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Marine natural products

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Covering: 2013. Previous review: *Nat. Prod. Rep.*, 2014, **31**, 160–258

This review covers the literature published in 2013 for marine natural products (MNPs), with 982 citations (644 for the period January to December 2013) 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 (1163 for 2013), together with the relevant biological activities, source organisms and country of origin. Reviews, 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 literature for 2013 and describes 1163 new compounds from 379 articles, a 6% decrease in the number of compounds reported in 2012.¹ 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 2011 has appeared,² as well as the highlights of compounds reported in 2012.³ Marine pharmacology papers for 2009–2011 have been collated,⁴ two reviews summarise natural products (NPs), including from marine sources, as drug leads,^{5,6} while another paper describes recent advances in marine drug research.⁷ A synopsis of the project BAMMBO for the sustainable production of biologically active molecules of marine based origin has appeared.⁸ General classes of compounds have been reviewed in papers on marine triterpenoids as anticancer

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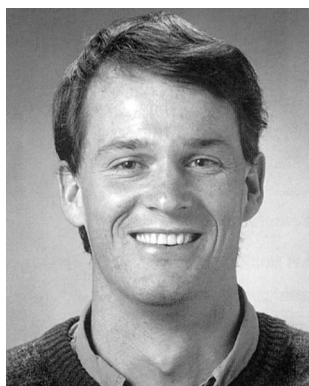
agents,⁹ alkaloids from corals,¹⁰ meroterpenes from marine invertebrates,¹¹ 'head-to-sidechain' cyclodepsipeptides,¹² marine alkaloids containing an 1-(indol-3-yl)ethane-1,2-diamine fragment,¹³ tetrahydrofuran-containing macrolides,¹⁴

terpenes from *Sarcophyton* sp.,^{15,16} antimicrobial peptides from proteobacteria,¹⁷ diarrhetic shellfish toxins in Washington State,¹⁸ di- and sesquiterpenes from *Cystosiera* sp.,¹⁹ and halogenated compounds from Rhodomelaceae.²⁰ Some general reviews on various classes of compounds include data on marine compounds – anticancer steroids,²¹ sesterterpenoids,²² NPs containing a nitrogen–nitrogen bond,²³ and muscarine, imidazole, oxazole and thiazole alkaloids.²⁴ Reviews on various aspects of specific compounds include lamellarins N and L,²⁵ STX,²⁶ lyngbouillose and related macrolides,²⁷ thiomarinol and related dithiopyrrolone compounds,²⁸ okadaic acid,²⁹ and the marinopyrroles.³⁰ There have been many reviews covering a variety of groups of marine organisms, including bioprospecting of plankton,³¹ actinomycetes,^{32,33} S. China Sea opisthobranch molluscs,³⁴ actinobacteria,^{35,36} filamentous marine cyanobacteria,³⁷ and microbes in general.^{38–40} Reviews on specific organisms include Australian *Dicathais orbita*,⁴¹ metabolites from *Osmundaria* spp.,⁴² *Aspergillus* spp.,⁴³ and *Bacillus* spp.⁴⁴ A focus on bioactivities is made in reviews on anti-inflammatory compounds,^{45,46} trypanocidal products,⁴⁷ neuroprotective compounds,⁴⁸ antitumour/anticancer



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 prod-

ucts, the application of NMR techniques to structural problems, and the construction of databases to facilitate natural product investigations.



Brent Copp received his BSc (Hons) and PhD degrees from the University of Canterbury, where he studied the isolation, structure elucidation and structure–activity relationships of biologically active marine natural products under the guidance of Professors Blunt and Munro. He undertook postdoctoral research with Jon Clardy at Cornell and Chris Ireland at the University of Utah. 1992–93 was spent

working in industry as an isolation chemist with Xenova Plc, before returning to New Zealand to take a lectureship at the University of Auckland, where he is currently an Associate Professor.



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 prod-

ucts 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.



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.



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.



