florida) was the source of three bicyclic C₂₁ terpenoids **837–839**.⁷¹¹



836

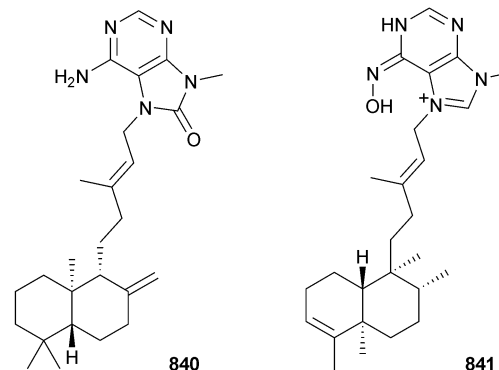


837 R = OH

838 R = NHCH₂CH₂SO₃H

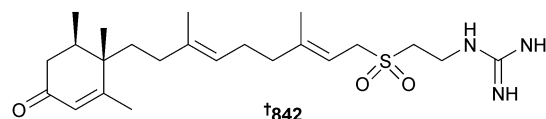
839

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

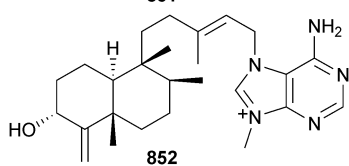
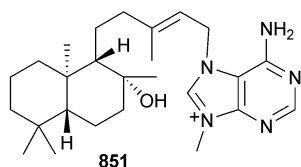
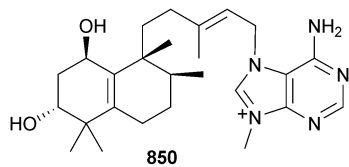
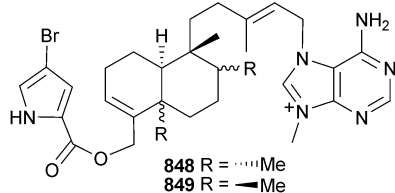
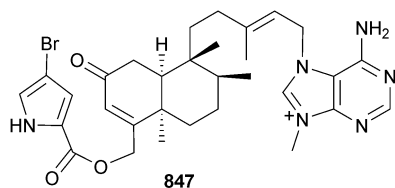
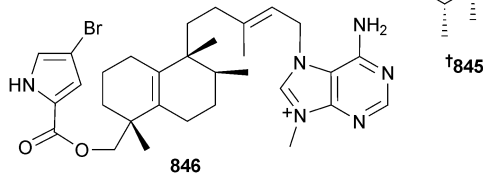
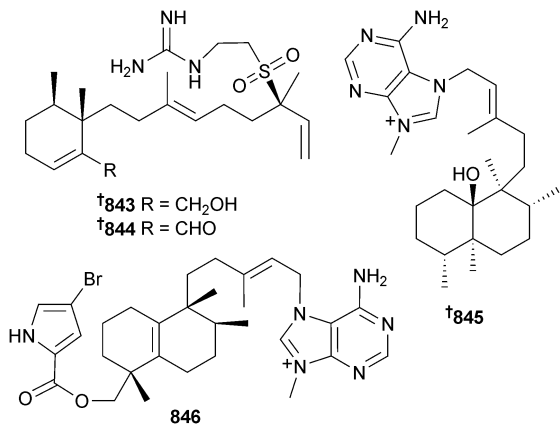
841



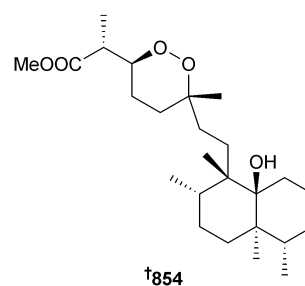
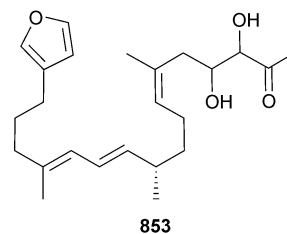
†842



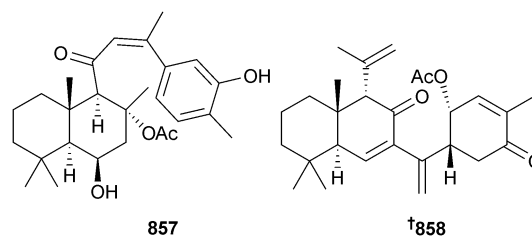
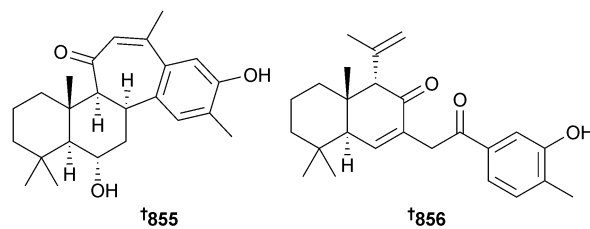
Agelasidines E **843** and F **844** are weakly antifungal compounds from *Agelas citrina* (Bahamas) that were isolated along with agelasine N **845**,⁷¹² while agelasines O–U **846–852** are broadly active diterpene alkaloids isolated from an Okinawan *Agelas* sp.⁷¹³



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 megaspinothabdosia* (Pula Baranglombo Is., Indonesia).⁷¹⁵ The total syntheses of (–)-alotaketol A (*Hamigera* sp.)⁷¹⁶ by two independent groups have confirmed the absolute configuration.^{717,718}

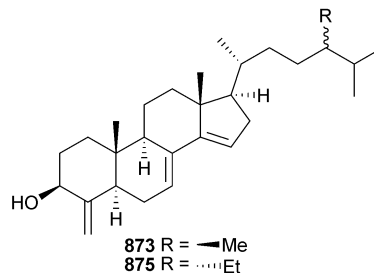
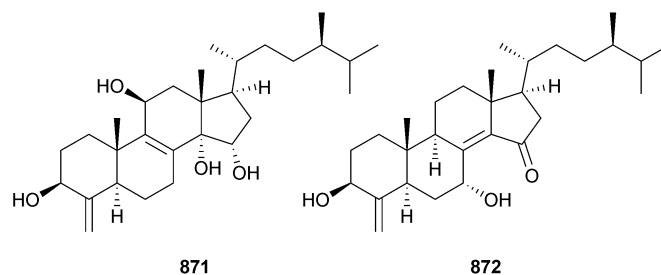
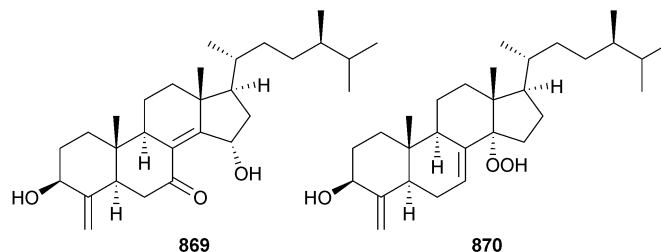
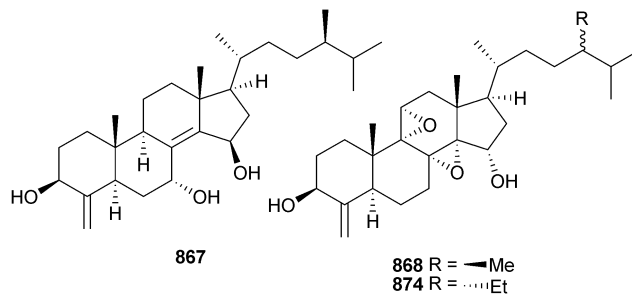
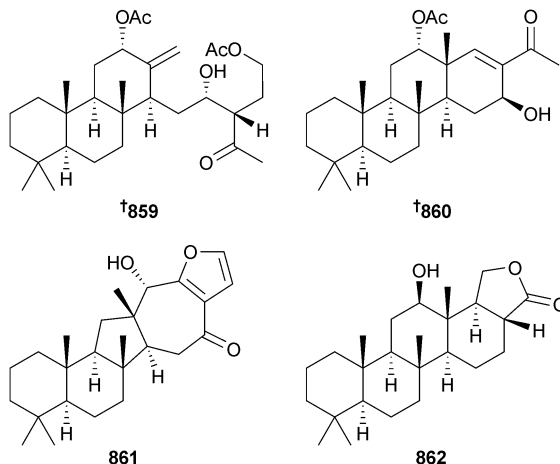


Four sesterterpenoids, phorone A **855**, isophorbasone A **856**, ansellone B **857** and phorbasone A acetate **858**, were isolated from a S. Korean *Phorbas* sp. Compounds **857** and **858**, described in the paper's supporting information, were low μM inhibitors of NO production in LPS-stimulated 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

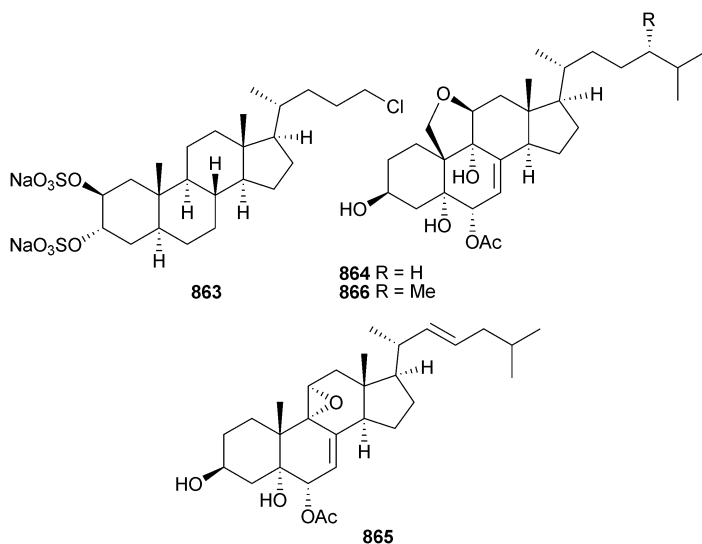




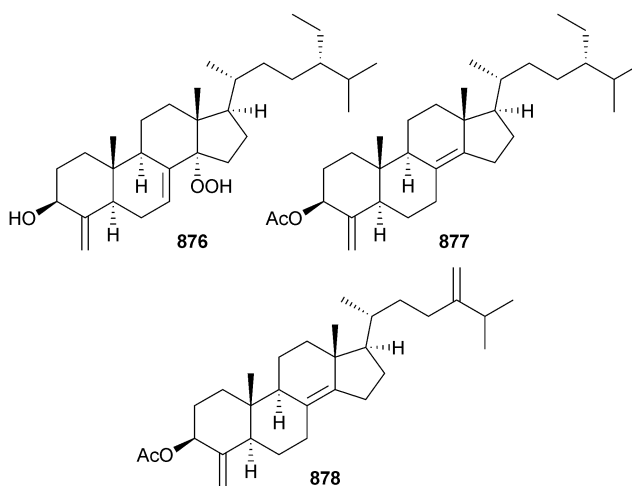
Hippospongia sponge (Taitung, Taiwan) was the source of hippospongides A **861** and B **862**.⁷²¹

The archetypical anti-inflammatory scalarane sesterterpenoid scalaradiol (*Cacospongia mollior*)⁷²² acted as a non-covalent binder in the active site of phospholipase A₂ and chelates Ca²⁺ 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



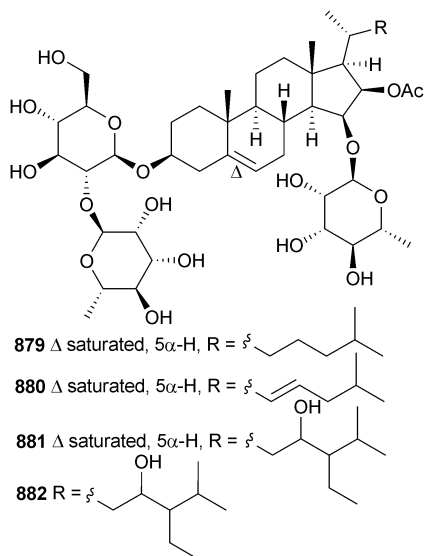
T. swinhoei (Pingtung, Taiwan) was the source of theonellasterol K **876**, acetyltheonellasterol **877** and acetyldehydroconicasterol **878**, with theonellasterol K being moderately active against a panel of cancer cell lines.⁷³¹



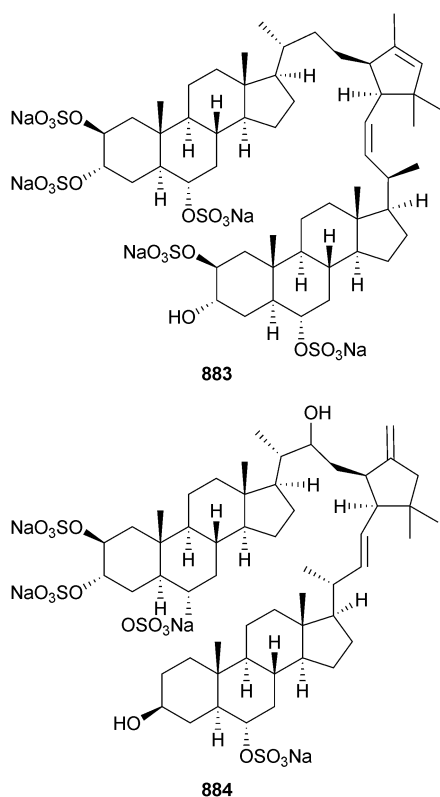
Theonella swinhoei from various locations in the Solomon Islands (Malaita and Vangunu Is.) have yielded conicasterols E **867**,⁷²⁸ F **868**,⁷²⁹ and G–K **869–873**,⁷³⁰ along with theonellasterol I **874**,⁷²⁹ and J **875**.⁷³⁰ All are dual ligands of the pregnane X (PXR) and farnesol X receptors (FXR)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



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

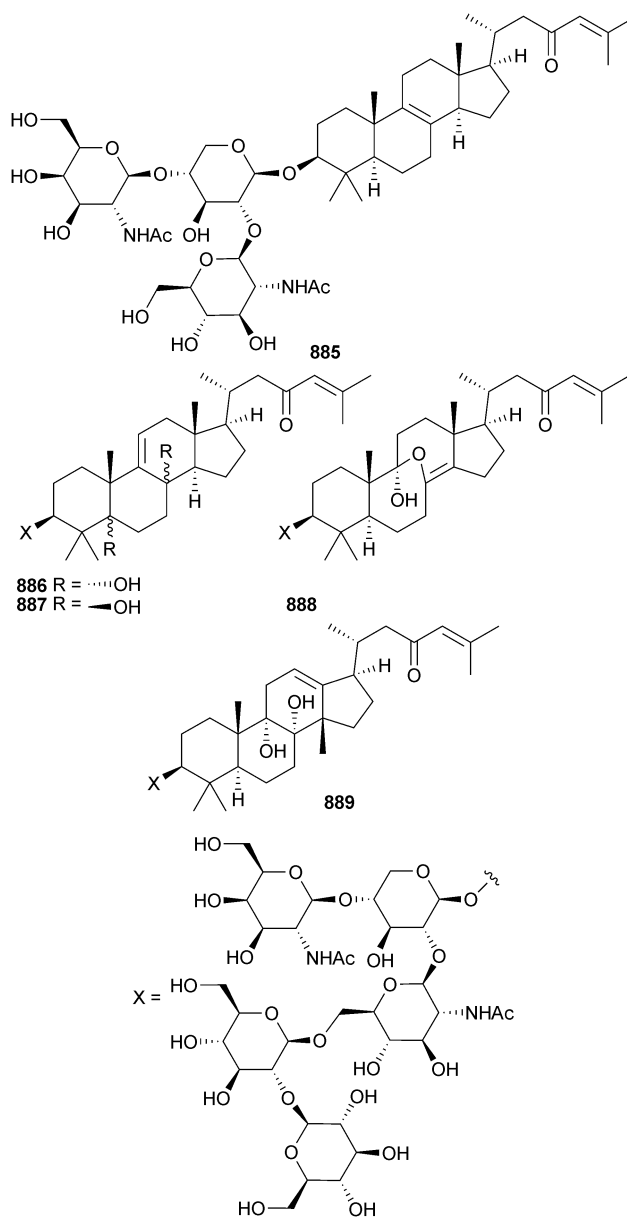


The sponge *Lissodendryx fibrosa* (North Sulawesi, Indonesia) was the source of manadosterols A **883** and B **884**, dimeric sterols that are potent inhibitors of the ubiquitin