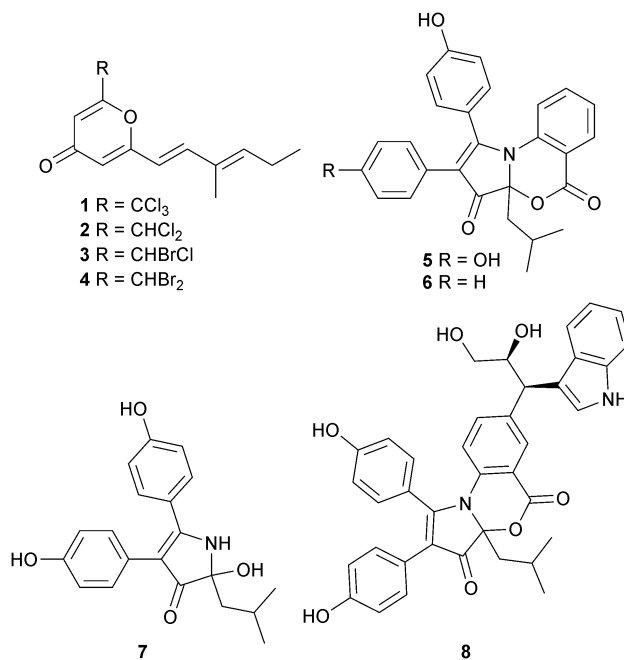
agents,^{49–52} kinase inhibitors,⁵³ anti-*Herpes simplex* agents,⁵⁴ anti-HIV actives,⁵⁵ angiogenesis inhibitors,⁵⁶ cardioprotective peptides,⁵⁷ antithrombotic peptides,⁵⁸ antimicrobial peptides,⁵⁹ therapeutics for Gram-negative sepsis,⁶⁰ and bioactives from Antarctic and Arctic organisms.⁶¹ The chemical ecology of plankton⁶² and the possible ecological roles of cyanotoxins⁶³ have been reviewed. The eighth in a companion series providing an overview of synthetic aspects of MNPs has appeared with coverage of publications from 2010.⁶⁴ Further reviews of syntheses of specific compounds include marine alkyl purines,⁶⁵ tetrodotoxin,⁶⁶ (+)-spirastrellolide A methyl ester,⁶⁷ and 'upenamide, the structure of which still remains elusive.⁶⁸ A number of papers which, while not necessarily being reviews, are useful to reference here as they describe advances in techniques or approaches to discovery that are relevant to MNP studies. These include papers on novel extraction technologies for bioactives from marine algae,⁶⁹ dereplication of marine actinomycetes by LCHRMS profiling,⁷⁰ X-ray analysis on the nanogram to microgram scale using porous complexes,^{71,72} rapid screening of bioactive compounds by integrating 5-channel parallel chromatography coupled with on-line mass spectrometry and microplate based assays,⁷³ molecular networking as a dereplication strategy,⁷⁴ NMR-based metabolomic analysis of macroalgae,⁷⁵ biogeography and biodiscovery hotspots of macroalgal compounds,⁷⁶ and coral aquaculture to support drug discovery.⁷⁷ The MarinLit database has been updated and was used as the literature source for the preparation of this present review. This database has now been transferred to the Royal Society of Chemistry from where it is available as a web-accessible version.⁷⁸

3 Marine microorganisms and phytoplankton

MNP research effort is being increasingly directed towards marine microorganisms with 491 new compounds reported in 2013, an increase of 14% from 2012 (see 15 Conclusion). Unless otherwise stated, compounds described in this section were obtained from cultures of the named microorganisms.

3.1 Marine-sourced bacteria (excluding from mangroves)

The chlorinated pyrones halomadurone A **1** and B **2** were isolated from *Actinomadura* sp. (ascidian *Ecteinascidia turbinata*, Florida Keys, U.S.A.) and with increased concentration of potassium bromide in the growth media produced the brominated analogues halomadurone C **3** and D **4**. The halomadurones A–D activated the nuclear factor E2-related antioxidant response element, an indication of potential for treatment of neurodegenerative diseases.⁷⁹ Discoipyrroles A–D **5–8** are alkaloids isolated from *Bacillus hunanensis* (sediment, Galveston Bay, Texas, U.S.A.) that inhibit the signaling pathway of the tyrosine kinase, discoidin domain receptor 2. They were each obtained as racemates and feeding experiments with several substituted benzaldehyde precursors indicated formation through a nonenzymic process, which led to a one-pot total synthesis of discoipyrrole A **5**.⁸⁰



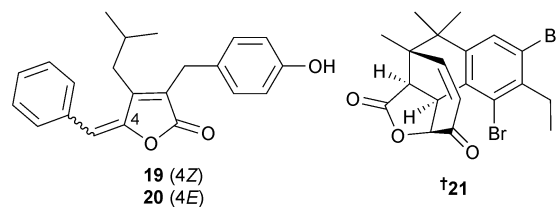
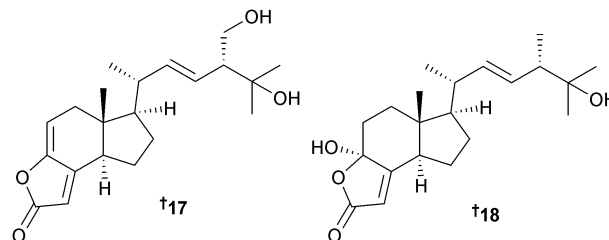
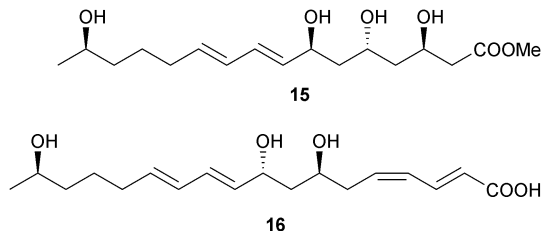
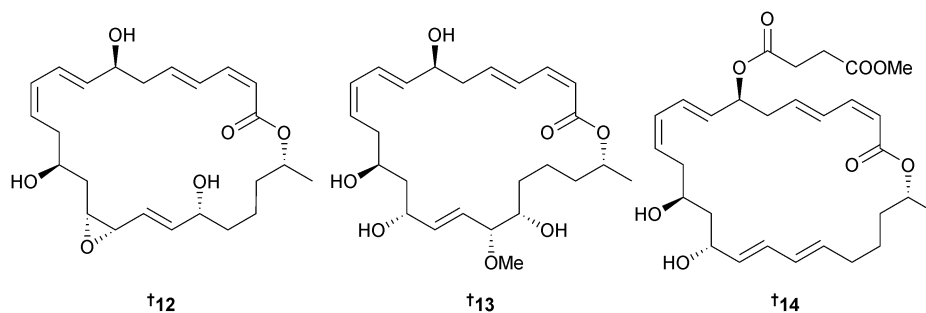
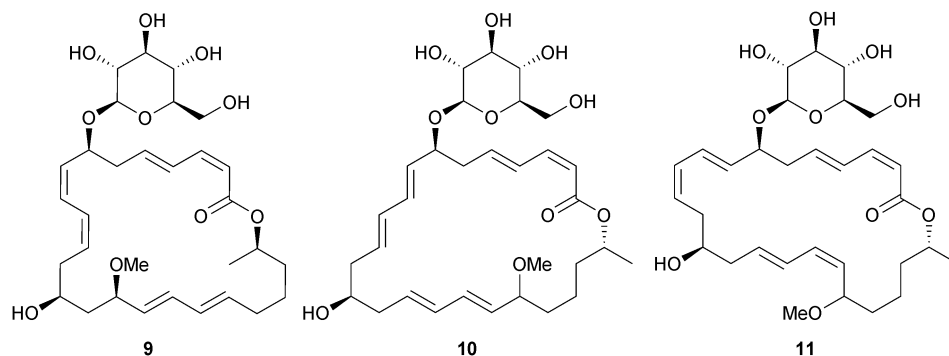
Three glycosylated methoxy-macrolactins **9–11** were isolated from *Bacillus subtilis* (*B. subtilis*) (sediment, Gageocho, S. Korea) and all displayed inhibition of Gram-positive and Gram-negative bacterial strains, in addition to modest antifungal activity.⁸¹ A strain of *B. subtilis* (sponge *Haliclona simulans*, Gurraig Sound, Galway, Ireland) yielded subtilomycin, a partially characterised 32-amino acid compound that was partly responsible for the observed broad spectrum antimicrobial activity of the bacterium.⁸²