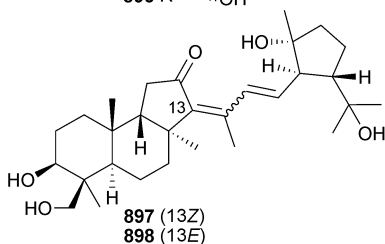
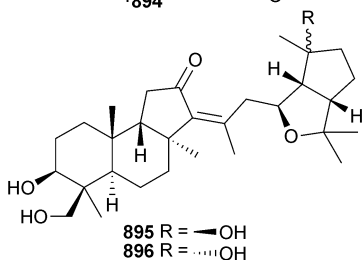
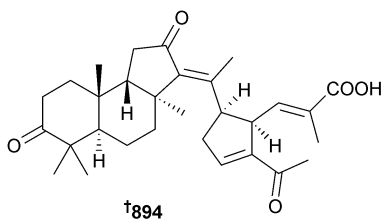
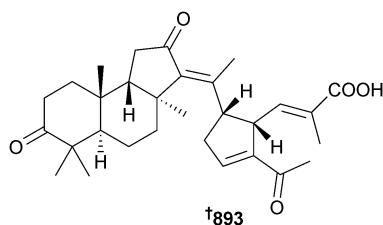
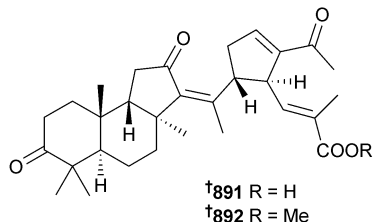
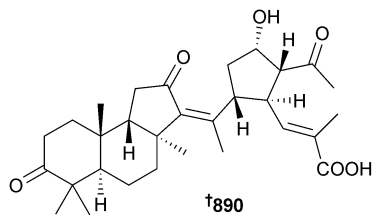
Ubq13-Uev1a complex and therefore have potential as anti-cancer agents.⁷³³

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

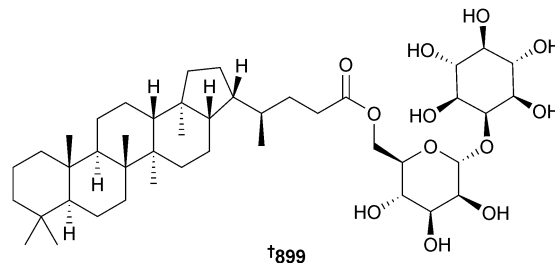


The isomalabaricane triterpenoids globostelletin J–R **890–898** were isolated from *Rhabdastrella globostellata* (Hainan Is., South China Sea), although in the paper there is no mention of the congener globostelletin S referred to in the title.⁷³⁷



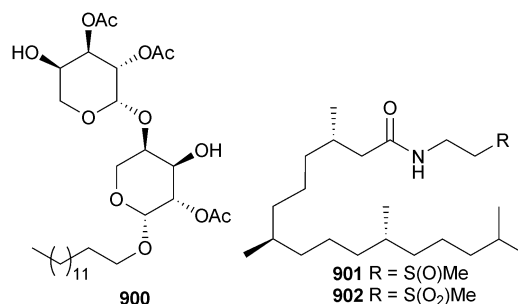


Plakortis lita (Manado, Indonesia) was the source of the hopanoid glycoside plakohopanoid **899**, although the terpenoid and carbohydrate components are reminiscent of bacterial secondary metabolites and it is likely that **899** is of symbiotic origin.⁷³⁸

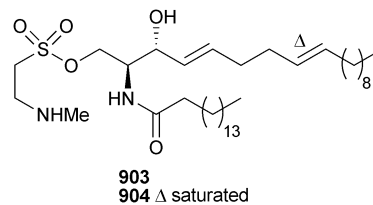


8 Cnidarians

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-arabino-pyranosyl 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.



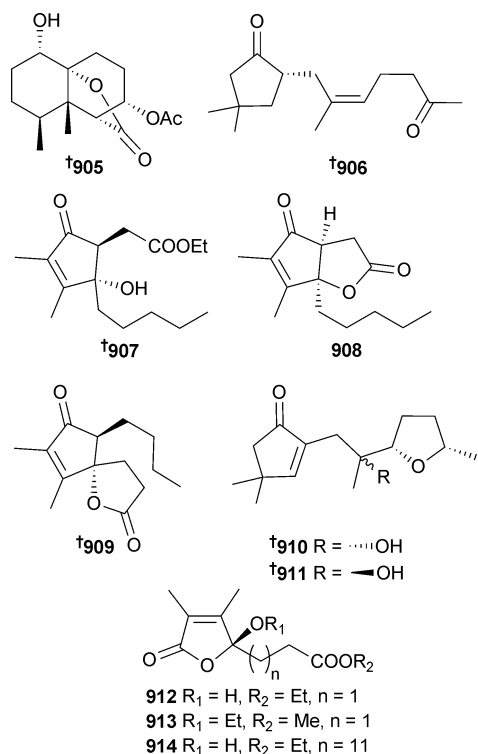
Brazilian collections (Paracuru Beach, near Fortaleza) of the zoanthids *Palythoa caribaeorum* and *Protopalythoa variabilis* yielded the sulfonlated ceramides palyosulfonoceramides A **903** and B **904**.⁷⁴¹ The structure elucidation of palyosulfonoceramides A and B was aided by comparison with two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



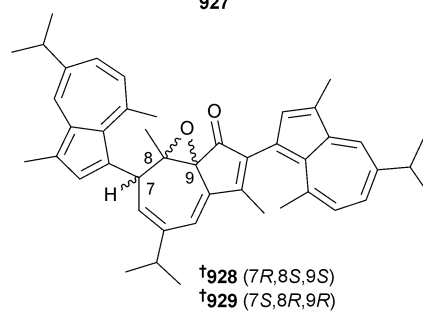
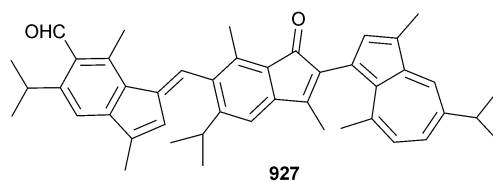
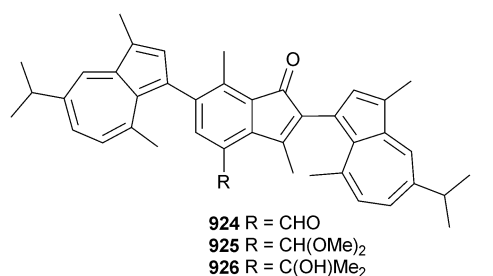
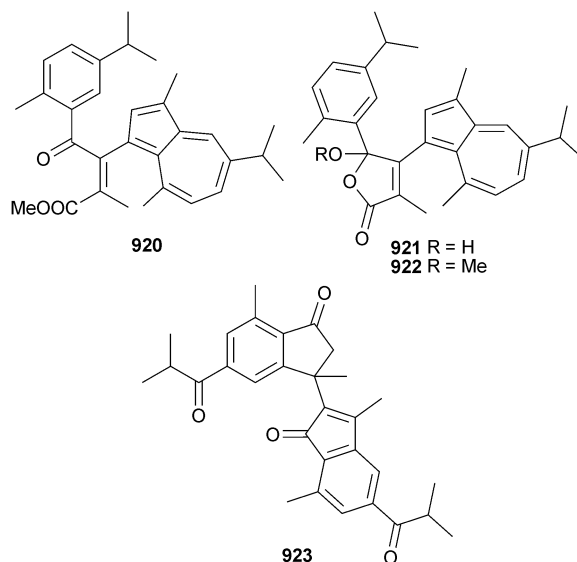
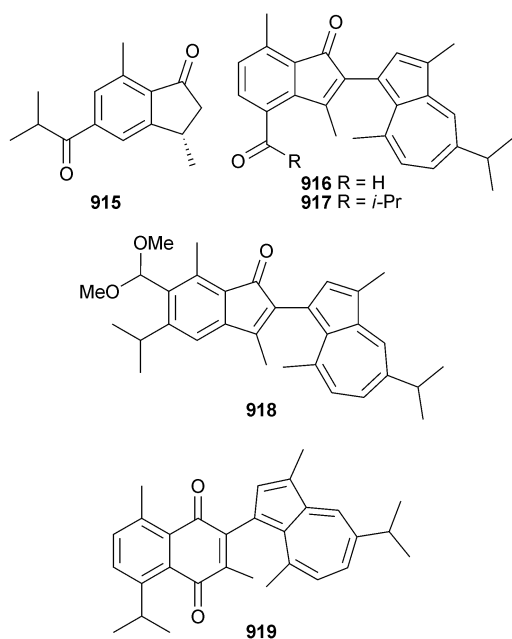
A new method of detection and quantification of palytoxin has been reported based on detection of the interaction of fluorescein-labeled Na,K-ATPase with palytoxin using fluorescence polarisation.⁷⁴² The method has a limit of detection of 2 nM. Paralemmolide A **905** is an unusual bisnorsesquiterpene from *Paralemmalia 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*).

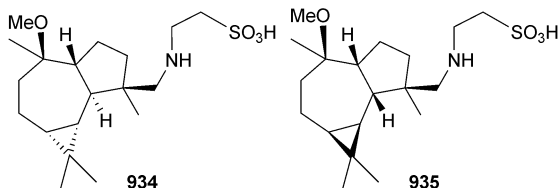
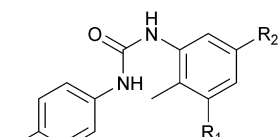
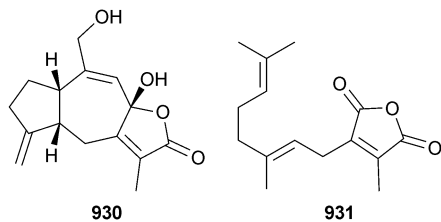


In addition to known congeners, fifteen new terpenes anthogorgienes A–O 915–929, based on a guaiazulene sesquiterpene scaffold, were isolated from *Anthogorgia* sp. (Weizhou Is., China).⁷⁴⁵ Absolute configurations were assigned to enantiomers 928 and 929 by CD analysis. Anthogorgiene G and known analogues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

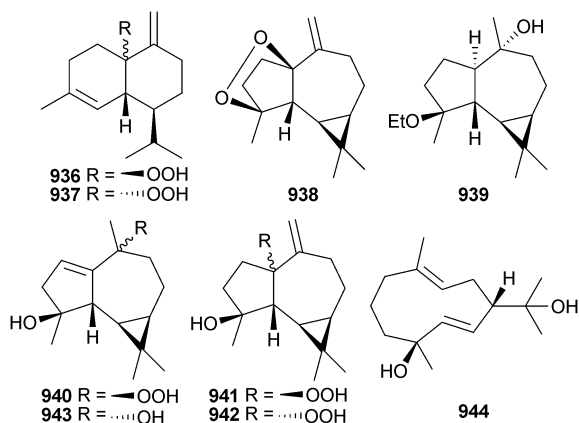


Menelloide E 930, a germacrane-type sesquiterpene, and *seco*-germacrane anhydride 931, previously reported from fruit of a Turkish plant,⁷⁴⁶ were isolated from a deep-sea trawl collection of *Menella* sp. (southern coast of Taiwan).^{747,748} Two carbamates obtucarbamate C 932 and D 933 and two sesquiterpene-taurine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



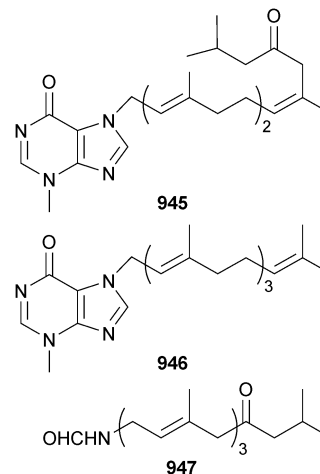


Of the two epimeric sesquiterpene hydroperoxides scabralin A **936** and B **937** (*Sinularia scabra*, Southern Taiwan), the former was found to exhibit mild antitumour activity and to reduce levels of iNOS protein in LPS-stimulated macrophages.⁷⁵⁰ Sesquiterpenes lochmolin A–G **938–944** were reported 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

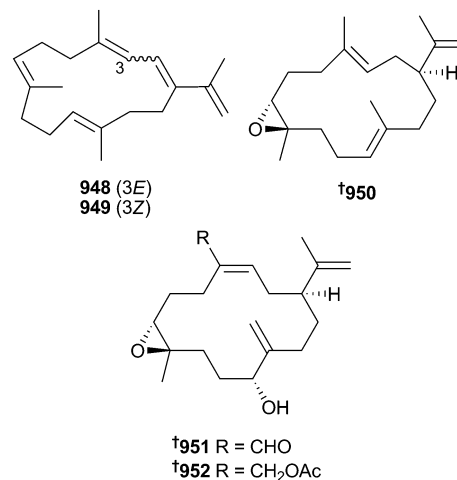


Prenylated purines **945**, **946** and formamide **947** (malonganenones I–K), and a number of previously reported congeners were isolated from *Euplexaura robusta* (Weizhou Is.,

South China Sea).⁷⁵² While **945–947** exhibited mild cytotoxicity, related co-metabolites malonganenones A, D and E^{753,754} were more cytotoxic.

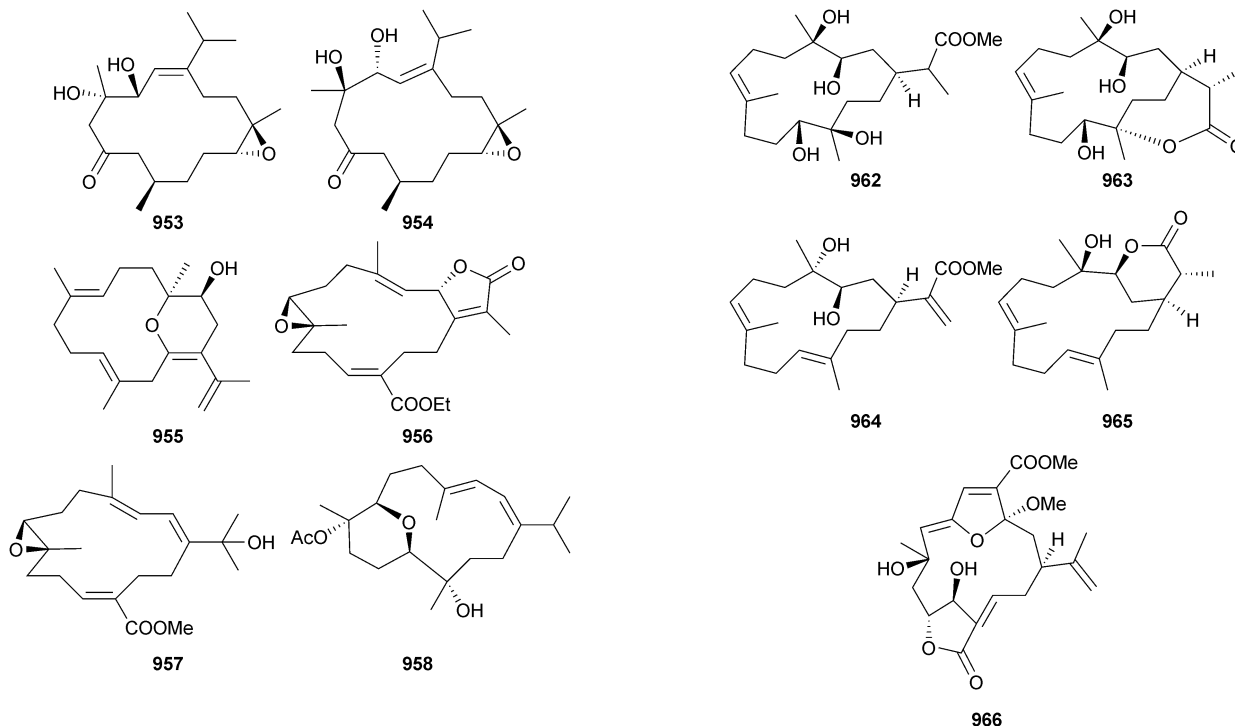


Two cembranes yalongene A **948** and B **949** were identified in extracts from *Sarcophyton trocheliophorum* (Yalong Bay, Hainan, South China Sea), with the former exhibiting cytoprotective effects towards cells injured with H_2O_2 .⁷⁵⁵ In addition to a number of congeners, epoxy-containing cembranes 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.

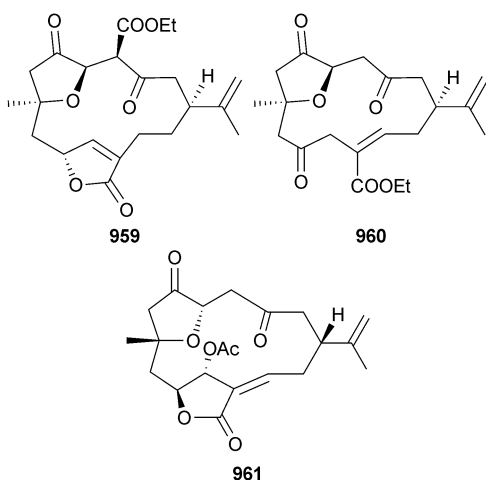


Epoxy-diol cembranes sicrassarine A **953** and B **954** (*Sinularia crassa*, Taitung County, Taiwan) were non-cytotoxic⁷⁵⁷ while the C-4/C-14 ether linked cembrane lobocrassin F **955** (*Lobophytum crassum*, Northeast Taiwan) was a moderate inhibitor of elastase release from human neutrophils.⁷⁴⁷ 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



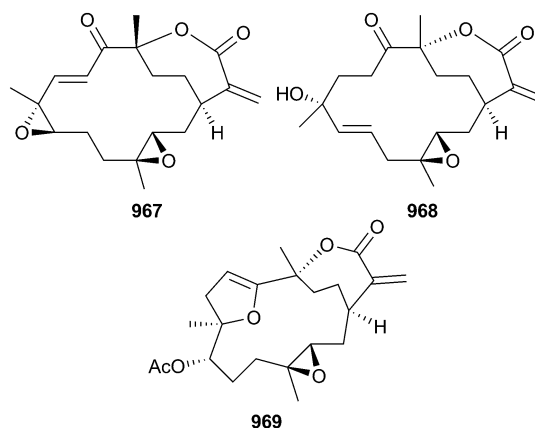


Of two cembranes sinumerolide A **959** and B **960** reported from *Sinularia numerosa* (Hainan Is., South China Sea) the latter contains the more usual combination of 5,8-epoxy linkage and C-4 norcembrane skeleton, while the former is unusual in possessing a complete C₂₀ diterpene backbone.⁷⁵⁹ One 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



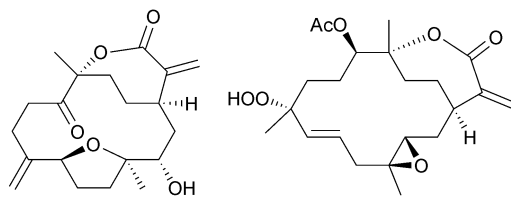
A collection of *Sinularia* sp. (Dongluo Is., Hainan, South China Sea) afforded sinuflexibilins A-E **962–966**, with the authors speculating about the potential artefactual nature of α -methoxyfuranocembranoid **966**.⁷⁶¹ Co-metabolite flexibilide⁷⁶² was the only compound in the study found to inhibit NF- κ B activation.

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



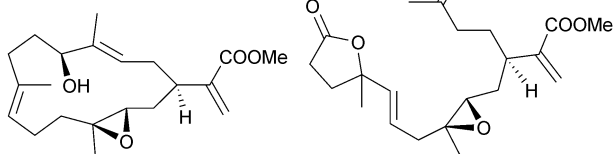
From a suite of new diterpenes sinumaximol A-I **974–982** and known congeners (*Sinularia maxima*, Nha trang Bay, Vietnam), sinumaximols B and C were found to inhibit IL-12, IL-6 and TNF- α production in LPS-stimulated bone marrow dendritic cells.⁷⁶⁴





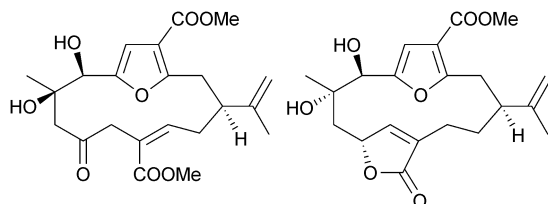
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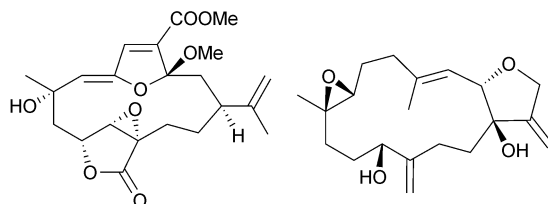
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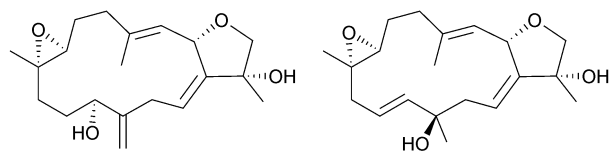
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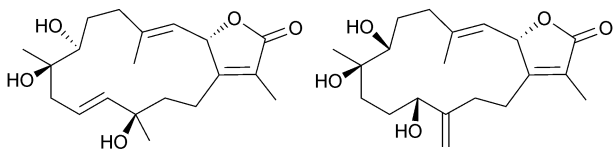
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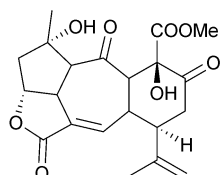
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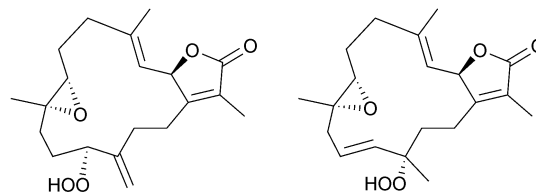
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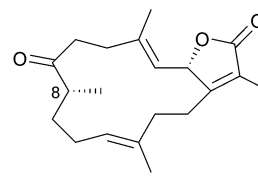
982

the co-metabolite 8-*epi*-sarcophinone **985** were different to those previously reported for the isomeric *iso*-sarcophinone⁷⁶⁶ 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.



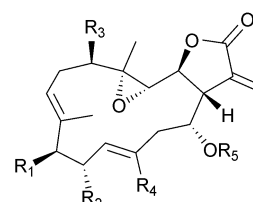
983

984

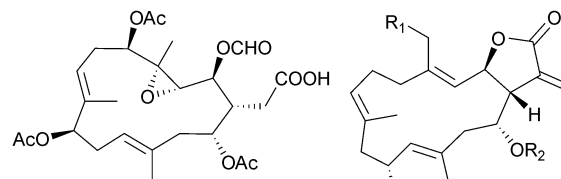


985

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 R₁ = R₃ = R₅ = H, R₂ = OAc, R₄ = Me
987 R₁ = H, R₂ = R₃ = OAc, R₄ = Me, R₅ = Ac
988 R₁ = R₃ = OAc, R₂ = H, R₄ = CHO, R₅ = Ac



989

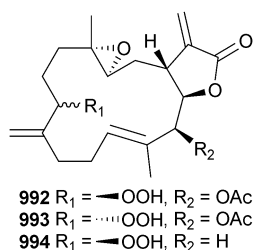
990 R₁ = R₂ = H
991 R₁ = OAc, R₂ = Ac

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

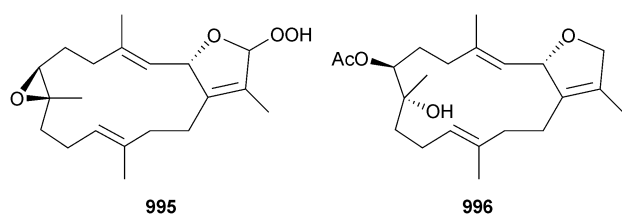
All three hydroperoxides sarcocrassocolide M–O **992–994** (*Sarcophyton crassocaule*, Dongsha Atoll, Taiwan) exhibited some degree of cytotoxicity towards tumour cell lines, with **992**



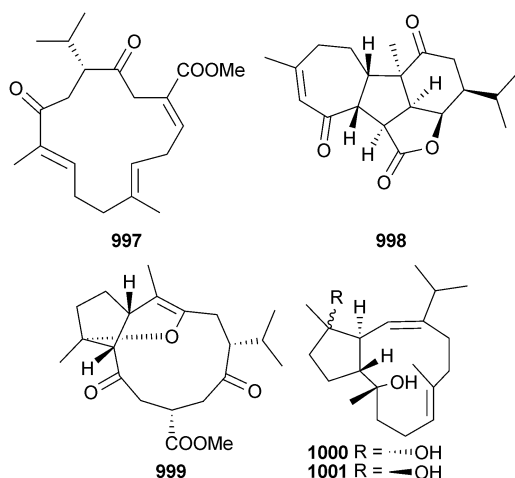
and **994** and to a lesser extent **993** also inhibiting the induction of iNOS protein.⁷⁶⁹



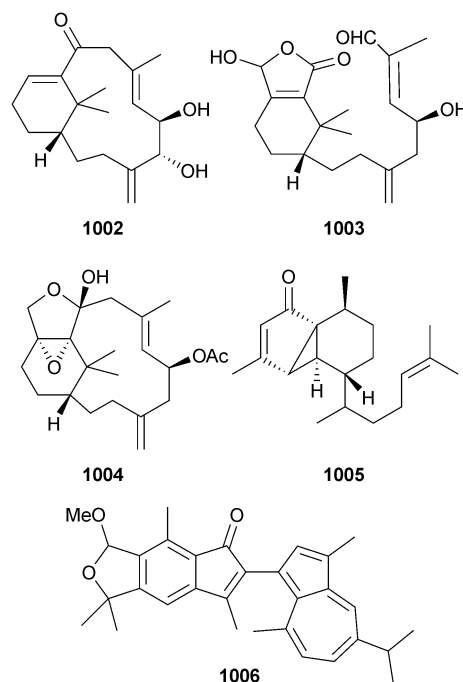
Dihydrofuranocembranoids sarcophytonin F **995** and G **996** (*Sarcophyton* sp., Dongsha Atoll, Taiwan)⁷⁷⁰ are, respectively, the hydroperoxide and acetate derivatives of the co-metabolites sarcophytoxide and sarcophytonin C.⁷⁷¹ Sarcophytonin G can also be classified as *ent*-crassumol C.⁷⁷²



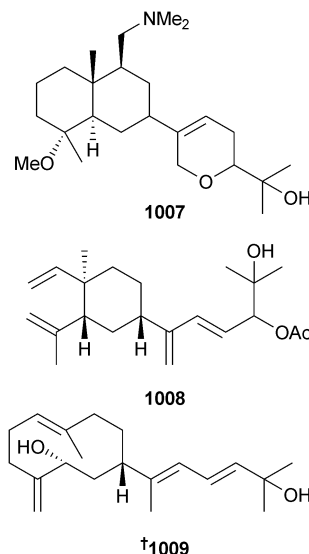
A structurally diverse set of diterpenes, the pavidolides A–E **997–1001**, were isolated from *Sinularia pavida* (Sanya Bay, Hainan Is., South China Sea). While pavidolides B and C were mildly cytotoxic, pavidolides C and D inhibited settlement of *B. amphitrite*.⁷⁷³



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

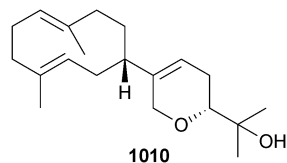


Dimethylamino-naphthalene **1007** and lobane **1008** (*Sinularia* sp., Bowden reef, Great Barrier Reef, Australia) exhibited mild to moderate cytotoxicity towards three HTCLs.⁷⁷⁶ Eunicidiol **1009** and known related diterpenes eunicol⁷⁷⁷ and fuscol⁷⁷⁷ were identified as potent topical anti-inflammatory metabolites of *Eunicea fusca* (Hillsboro Ledge, Florida).⁷⁷⁸

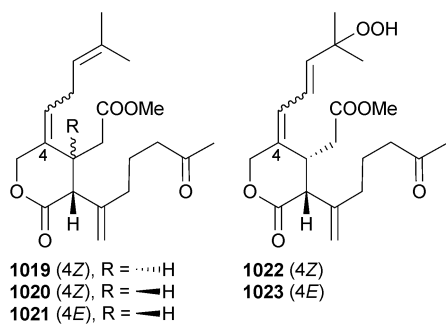
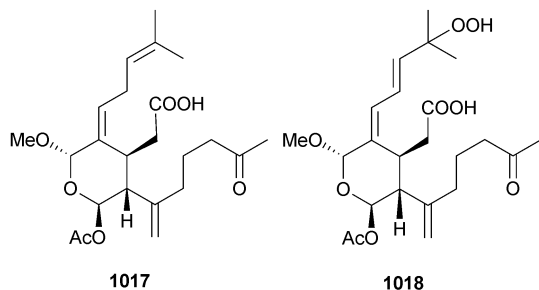
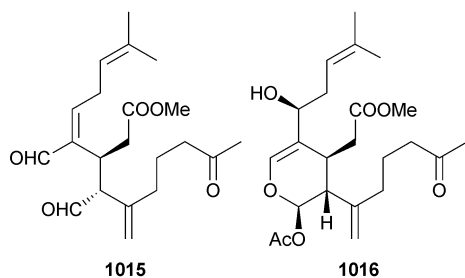
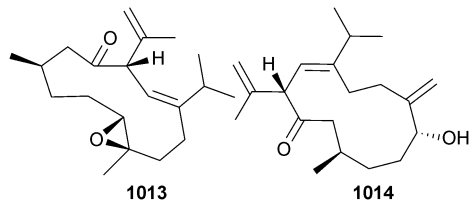
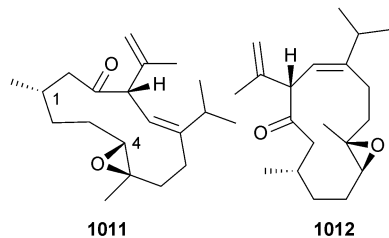


Extracts of *Lobophytum pauciflorum* (Taketomijima Is., Okinawa)⁷⁷⁹ provided cyclolobatriene **1010** and the related metabolites lobatriene,⁷⁸⁰ eunicol⁷⁷⁷ and fuscol.⁷⁷⁷ A low temperature (7 °C) NMR spectrum of **1010** identified three conformational isomers, while heating to 70 °C induced a thermal Cope rearrangement to lobatriene (identical by NMR and sign of [α]). A similar rearrangement was induced for eunicol, converting it to fuscol. All four natural products showed moderate cytotoxicity towards a tumour cell line.