Bacillus sp. (sediment, Ieodo Reef, S. Korea)⁸³ produced the 24-membered macrolactones macrolactin X–Z **12–14** and the unsaturated fatty acids lineodolide A **15** and B **16**, all with modest antibacterial and antifungal activity.⁸⁴

Two separate isolates of the myxobacterium *Enhygromyxa salina* yielded antibiotics. Salimyoxins A **17** and B **18** were obtained from one strain (sediment, Santa Barbara, California, U.S.A.) whilst the geometric isomers enhygrolide A **19** and B **20** were isolated from another strain (sediment, Prerow, Germany). Salimyoxins A **17** and B **18** are structurally very similar to demethylcisterol obtained from the sponge *Homaxinella* sp.,⁸⁵ whilst enhygrolides A **19** and B **20** are structurally related to the nostoclates, first obtained from a *Nostoc* species of cyanobacterium.⁸⁶ Salimyoxin B **18** and enhygrolide A **19** were moderate growth inhibitors of the Gram-positive bacterium *Arthrobacter cristallopoietes*.⁸⁷ The obligatory marine myxobacterium *Enhygromyxa salina* (sediment, Prerow Is., Germany) was the source of the tetracyclic salimabromide **21** which was a moderate inhibitor of *Arthrobacter cristallopoietes*.⁸⁸

Kocuria palustris (sponge *Xestospongia muta*, Key Largo, Florida)⁸⁹ produced a thiazolyl peptide kocurin **22** with antibacterial activity including strong inhibition of methicillin-resistant *Staphylococcus aureus* (MRSA).⁹⁰ A molecule with the same planar structure as **22** was previously isolated from *Kocuria* sp. in Southeast Spain⁹¹ as baringolin and is also