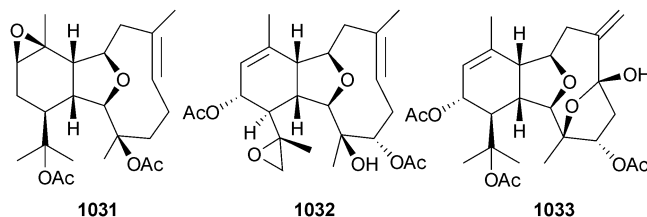
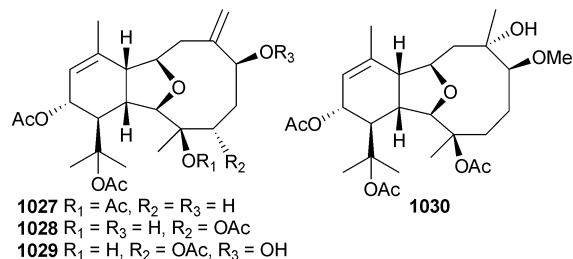
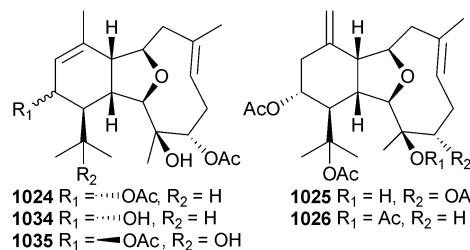
Two metabolites calyculone H **1011** and I **1012** (*Eunicea* sp., Old Providence Is., Colombia)⁷⁸¹ appear to be respectively the C-4,5-bis-epimers of previously reported calyculones C and A,⁷⁸² while triangulene C **1013** (*Sinularia triangula*, Taitung County, Taiwan) is another (possibly C-1) stereoisomer of calyculone C.⁷⁸³ Calyculones A, B, C and H exhibited mild antimalarial activity, while calyculone A displayed strong cytotoxicity in



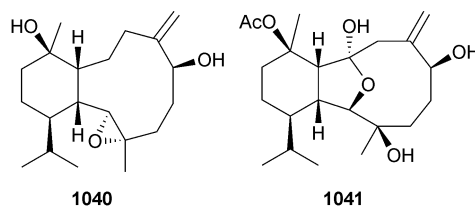
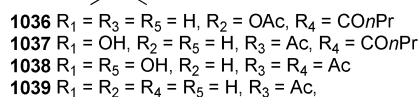
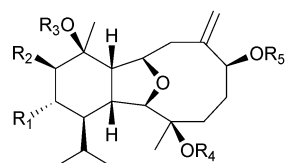
testing at the NCI. In contrast, the related cubitanone crassalona A **1014** (*Sinularia crassa*, Taitung County, Taiwan) exhibited no cytotoxicity towards a panel of tumour cell lines.⁷⁸⁴

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 CDCl₃ NMR solvent – the diene product was named astrogorgin N. Astrogorgins A–C exhibited moderate potency in a *B. amphitrite* antifouling bioassay.

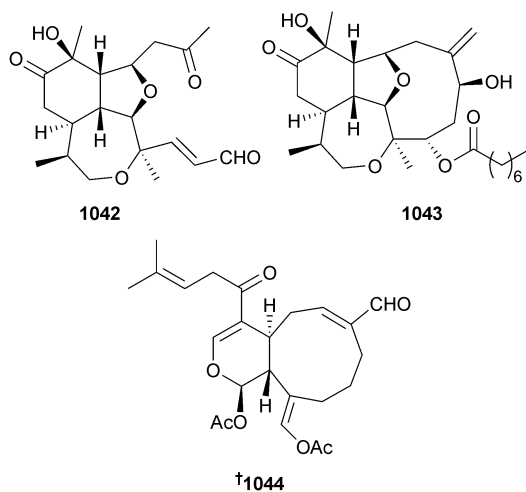


Duplicate structures were evident in the case of metabolites simplexin P–S **1036–1039** reported from *Klyxum simplex* (Dongsha Atoll, Taiwan).⁷⁸⁸ Simplexin Q is identical to

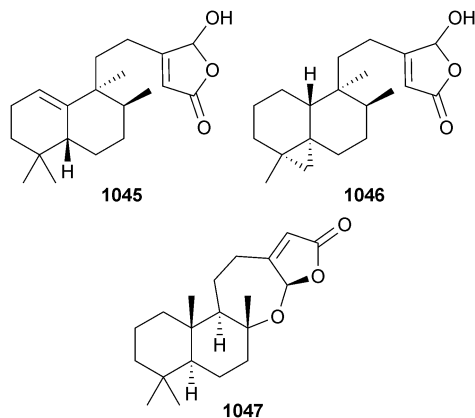


klysimplexin C,⁷⁸⁹ while simplexin S is identical to cladiuicellin G concurrently reported from *Cladiella* sp. (Indonesia).⁷⁹⁰ In addition, this latter study noted the presence of 6-*epi*-cladiuicellin F **1040** in the organism. The same specimen of *Cladiella* sp. also yielded the hemiketal congener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

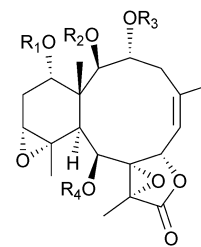
Seco-briarellinone **1042** and briarellin S **1043** are C-12 keto eunicellin diterpenes (*Briareum asbestinum*, Bocas del Toro, Panamanian Caribbean) that mildly inhibited the production of NO by LPS-stimulated macrophages.⁷⁹² Cristaxenicin A **1044** from *Acanthoprimnoa cristata* (dredging, Yakushima-Shinsoe, Kagoshima, Japan) exhibited sub-micromolar activity towards the human protozoal targets *Leishmania amazonensis* (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.



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.

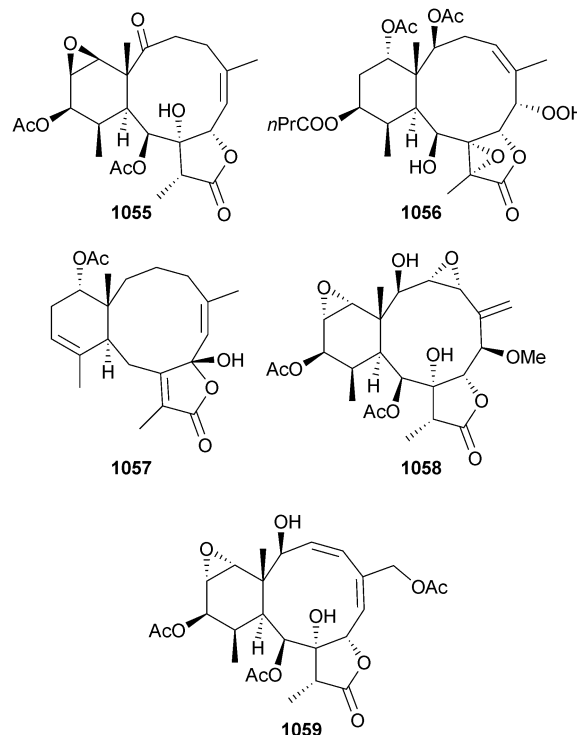


Diepoxybriaranes briaroxalide A–G **1048–1054** (*Briareum* sp., Ishigaki Is., Okinawa) all share the same absolute configuration; the configuration of briaroxalide A was determined (derivative, X-ray) and related to the others by peracetylation.⁷⁹⁷



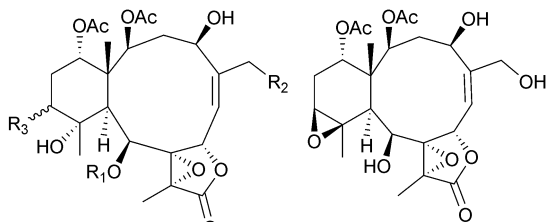
- †**1048** R₁ = R₃ = Ac, R₂ = R₄ = H
 †**1049** R₁ = R₄ = Ac, R₂ = R₃ = H
 †**1050** R₁ = R₃ = R₄ = Ac, R₂ = H
 †**1051** R₁ = R₂ = R₃ = H, R₄ = Ac
 †**1052** R₁ = R₂ = H, R₃ = R₄ = Ac
 †**1053** R₁ = H, R₂ = R₃ = R₄ = Ac
 †**1054** R₁ = R₂ = R₄ = Ac, R₃ = H

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.



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.



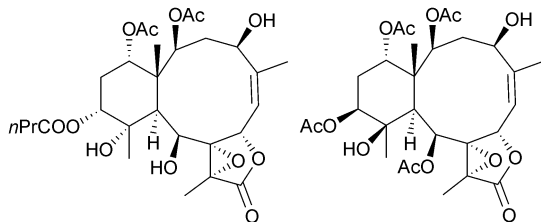


1060 $R_1 = R_2 = H, R_3 = \text{OH}$

1061 $R_1 = Ac, R_2 = OAc, R_3 = \text{OH}$

1062 $R_1 = Ac, R_2 = H, R_3 = \text{OCO}n\text{Pr}$

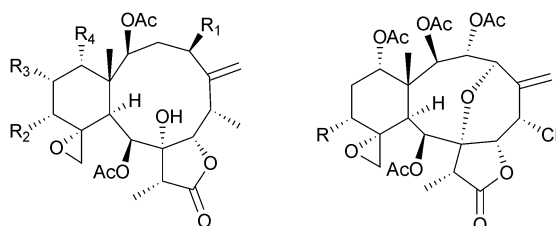
1063



1064

1065

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



1066 $R_1 = R_4 = OAc, R_3 = H, R_2 = \text{OCO}/\text{Bu}$

1067 $R_1 = R_2 = OAc, R_3 = H, R_4 = \text{OCO}/\text{Bu}$

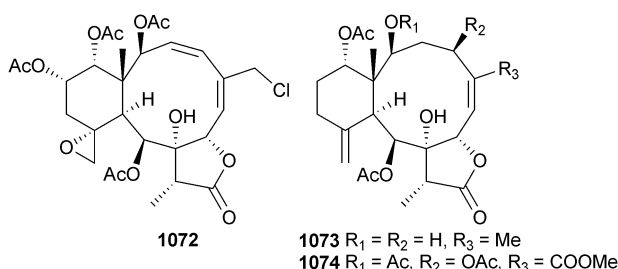
1068 $R_1 = R_2 = R_4 = OAc, R_3 = H$

1069 $R_2 = R_4 = OAc, R_1 = R_3 = \text{OCO}/\text{Bu}$

1070 $R = OAc$

1071 $R = \text{OCO}/\text{Bu}$

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

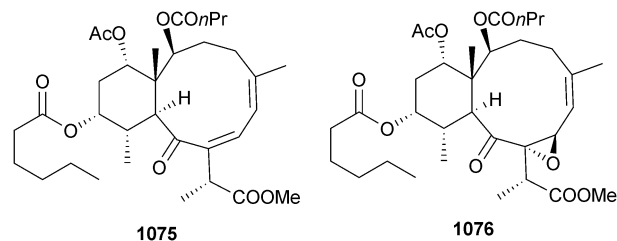


1072

1073 $R_1 = R_2 = H, R_3 = \text{Me}$

1074 $R_1 = Ac, R_2 = OAc, R_3 = \text{COOMe}$

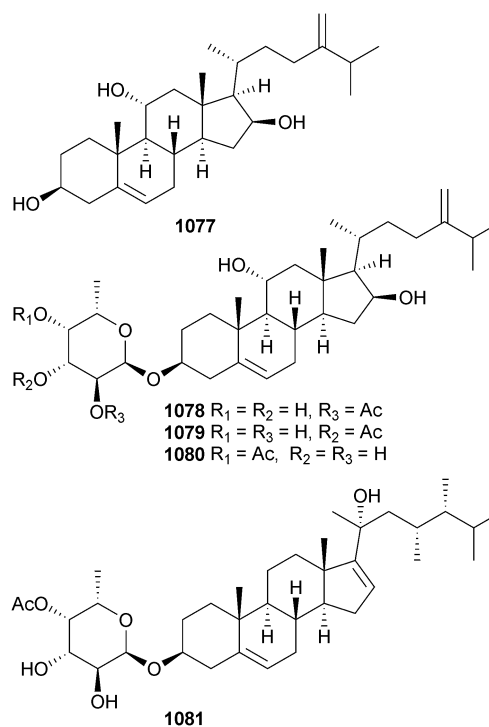
Briareolate esters J **1075** and K **1076** (*Briareum asbestinum*, Boca Raton, Florida)⁸⁰⁶ are hexanoate esters of briareolate esters G and D,⁸⁰⁷ respectively. Briareolate ester K was a weak growth inhibitor of human embryonic stem cells.



1075

1076

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



1077

1078 $R_1 = R_2 = H, R_3 = Ac$

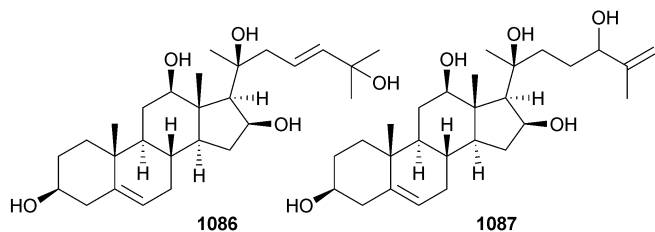
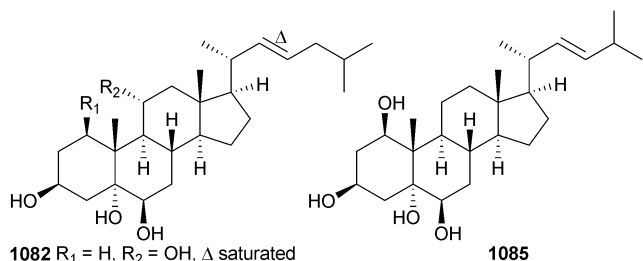
1079 $R_1 = R_3 = H, R_2 = Ac$

1080 $R_1 = Ac, R_2 = R_3 = H$

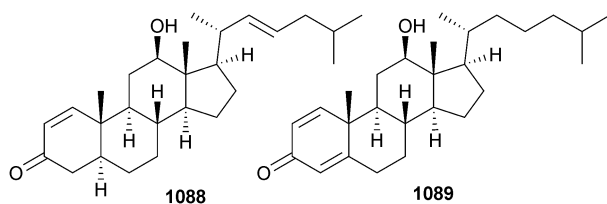
1081

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 C⁸⁰⁹ (*Menella* sp.).⁸¹⁰ Mildly cytotoxic pentaols **1086** and **1087** were isolated from *Subergorgia suberosa* (Naozhou Is., South China Sea).⁸¹¹

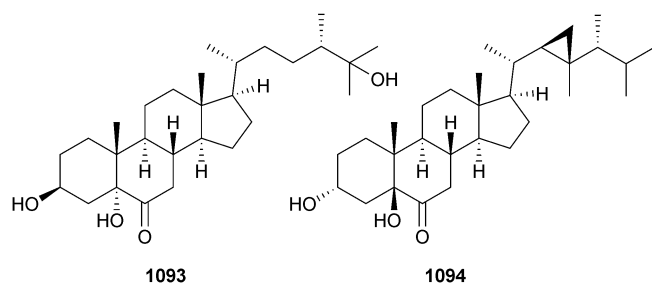
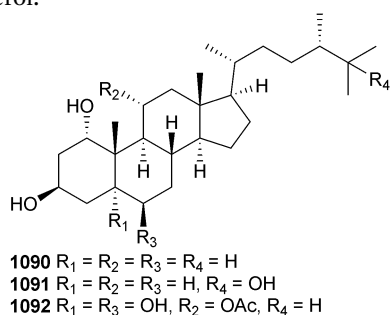




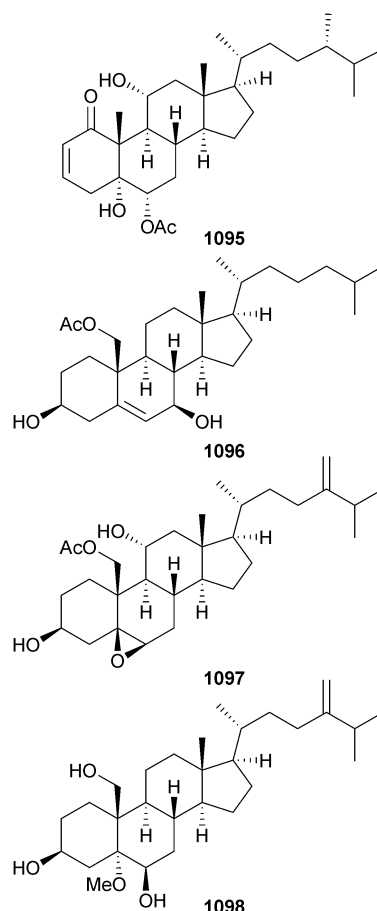
Two studies reported sterols with antagonistic activity towards FXR. In the first study, two new sterols **1088** and **1089** were isolated from *Dendronephthya gigantea* (Geo-je Is., S. Korea);⁸¹² although three sterols were claimed to be new, one had in fact been reported the previous year from a 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.



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



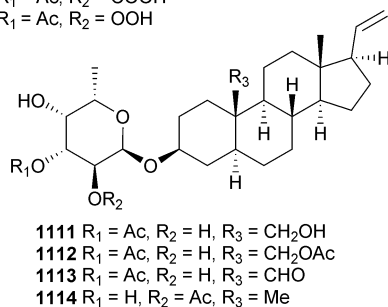
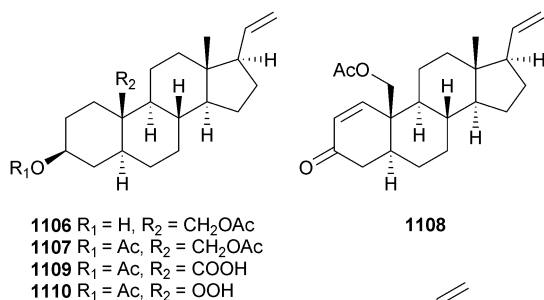
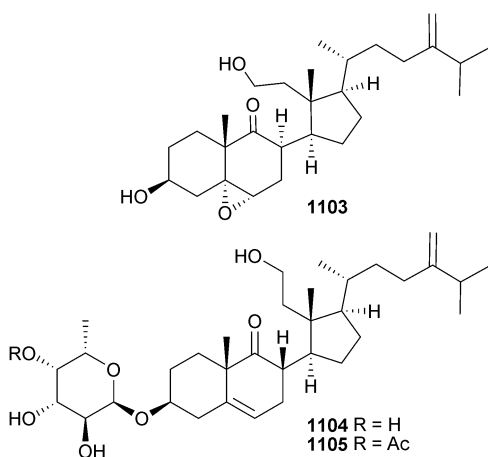
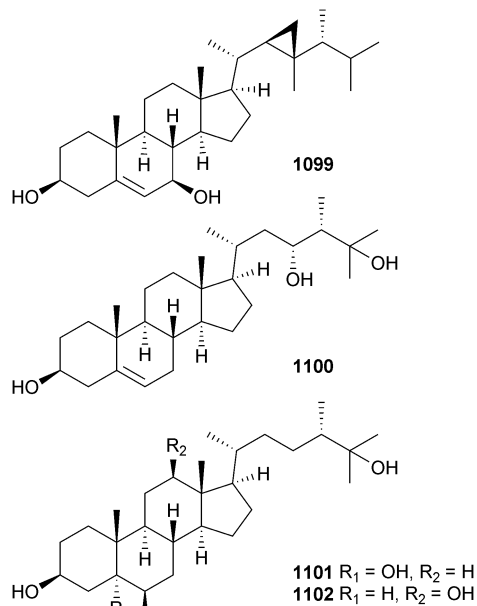
Extraction of *Echinomuricea* sp. (Taiwan) that had afforded a new labdane diterpene **1047** (see earlier) also yielded 6-*epi*-onarasterol B **1095** which was notable for the ability to inhibit the generation of superoxide and the release of elastase from stimulated human neutrophils.⁷⁹⁶ Three examples 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



In addition to two cembranes **959** and **960** (see earlier), specimens of *Simularia 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 *Simularia* sp. (Weizhou Is., South China Sea).⁸¹⁶

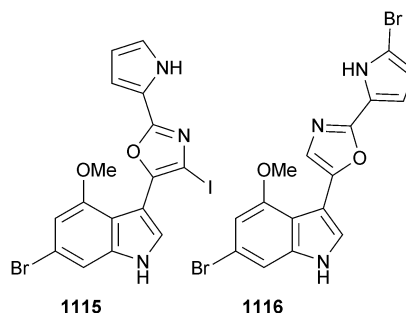
The 9,11-secosterol **1103** (*Simularia granosa*, Pingtung, Taiwan) is an H-8, 5,6-epoxy diastereomer of a previously reported co-metabolite (*Simularia lochmodes*);⁸¹⁷ both compounds exhibited cytotoxicity and inhibited expression of iNOS and COX-2 proteins in stimulated macrophages.⁸¹⁸ The first examples of 9,11-secosterol glycosides, sinularoside A **1104** and B **1105** (*Simularia 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 breiffussi* (Bear Is., Arctic) identified the halogenated alkaloids breiffussin 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 'trocheliophoride 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 A⁸²⁷ and clovane rumphelleclovane A⁸²⁸ (*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.

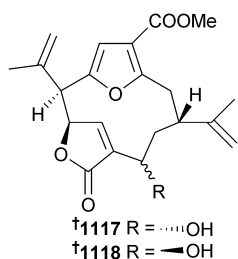
Several studies have been reported on further biological investigation of purified cembranoids. Sinularin (*Sinularia flexibilis*)⁸³² inhibits the up-regulation of pro-inflammatory proteins iNOS and COX-2 as well as TGF- β in stimulated macrophages.⁸³³ Such *in vitro* results also translated to *in vivo* studies, where sub-cutaneous application led to observable analgesic effects. While one study of 11-dehydrosinulariide⁸³⁴ 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 neuro-protective candidate.⁸³⁶ The related cembrane sinulariide⁸³⁷ 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

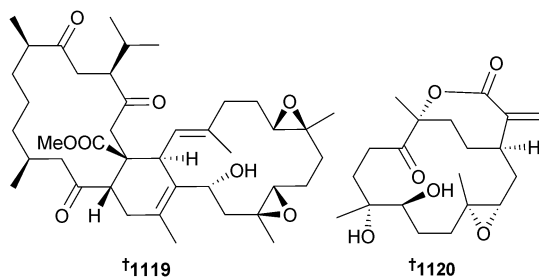


that it functions by activation of apoptosis *via* reactive oxygen species (ROS) generation, which has further downstream consequences of inhibiting signal transduction.⁸⁴⁰ A semi-synthetic analogue of cembranoid sarcophine, sarcophine diol, inhibited mouse melanoma cell proliferation by arresting cell division at G₀ and by also activating apoptosis.⁸⁴¹

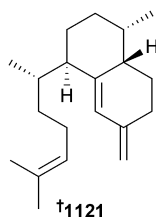
A configurational reassignment of 11-gorgiacerol⁸⁴² (= 11-pseudopteranol?)⁸⁴³ and 11-*epi*-gorgiacerol (aka 11-*epi*-pseudopteranol)⁸⁴⁴ to those shown in **1117** and **1118** has been reported; the syntheses made use of a stereospecific photochemical ring contraction reaction.⁸⁴⁵



The absolute configurations of bis-cebranoid ximaolide A⁸⁴⁶ **1119** and cembrane (+)-sinulaparvalide A⁸⁴⁷ **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 tetrahydro-sarcoate)⁸⁴⁸ and (+)-sinulaparvalide B.



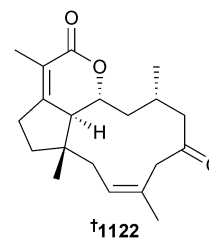
By stereospecific synthesis of a stereoisomer, the absolute configuration of elisabethatriene,⁸⁴⁹ a diterpene representing the first committed step in pseudopteroin biosynthesis, has been corrected to that shown here, **1121**.⁸⁵⁰



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 pseudopteroxazole⁸⁵² and homopseudopteroxazole⁸⁵³ 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 A⁸⁵⁵ could also be realised by a thermal step-wise proton-promoted process.⁸⁵⁶

The absolute configuration of clavulactone **1122** (*Simularia* sp.)⁸⁵⁷ has been established by enantioselective synthesis.⁸⁵⁸ As indicated in the previous review in this series,¹ the structure of gemmacolide H⁸⁵⁹ has been confirmed⁸⁶⁰ as identical to the previously reported briarane 12-*epi*-fragilide G.⁸⁶¹



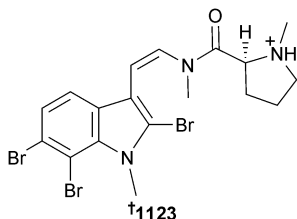
The structure of pregnane krempene B (*Cladiella krempfi*)⁸⁶² has been confirmed by synthesis from 3 β -acetoxy-5-pregnen-20-one,⁸⁶³ while two cholestane-dienones previously reported from *Minabea* sp.⁸⁶⁴ and *Anthomastus bathyproctus*⁸⁶⁵ have been prepared from (25*S*)- Δ^4 -dafachronic acid.⁸⁶⁶

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





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

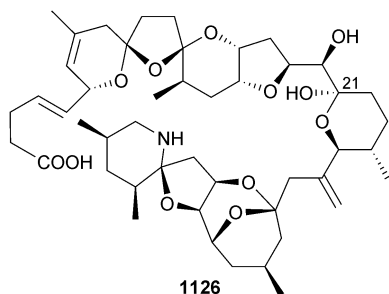


1124



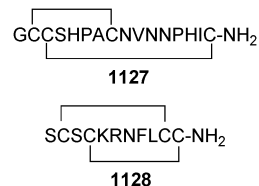
1125

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.



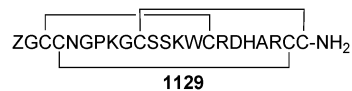
A diverse array of fatty acid esters of pinnatoxin G were identified in extracts of *M. edulis* (Atlantic coast, Canada).⁸⁸¹ Specimens of the sea snails *Gibbula umbilicalis* (flat top shell) and *Monodonta lineata* (thick top shell) collected on the Portuguese coast were found to contain low levels 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 α 4/7-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 α 3 β 4 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



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 μ O-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.



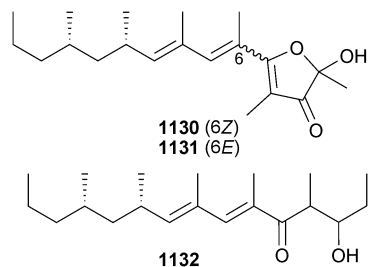
A hydrophobic 32-residue peptide, μ O-conotoxin MfVIA (*Conus magnificus*, unspecified location) preferentially inhibited Na_v 1.8 and Na_v 1.4 sodium channel isoforms.⁸⁸⁷ Synthesis of the peptide made use of an interesting sequence of selective oxidative deprotections of cysteine residues that allowed 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*-

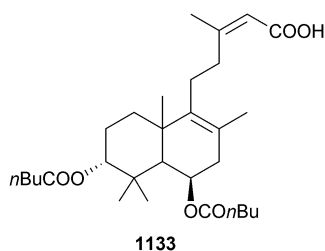


trans isomerase and immunoglobulin-binding protein in directing the oxidative folding of cysteine-rich peptides has been studied.⁸⁸⁹

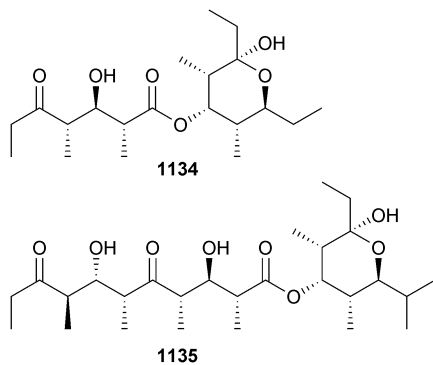
Investigation of the chemistry of *Siphonaria oculus* (Eastern Cape, South Africa) afforded new polypropionates **1130**–**1132**.⁸⁹⁰ The potential artefactual nature of cyclic products **1130**, **1131** and a fourth known polypropionate was suggested when analysis of the crude mucous released from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



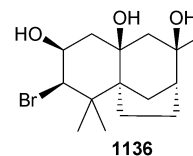
The more structurally complex labdane diterpene **1133** was reported from specimens of the limpet *Trimusculus peruvianus* (Bahía de Pichidangui, Chile).⁸⁹¹ Enantioselective synthesis of *ent*-caloundrin B (*Siphonaria zelandica*)⁸⁹² confirmed the proposed relative and absolute configuration and in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



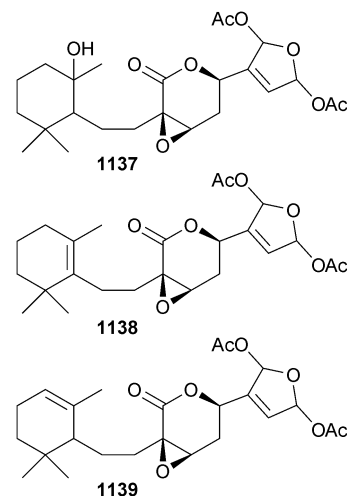
The absolute configurations of the bis- γ -pyrone polypropionate onchidione (*Onchidium* sp.)⁸⁹⁴ and two methanolysis products have been assigned by analysis of X-ray diffraction data and TDDFT calculated ECD spectra.⁸⁹⁵ *Dolabrifera dolabrifera* (El Escambron, Puerto Rico) afforded the known non-contiguous polypropionate ester dolabriferol⁸⁹⁶ and two new congeners dolabriferol B **1134** and C **1135**.⁸⁹⁷ The artefactual nature of all three metabolites was suggested.