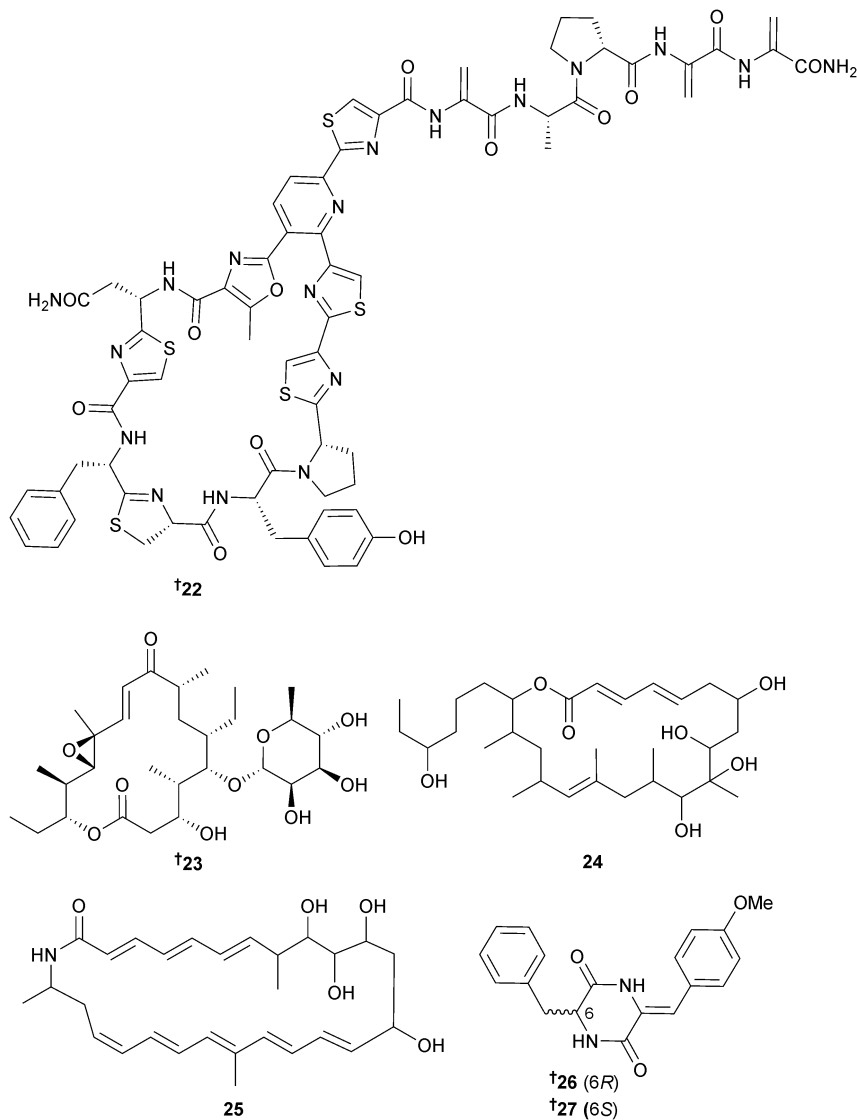




believed to be a correction of the structure previously assigned to PM181104,⁹² (also obtained from a *Kocuria* sp.) mentioned in a patent.⁹⁰ Kocurin, also produced by *Kocuria marina* and a *Micrococcus* sp. (Florida Keys),⁹³ has been synthesised by a convergent strategy in good overall yield.⁹⁴ The macrolide juvenimicin C 23 was obtained from *Micromonospora* sp. (sediment, Palau) and enhanced the activity of the enzymes quinone reductase I, glutathione reductase and glutathione peroxidase, suggesting potential as a cancer chemopreventive agent.⁹⁵ Levantilide C 24 is a 20-membered macrolide isolated from a *Micromonospora* strain (Golfo Corcovado, Chiloe Is., Chile) with moderate antiproliferative activity against human tumour cancer cell lines (HTCLs).⁹⁶ Two strains of *Micromonospora* (sediment, North Carolina coast, U.S.A.) yielded the polyene macrolactam micro-monolactam 25, a constitutional isomer of salinilactam A⁹⁷ but with a different polyene pattern and a (Z)-double bond,

in contrast to the all (E)-structure of salinilactam A. Genome sequencing of one of the strains determined that 25 was derived from eleven polyketide units and a modified glutamate starter unit.⁹⁸ *Nocardioopsis alba* (deep-sea sediment, Indian Ocean) produced several diketopiperazines, including the new C-6 epimers nocazine D 26 and E 27 and the known synthetic compounds (S,Z)-3-benzylidene-6-methylpiperazine-2,5-dione and (S,Z)-3-benzylidene-6-isopropylpiperazine-2,5-dione,⁹⁹ both isolated for the first time



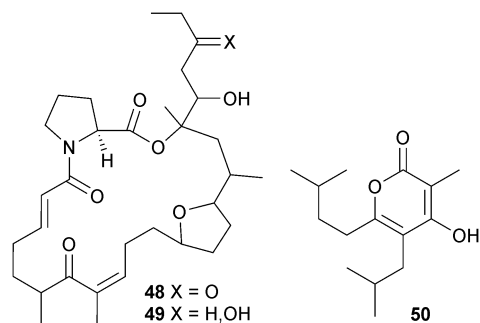
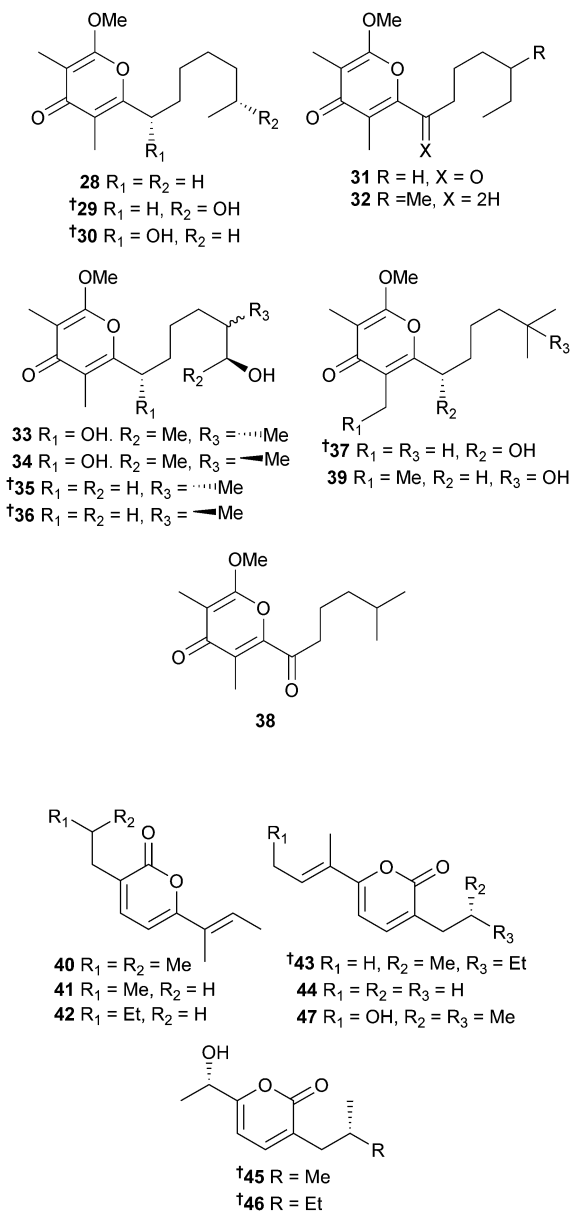


as NPs. Methoxyneihumicin was also isolated. This is a structure that had been previously reported in a conference poster¹⁰⁰ but not in the chemical literature. Both methoxyneihumicin and the known bacterial metabolite XR334 (ref. 101) (first time marine isolate) were modestly active against HTCLs.¹⁰²