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 isolated⁸⁹⁹ from a liverwort.⁹⁰⁰

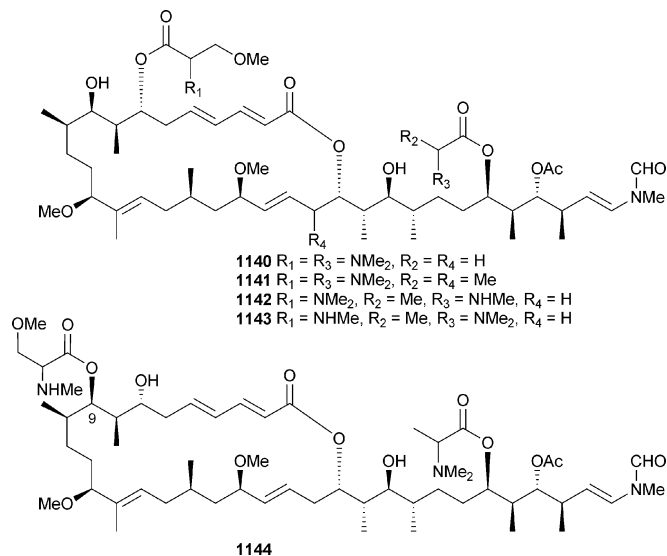


Use of either silica gel or AgNO₃-impregnated silica gel chromatography yielded diterpenes thuridillin D–F **1137**–**1139** from the sacoglossan mollusc *Thuridilla splendens* (Mooloolaba, Queensland).⁹⁰¹ Alkenes **1138** and **1139** may be purification artefacts of tertiary alcohol **1137**.



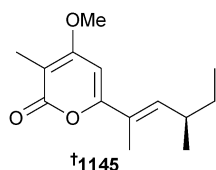
Five new aplyronine congeners D–H **1140**–**1144** were reported as cytotoxic constituents of *Aplysia kurodai* (Mie Prefecture, Japan).⁹⁰² While aplyronines D–G were equipotent or more cytotoxic (HeLa S₃ cells) than aplyronine A,⁹⁰³ aplyronine H was less cytotoxic highlighting that translocation of 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 S₃ cells.⁹⁰⁶





Biosynthetic incorporation studies have established that the C₃ units present in the opisthobranch mollusc *Ercolania funerea* metabolite 7-methyl-cyercene⁹⁰⁷ 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 kulokekahillide-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

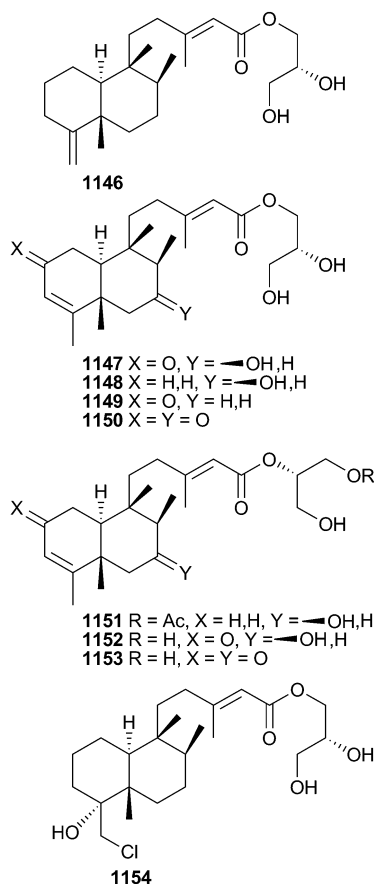


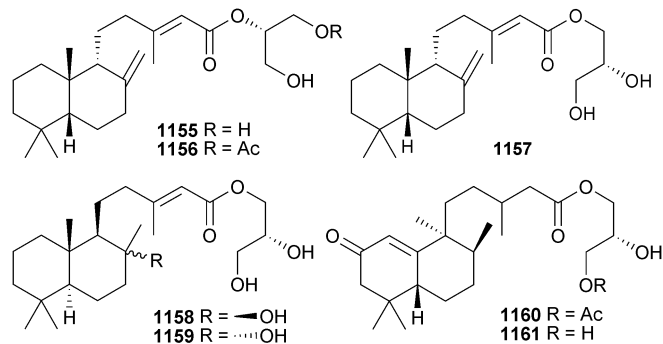
Also confirmed by synthesis are the structures of the 1,2,4-oxadiazole ring-containing alkaloids phidianidine A and B (*Phidiana militaris*).^{916–918} In addition to a number of known PUFAs, heneicosa-5,8,11,14-tetraenoic acid (21;4 *n*-7) was reported as a new natural product from the opisthobranch 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

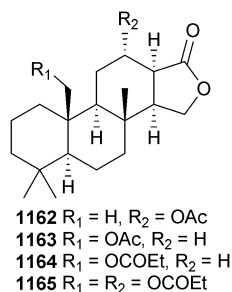
The γ -pyrone tridachiahydropyrone (*Tridachia crispata*)^{923,924} and two putative polyene precursors insert themselves into two phospholipid vesicle models of membranes, indicative perhaps of their location in molluscan cells.⁹²⁵ Mass spectrometry imaging, using a perfluorinated siloxane-pretreated 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 (μ M) the growth of human erythroleukaemia cells, with the most potent analogue **1155** also inhibiting Jak2-STAT5 and Erk1/2 activation pathways.

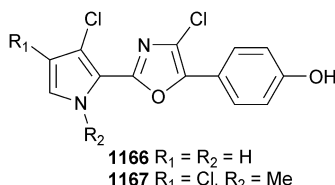




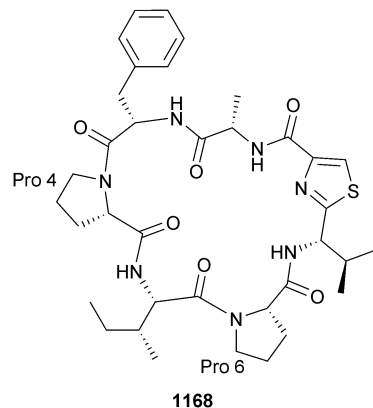
Investigation of the organelle distribution of metabolites in a single specimen of *Chromodoris albopunctata* (Inner Gneerings Reef, Mooloolaba, Queensland) yielded the sponge-derived diterpene **1162** and known analogues^{930,931} from the internal organs, while **1163–1165** were isolated from the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



New phorbotoxin 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.



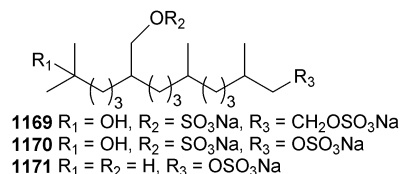
Tambjamine alkaloids C, E, F and BE-18591,^{934–936} isolated from nudibranchs, ascidians or a bacterium, acted as efficient transmembrane anion transporters, releasing chloride from phospholipid vesicles.⁹³⁷ Syntheses of the *Hexabranchnus sanguineus* cyclic peptides⁹³⁸ sanguinamide A **1168**⁹³⁹ and B⁹⁴⁰ 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.



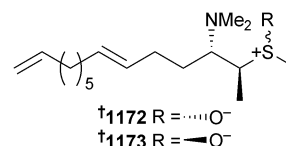
Analogues of (–)-jorumycin (*Jorunna funebris*),⁹⁴¹ with variation at the pendant methylene C-22, exhibited varied levels of potency towards a panel of HTCLs. A hippuric acid ester derivative exhibited broad spectrum nM potency.⁹⁴²

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.

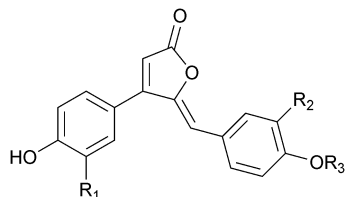


Two unusual dimethylamino lipidsulfoxides aplisulfamine A **1172** and B **1173** were isolated from *Aplidium* sp. (Pozzuoli, Naples).⁹⁴⁴ A comprehensive combination of nOe analysis, *J*-based configurational analysis, and calculated ¹³C chemical shift and ECD data secured the absolute configurations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



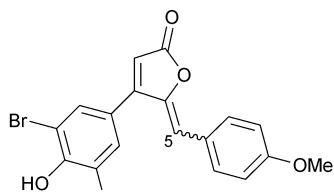
Three separate studies reported new congeners of the rubrolide and cadiolide families of furanones. In the first, South African specimens of *Synoicum globosum* (Algoa Bay) yielded known rubrolides E and F⁹⁴⁵ in addition to new more highly brominated analogues **1174–1177**.⁹⁴⁶ Variable levels of antibacterial activity were observed for all six metabolites.



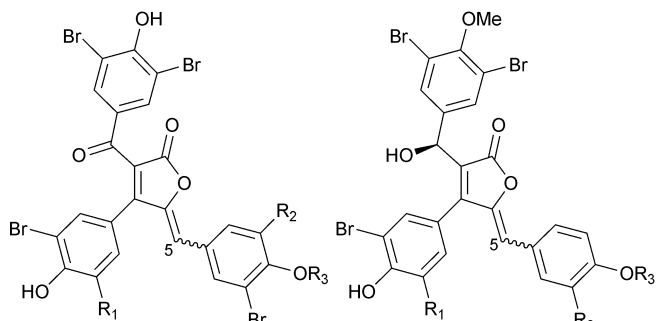


1174 R₁ = H, R₂ = Br, R₃ = Me
 1175 R₁ = Br, R₂ = R₃ = H
 1176 R₁ = Br, R₂ = H, R₃ = Me
 1177 R₁ = R₂ = Br, R₃ = H

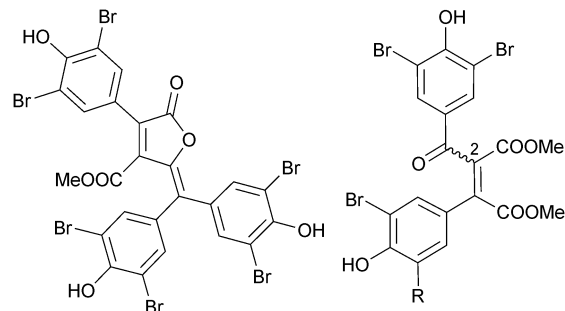
As well as rubrolide P **1178** and **1179** and **1177** (3'-bromo-rubrolide F, which the authors of this second study named rubrolide Q), a collection of *Pseudodistoma antinboja* (Tong-Yeong City, South Sea, S. Korea) also afforded four new cadiolide analogues C–F **1180–1184**.⁹⁴⁷ Some of the latter 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 synoilde 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 (5E)
 1179 (5Z)



1180 R₁ = R₂ = R₃ = H, (5Z)
 1181 R₁ = Br, R₂ = R₃ = H, (5Z)
 1182 R₁ = R₃ = H, R₂ = Br, (5Z)
 1183 R₁ = R₂ = H, R₃ = Me, (5Z)
 1184 R₁ = R₂ = H, R₃ = Me, (5E)
 †1185 R₁ = R₃ = H, R₂ = Br, (5Z)
 1186 R₁ = Br, R₂ = H, R₃ = Me, (5Z)
 1187 R₁ = Br, R₂ = H, R₃ = Me, (5E)

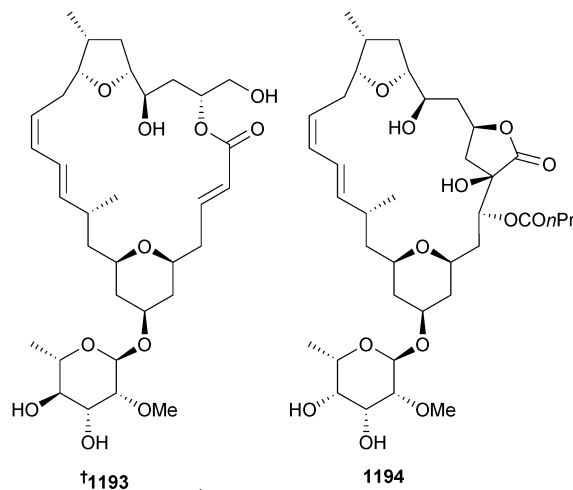


1188

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

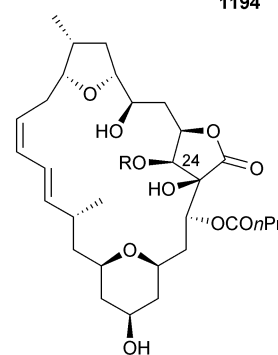
A small library of semi-synthetic analogues of eudistomin Y₂ and Y₃ was prepared and evaluated against the same set of biological targets used for the cadiolides; only one analogue exhibited increased cytotoxic potency, while all other analogues were less active than the natural products in the respective 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 paper⁹⁵² 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

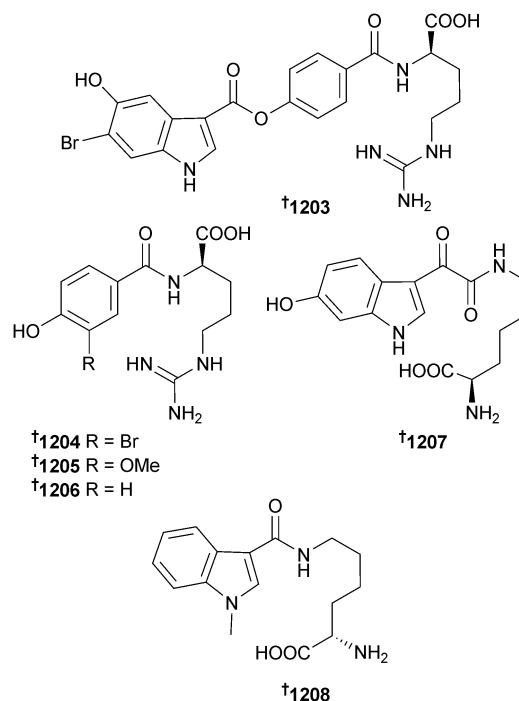
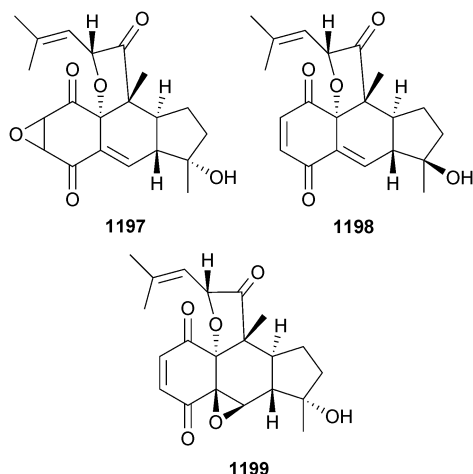
1194