Three different groups of researchers have isolated metabolites from *Nocardiopsis* species and all have named them nocapyrones. To avoid confusion they are presented here in order of publication. Firstly, symbiotic *Nocardiopsis alba* (cone snail *Conus rolandi*, Mactan Is., Philippines) produced the γ -pyrones nocapyrone H–Q 28–39. Of these, nocapyrone N 35/36 was isolated as a mixture of enantiomers in a 10 : 1 ratio and nocapyrone M 33/34 occurred as an inseparable mixture of diastereoisomers. Both nocapyrone H 28 and the co-isolated nocapyrone B, previously obtained from a sponge-associated *Nocardiopsis* strain,¹⁰³ modulated

nerve cell depolarisation and were active against a wide range of dorsal root ganglion neuronal cell types. Nocapyrones B and H were moderately cytotoxic to cancer cell lines.¹⁰⁴ Secondly, three 3,6-disubstituted α -pyrones 40–42 were isolated from *Nocardiopsis* sp. (sediment, Ulleung Basin, Eastern sea, Korea) and named nocapyrones H–J. “Nocapyrone H” 40 inhibited pro-inflammatory factors such as nitric oxide (NO), prostaglandin E2 (PGE2) and interleukin-1 β (IL-1 β) (potential neuroprotective effects).¹⁰⁵ Lastly, *Nocardiopsis dassonvillei* subsp. *dassonvillei* (sediment, Lianyun gang, China) also produced α -pyrones named “nocapyrones H–N”. Of these “nocapyrone H” had the same structure as 40, “nocapyrone K” was identical to 41, while the balance, 43–47, were unique. “Nocapyrone I” 43 and “M” 46 displayed inhibition of quorum sensing (QS) controlled gene expression in *Chromobacterium violaceum* CV026 and *Pseudomonas aeruginosa* QSI-*lasI* biosensors.¹⁰⁶





The cyclic hexapeptides nocardiamide A **51** and B **52** were isolated from *Nocardioopsis* sp. (La Jolla Canyon, San Diego, California, U.S.A.) and then synthesised *via* solid-phase peptide synthetic methods.¹¹¹ A microorganism, nominally *Paenibacillus profundus* sp. nov., (sediment, Sea of Japan) yielded a linear glyceryl acid derived heptapeptide **53** with strong antibacterial inhibition and moderate inhibition of SK-MEL-28 cells,¹¹² while a species of *Photobacterium*, closely related to *P. halotolerans* (mussel, Solomon Is., Pacific Ocean), was the source of the cyclodepsipeptides ngercheumicin F-I **54–57** that inhibited quorum sensing in *Staphylococcus aureus*.¹¹³

A *Pseudoalteromonas* sp. (oil-contaminated surface water, Gulf of Mexico after the Deepwater Horizon oil spill) yielded the siderophores lystabactin A–C **58–60** which contained the unusual nonproteinogenic amino acid 4,8-diamino-3-hydroxyoctanoic acid (LySta). Since lystabactin C is 29-methoxy lystabactin A, it may have been an artefact of isolation.¹¹⁴

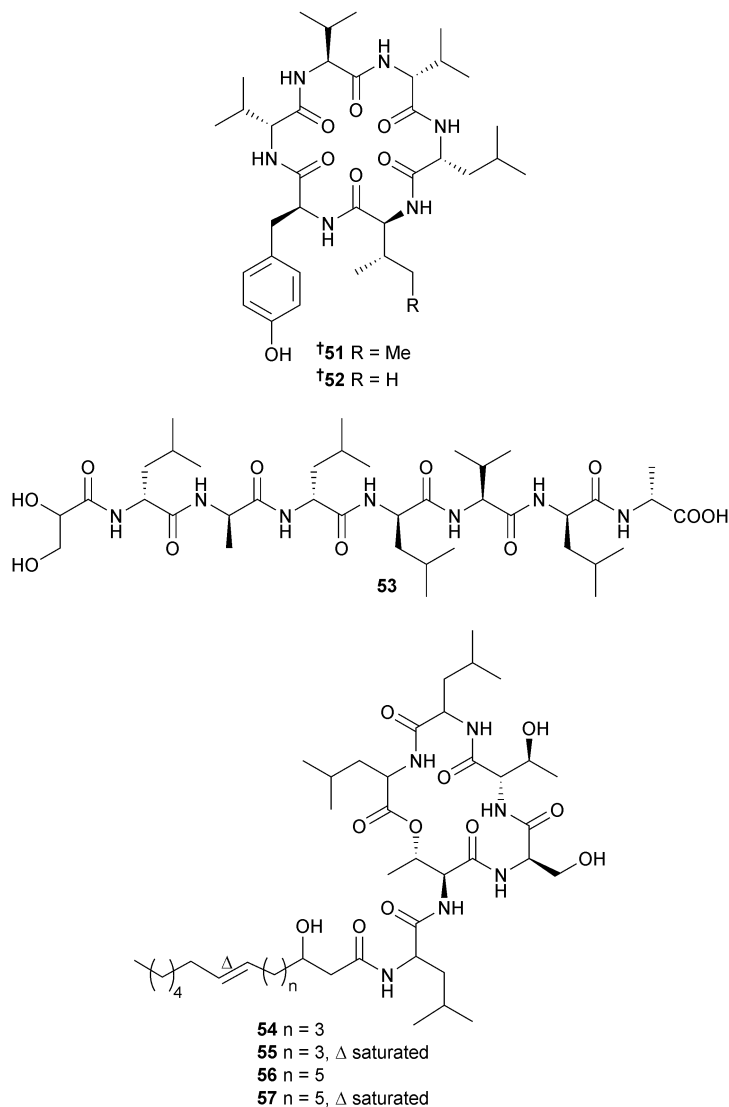
Cyanosporasides A and B are chloro- and cyano-cyclopenta[*a*] indene glycosides originally isolated from a Palauan *Salinispora pacifica* strain,¹¹⁵ while cyanosporasides C–E **61–63** came from investigation of another *S. pacifica* strain (sediment, Palau) and cyanosporasides D–F **62–64** from a *Streptomyces* sp. (sediment, Bahamas). Cloning, sequencing, and mutagenesis of cyanosporaside biosynthetic gene clusters from both bacteria demonstrated that the cyanosporasides are enediyne polyketides and a two-gene operon was identified which was implicated in the nitrile functionalisation of these metabolites.¹¹⁶ Further investigation of the strain of *S. pacifica* (USDA Agricultural Research Service) that produced lomaiviticins C–E¹¹⁷ resulted in the isolation of (–)-homoseongomycin **65**. Synthesis of an isotopically-labelled derivative, homoseongomycin-*d*₅, clarified aspects of the biosynthetic pathway.¹¹⁸

The alkaloid **66** was obtained from *Serinicoccus profundus* sp. nov. (deep-sea sediment, Indian Ocean) (weak activity against *Staphylococcus aureus* (*S. aureus*))¹¹⁹ and *Staphylococcus* sp. (red alga, *Corallina officinalis*, Nagasaki Shitsu Coast, Japan) provided the diketopiperazine derivatives staphyloamide A **67** and B **68**.¹²⁰ *Streptomyces antibioticus* (sediment, source not given) yielded the indanomycin-related antibiotics **69–71** as moderate growth inhibitors of *S. aureus*.¹²¹

The alkaloids nitrosporeusine A **72** and B **73** with an unprecedented skeleton (benzenecarbothiocyclopenta[*c*] pyrrole-1,3-dione) were isolated from *S. nitrosporeus* (sediment, Arctic Chukchi Sea). Both nitrosporeusines inhibited the H1N1 virus in infected MDCK cells.¹²² Some sesquiterpenoid

Very clearly the naming of these metabolites needs revision. Saline culture of *Nocardioopsis* sp. (sediment, S. Molle Is., Queensland, Australia) previously yielded nocardioazines A and B¹⁰⁷ whilst non-saline culture of the same strain yielded nocardioopsins A and B.¹⁰⁸ Further investigation of the strain cultivated under non-saline conditions has resulted in the isolation of the prolanyl-macrolactam polyketides nocardioopsin C **48** and D **49** and the highly substituted α -pyrone polyketide, nocardiopyrone A **50**.¹⁰⁹ It should be noted that the name nocardiopyrone A has coincidentally been given to a metabolite isolated from a terrestrial species, *Nocardioopsis alkaliphila*,¹¹⁰ and that the same CAS number appears to have been given to both compounds in error on the Scifinder database, with the terrestrial compound structure showing as corresponding to that CAS number.