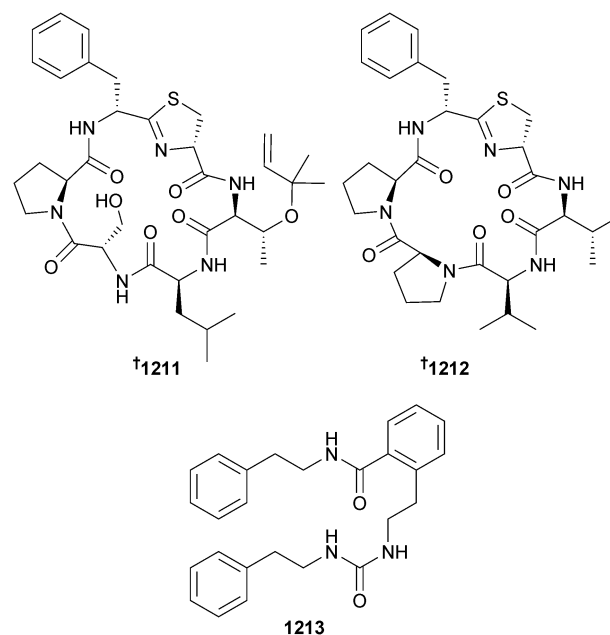
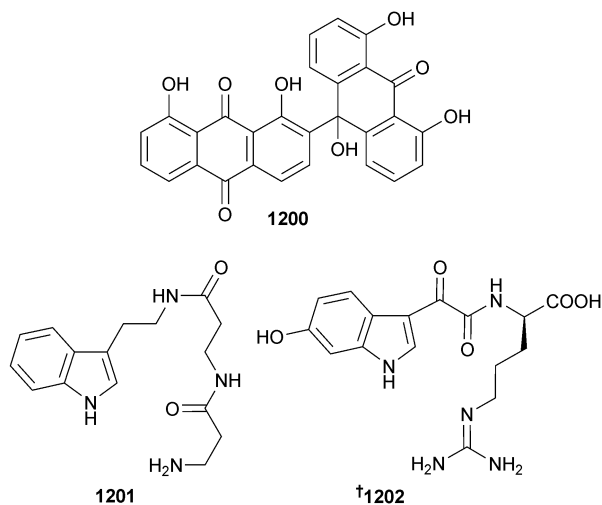
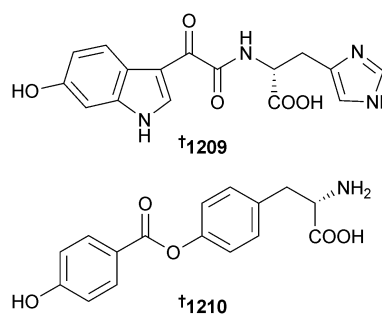
1195 R = H
 1196 R = CO_nPr



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 B⁹⁵⁷ and a mixture of meridianin alkaloids exhibited feeding deterrence towards the sea star *Odontaster validus* and amphipod *Cheirimedon femoratus*.⁹⁵⁸



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 (Lembah Strait, North Sulawesi) specimens of *L. dubius* have yielded leptoclinidamide **1201** and (–)-(*R*)-leptoclinidamine B **1202**.⁹⁶¹

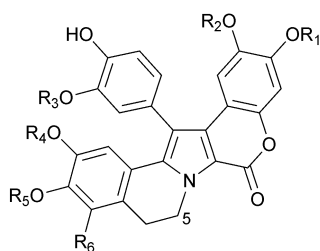


Further investigation of an extract of *Herdmania momus* (Jeju Is., S. Korea), from which anti-inflammatory amino acid derivatives had been previously identified,⁹⁶² afforded new congeners herdmanine E–L **1203–1210**, in addition to (–)-(*R*)-leptoclinidamine B.^{963,964} The latter compound and herdmanine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

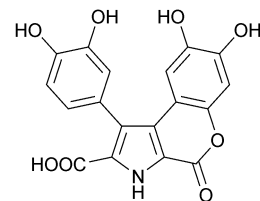
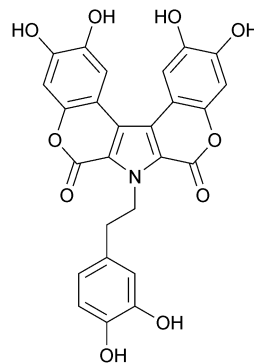
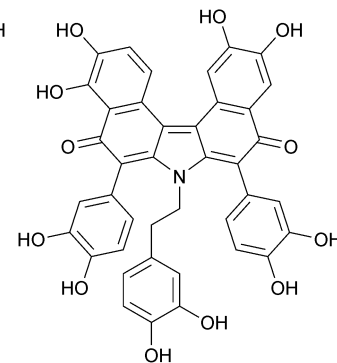
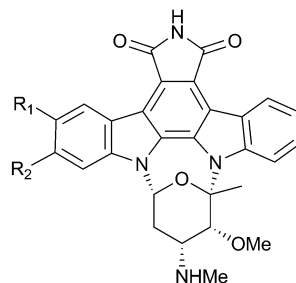


Mollamides E **1211** and F **1212** and molleurea A **1213** were obtained from *Didemnum molle* (New Britain, Papua New Guinea) with NMR chemical shift and nOe data defining the proline conformations as *cis* in **1211** and *cis* and *trans* in **1212**.⁹⁶⁵ These same two peptides have previously been identified as predicted products from the genome sequence of *Prochloron* spp., and detected by LC-MS in an ascidian⁹⁶⁶ or in *E. coli* heterologously expressing the pathway.⁹⁶⁷

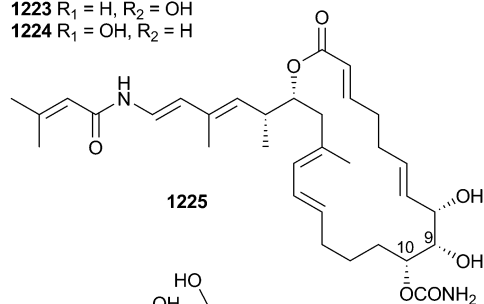
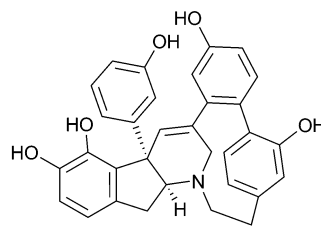
Australian collections of *Didemnum* sp. (Wasp Is., New South Wales, and Northern Rottneest Shelf, Western Australia) afforded an extensive number of lamellarin alkaloids including the new members lamellarin A1–A6 **1214–1219**.⁹⁶⁸ Evaluation of the library identified examples exhibiting cytotoxicity 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** R₁ = R₂ = R₅ = R₆ = H, R₃ = R₄ = Me
1215 R₁ = R₂ = H, R₃ = R₄ = R₅ = Me, R₆ = OH
1216 R₁ = R₇ = H, R₂ = R₃ = R₄ = R₅ = Me
1217 R₁ = R₂ = R₃ = R₄ = R₅ = R₆ = R₇ = H
1218 R₁ = R₂ = R₄ = R₅ = R₆ = H, R₃ = Me, Δ^{5,6}
1219 R₁ = R₃ = R₄ = Me, R₂ = R₅ = R₆ = H

**1220****1221****1222**

- 1223** R₁ = H, R₂ = OH
1224 R₁ = OH, R₂ = H

**1225****1226**

Further investigation of the Northern Rottneest 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

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

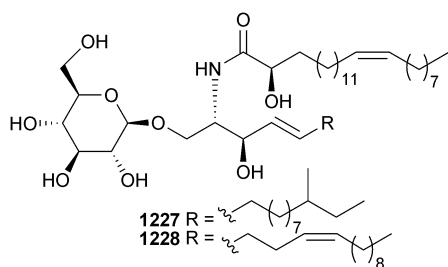


and absolute configurations of the brominated 1,2,3,4-tetrahydro- β -carboline alkaloids eudistomidin G–I (*Eudistoma glaucus*)^{981,982} have been confirmed by synthesis⁹⁸³ as have those of an iodinated nucleoside⁹⁸⁴ originally reported from *Diplosoma* sp.^{985,986}

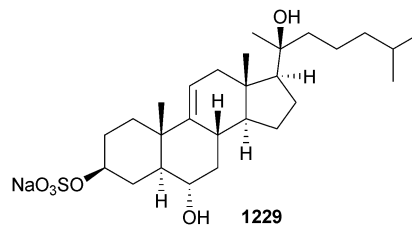
Biomimetic syntheses of the apoptosis-inducing prenylated thiazinoquinones thiaplidiuquinone A and B (*Aplidium conicum*)⁹⁸⁷ have been reported.^{988,989} Two different routes for the synthesis of the antimalarial pyrroloquinoline aplidiopsamine A (*Aplidiopsis confluenta*)⁹⁹⁰ have been reported,⁹⁹¹ with one⁹⁹² 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

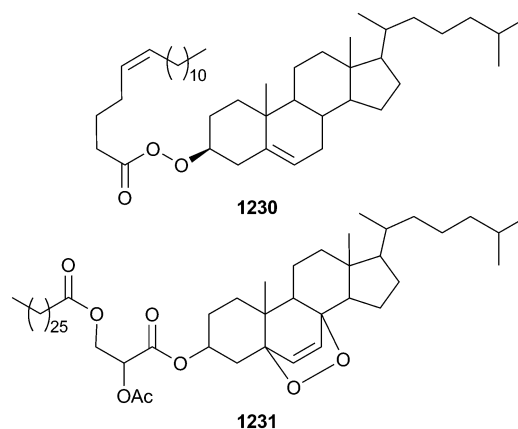
The 37 new metabolites reported from echinoderms in 2012 is a modest increase from the number reported in 2011. Known sulfated alkanes 2,6-dimethylheptyl sulfate, octyl sulfate and decyl sulfate as well as new sulfated alkenes (5*Z*)-dec-5-en-1-yl sulfate and (3*E*)-dec-3-en-1-yl sulfate were isolated 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



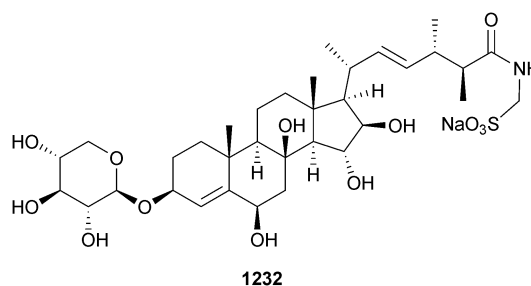
Crude preparations of cerebrosides from the sea cucumber *Acaudina molpadioides* (Zhejiang Province, China) and the starfish *Asterias amurensis* (S. Hokkaido, Japan) exhibited pronounced *in vitro* and *in vivo* antitumour activity and appear to function by induction of apoptosis *via* a mitochondrial-mediated 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 luconterperacetate **1230** and the more classical peroxy-bridged sterol peroxyluconterine **1231** were reported from the urchin *Echinometra lucunter* (Dakar, Senegal).¹⁰⁰¹

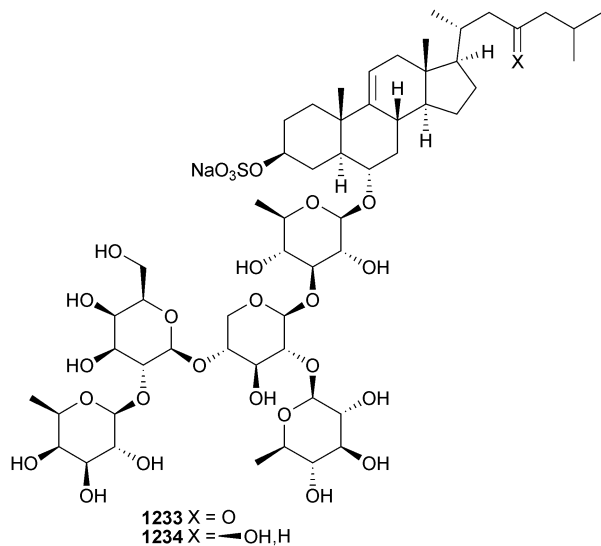


An amidotaurine β -D-xyloside, fisherioside A **1232**, was isolated from the starfish *Leptasterias fisheri* (Sakhalin Is., Sea of Okhotsk),¹⁰⁰² while pentaosides lethasteriosides A **1233** and B **1234** were reported from *L. fusca* (Posyet Bay, Sea of Japan).¹⁰⁰³ Lethasterioside A, while being weakly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

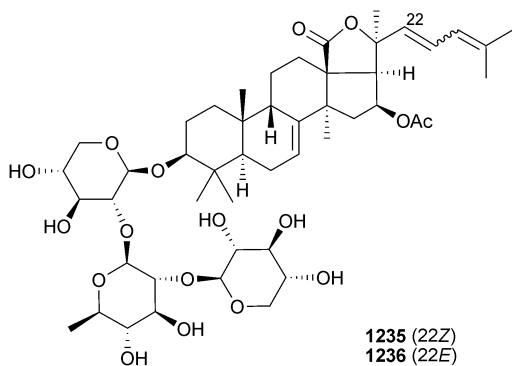


In five separate accounts, a series of tri-, tetra- and pentaosides were reported from the same collection of the sea cucumber *Eupentacta fraudatrix* (Peter the Great Gulf, Sea of Japan). Of the two side-chain isomeric triosides, cucumarioside B₁ **1235** and B₂ **1236**, only the latter demonstrated cytotoxicity and haemolytic activity (mild).¹⁰⁰⁴ Minor metabolite tetraosides cucumarioside A₁–A₁₅ **1237**–**1251** all incorporated the same tetrasaccharide unit.^{1005–1007} Cucumariosides A₁, A₅,

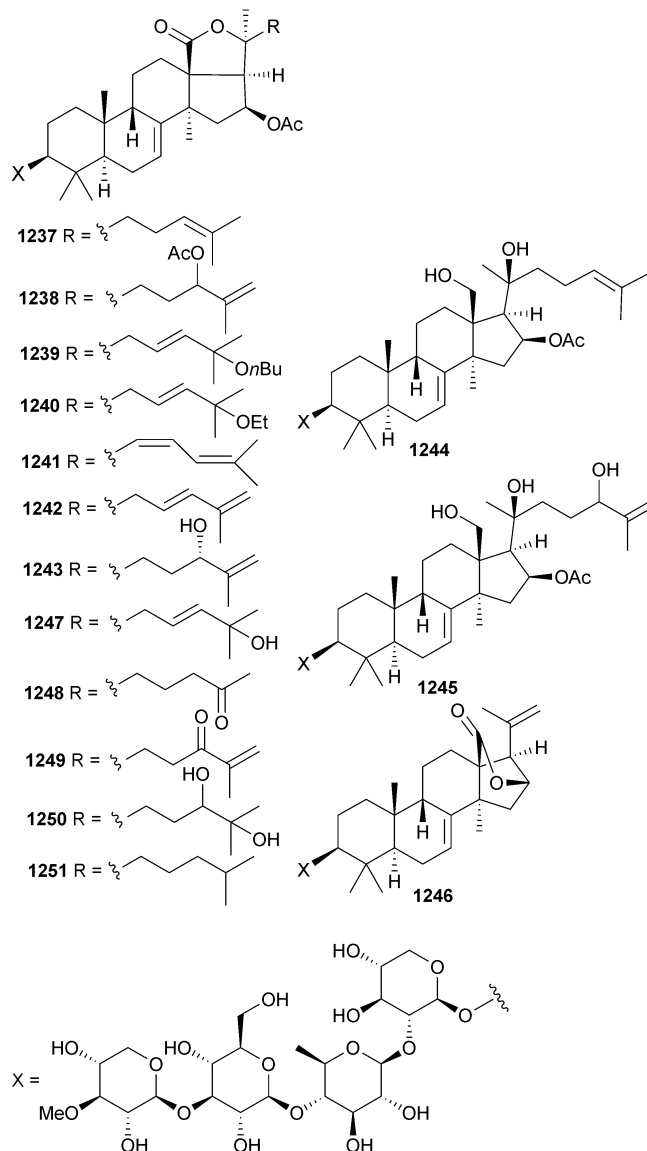




A₁₀ and A₁₁ are desulfated derivatives of previously reported cucumariosides G₁, G₃, G₂ and G₄, respectively^{1008–1011} and cucumarioside A₁₅ appears to be identical to a previously reported starfish metabolite.¹⁰¹² Cucumariosides A₁, A₂, A₆, A₈ and A₁₃ were the most active of the series in a range of biological studies assessing cytotoxicity, antifungal and haemolytic activities. Out of the three pentaosides cucumarioside H₂–H₄ 1252–1254, there was more pronounced cytotoxicity and haemolytic activity for the likely artefactual ethyl ether, cucumarioside H₄.¹⁰¹³