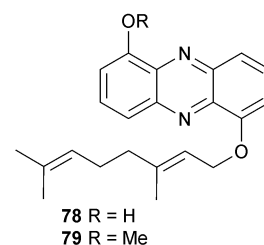
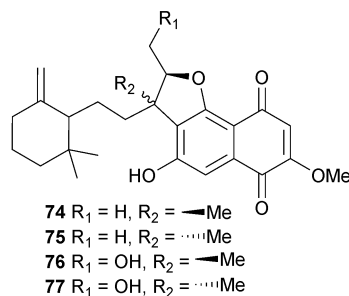
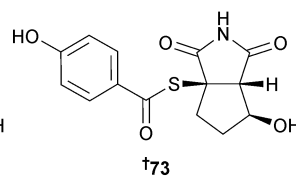
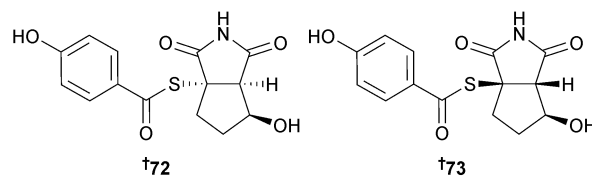
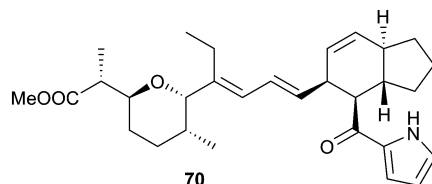
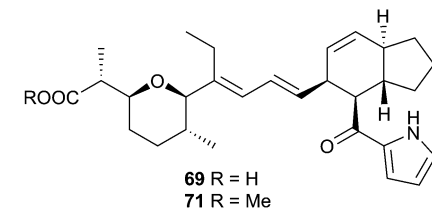
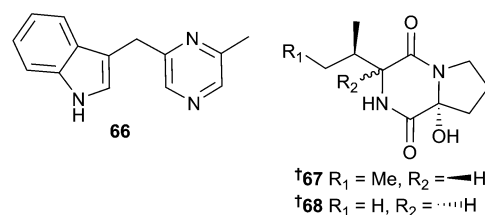
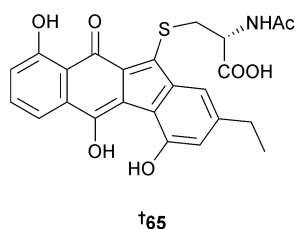
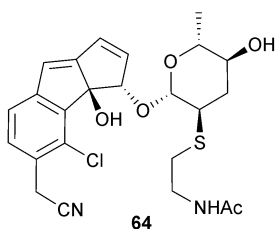
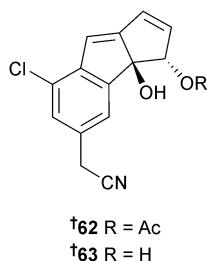
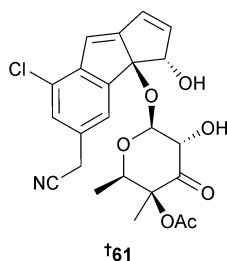
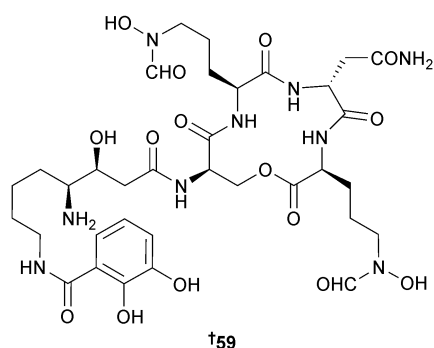
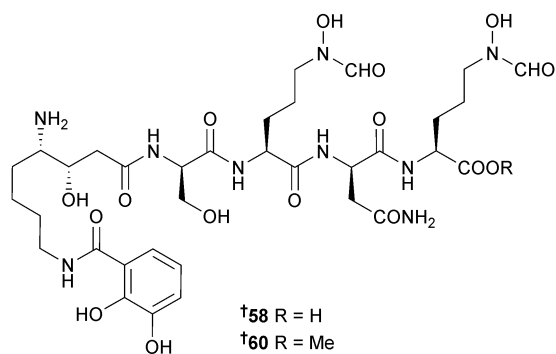
naphthoquinones marfuraquinocin A–D 74–77 and the geranylated phenazines phenaziterpene A 78 and B 79 were isolated from *S. niveus* (sediment, S. China Sea). Marfuraquinocins A 74 and C 76 were growth inhibitors of NCI–H460 cancer cells (moderate) whilst marfuraquinocins A, C and D 77 were moderate growth inhibitors of *S. aureus*, with marfuraquinocins C and D also inhibitors of methicillin-resistant *Staphylococcus epidermidis*.¹²³

Tetroazolemecins A 80 and B 81 are oxazole/thiazole derivatives obtained from *S. olivaceus* (deep-sea water, southwest Indian Ocean), both of which showed binding affinity for the metal ions Fe^{3+} , Cu^{2+} and Zn^{2+} .¹²⁴ *S. seoulensis* (shrimp gut *Penaeus orientalis*, Qingdao, China) yielded the neuraminidase inhibitors streptoseolactone 82, limazepine G 83 and a known synthetic compound^{125,126} isolated for the first time as an NP, and named limazepine H.¹²⁷ Endophytic *S. sundarbansensis* (brown alga *Fucus* sp., Bejaia, Algeria) provided the polyketide chromanone 84 (modest but selective activity against MRSA).¹²⁸

S. tateyamensis (sponge *Haliclona* sp., Tateyama City, Japan)¹²⁹ was the source of JBIR-107 85,¹³⁰ while the phenoxazine-based alkaloids venezueline A–E 86–90 and the aminophenols venezueline F 91 and G 92 were obtained from *S. venezuelae* (sediment, Guam) with the known analogues exfoliazone,¹³¹ chandrananimycin D¹³² and carboxyexfoliazone,¹³³ all previously obtained from terrestrial *Streptomyces* species but now first time marine isolates. Venezueline B 87 was moderately cytotoxic towards a panel of HTCLs.¹³⁴

Double mutation of a strain of *S. xiamenensis* (sediment, Eastern Pacific Ocean) led to production of two benzopyran derivatives xiamenmycin C 93 and D 94, which both inhibited proliferation of human lung fibroblasts (WI26),¹³⁵ and *Streptomyces* sp. (unidentified soft coral, Weizhou Is., Guangxi Province, China) was the source of the chlorinated polyketides strephchloritide A 95 and B 96 cytotoxic against MCF-7 cells (modest).¹³⁶ Chlorizidine A 97, comprised of a chlorinated 2,3-dihydropyrrolizine ring attached to an unprecedented chlorinated 5H-pyrrolo[2,1-a]isoindol-5-one, was isolated from a