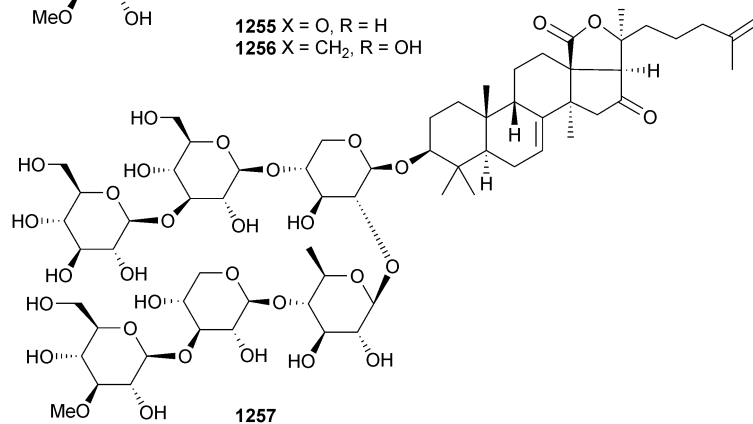
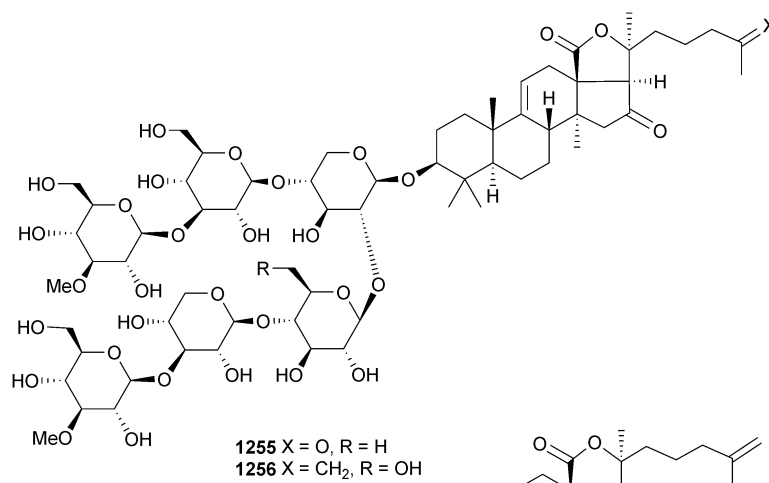
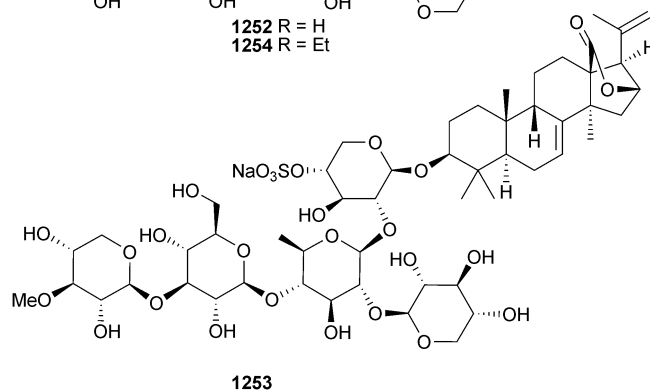
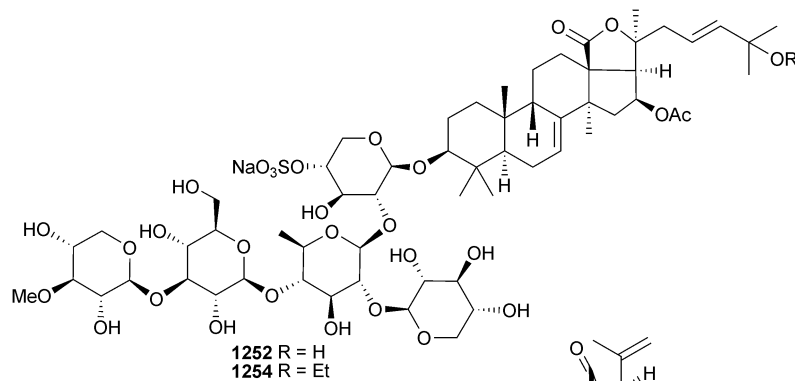


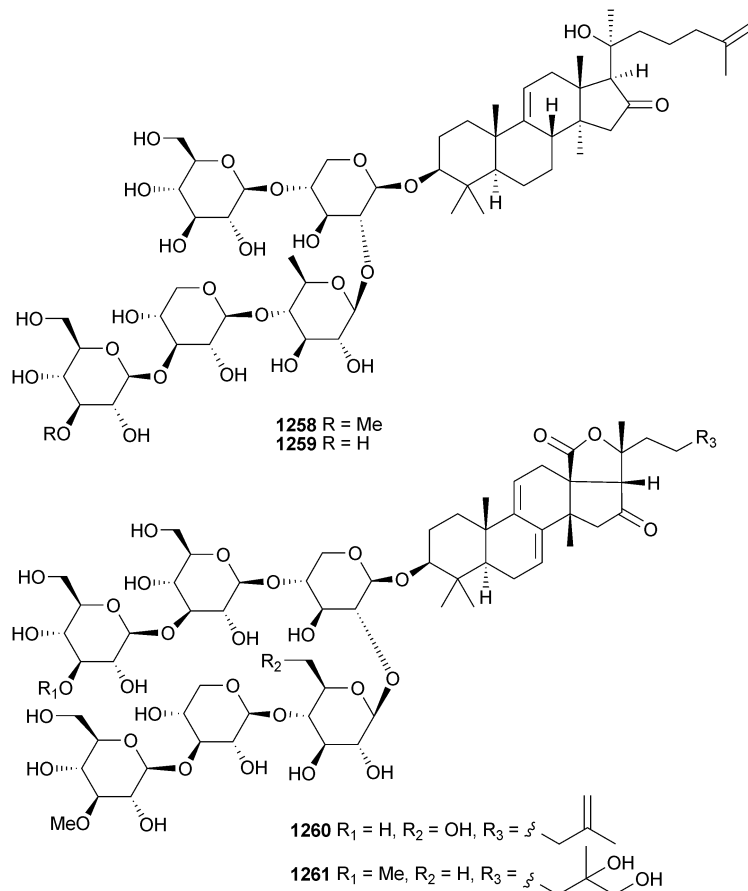
The sea cucumber *Apostichopus japonicus* is used as a food and a tonic in China – investigation of constituents of specimens (Dalian coast, Bohai Sea of China) identified penta- and hexaosides 1255, holotoxin D–G 1256–1259¹⁰¹⁴ and holotoxin D₁ 1260 and 24,25-dihydroxyholotoxin A₁ 1261.¹⁰¹⁵ Broad spectrum antifungal activity was observed for holotoxins D–G and holotoxin D₁, 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 investigated¹⁰¹⁷ while tetraosides echinosides A and B (*Actinopyga echinites* and *Holothuria polii*)¹⁰¹⁸ demonstrated schistocidal activity *in vitro*.¹⁰¹⁹ The anti-tumour 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 G₀/G₁ 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 neothyonidioside¹⁰²¹ (*Australostichopus mollis*) demonstrated antifungal activity by binding to ergosterol, leading to altered membrane curvature and fusion capability.¹⁰²²

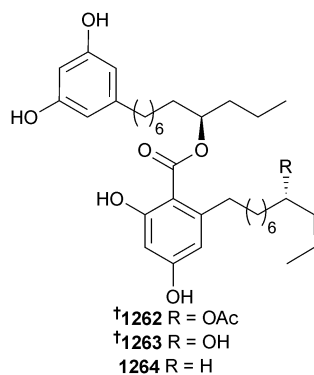




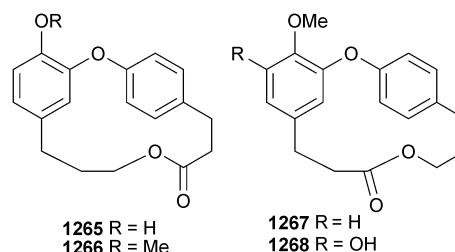


13 Mangroves

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

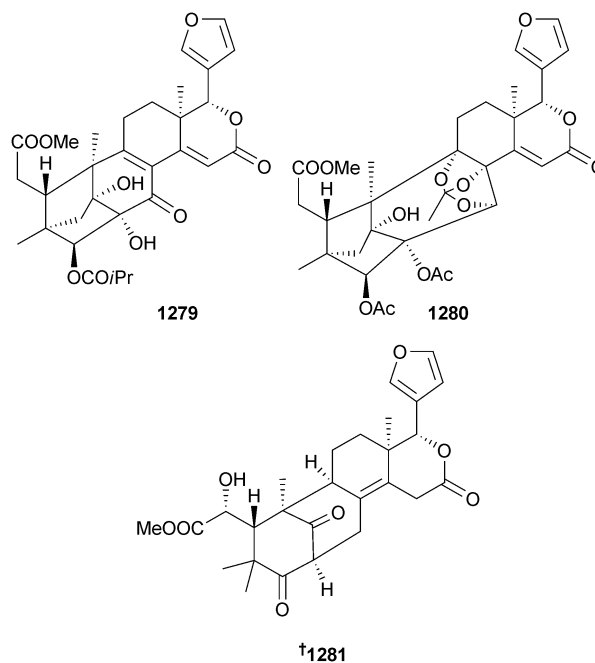
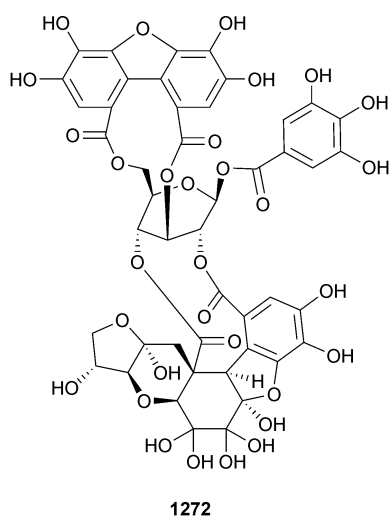
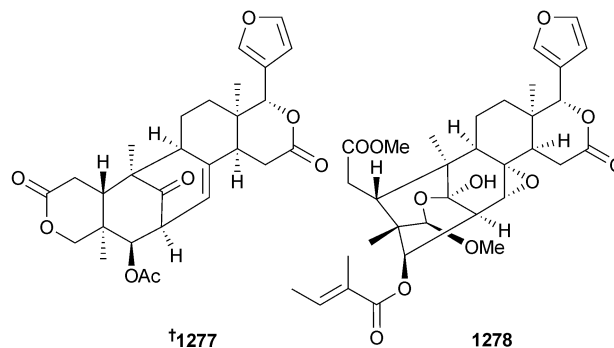
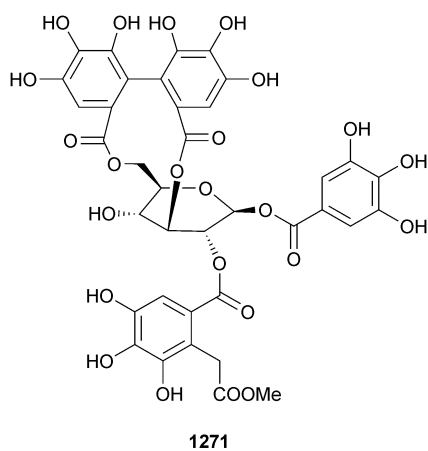
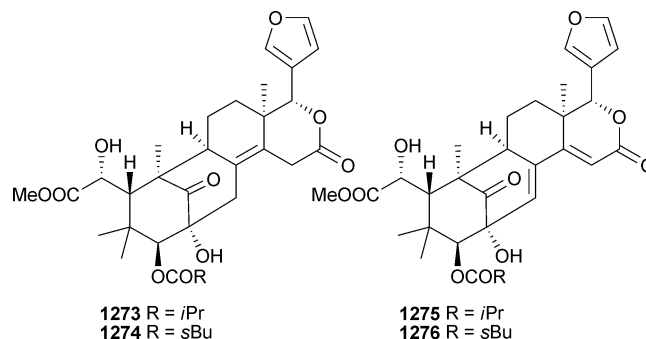
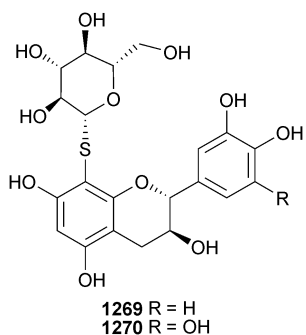


Investigation of the chemistry of the bark of *Aegiceras corniculatum* (Nizamapatnam coast, India) yielded corniculatolide macrolides **1265–1268**.¹⁰²⁴



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.

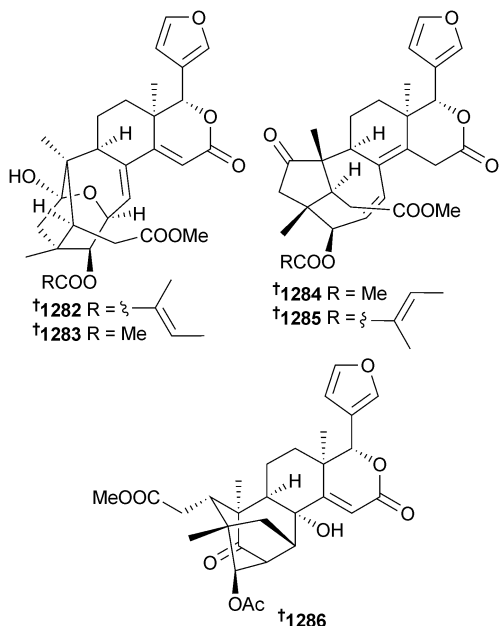




Extracts of seeds of *Xylocarpus moluccensis* collected at two sites (Godavari and Krishna estuaries, Andhra Pradesh, India) yielded new limonoids **1273–1280** in addition to several known congeners¹⁰²⁶ including **1281**.¹⁰²⁷ Absolute configuration was assigned to both **1277** and **1281**. The known 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*) neuropeptide¹⁰³² as a biologically inactive starting point, substitution of aza- β -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 MarInLit¹⁰³⁴ identified all papers reporting new compounds published over that period, the year of publication and the author responsible (**Compounds**) as well as 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

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.

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



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 MarinLit¹⁰³⁴ 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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