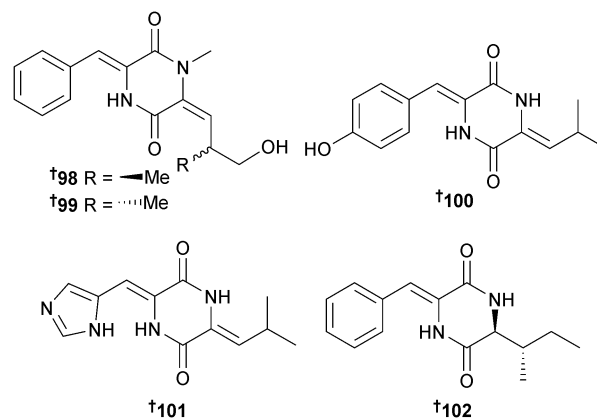
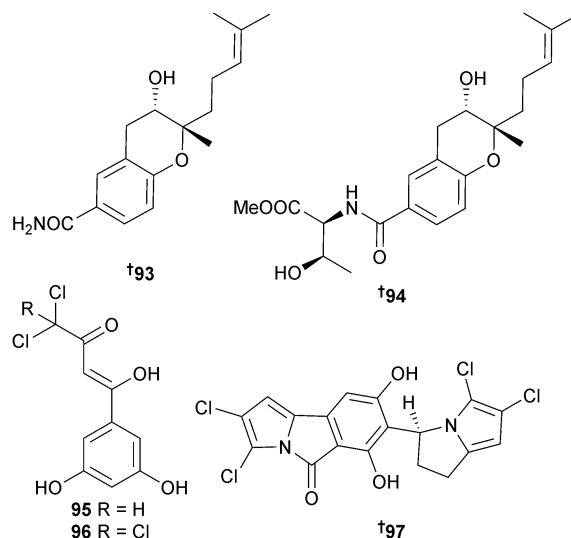
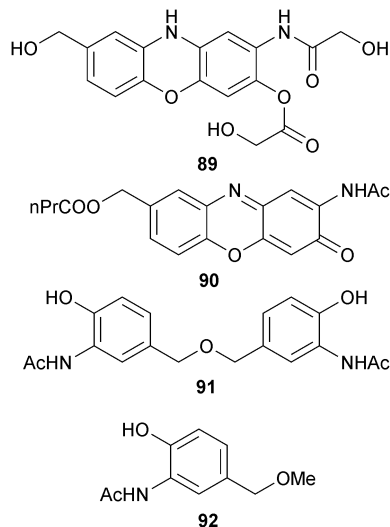
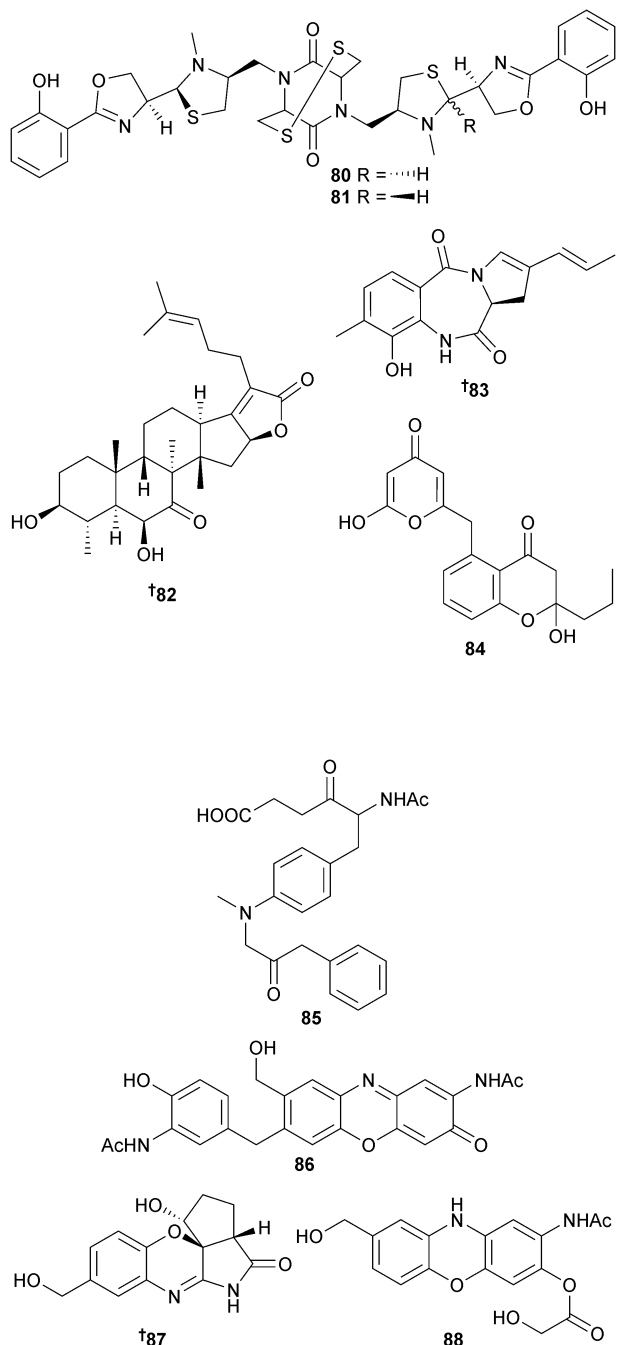
Streptomyces strain (sediment, San Clemente, California, U.S.A.) and was moderately cytotoxic to a panel of HTCLs.¹³⁷ The biosynthetic gene cluster of chlorizidine A **97** was identified and whole pathway heterologous expression and genetic manipulations were utilised to show that it is assembled by a polyketide synthase (PKS) that uniquely incorporates a fatty acid synthase-derived dichloropyrrolyl extender unit into the pyrroloisindolone enzymic product.¹³⁸

The diketopiperazine derivatives **98–102** were obtained from *Streptomyces* sp. (sediment, Huanghai Beach, Dalian, China)

and **100** displayed modest activity against the influenza A (H1N1) virus, whilst the co-isolated fungal metabolites (3Z,6S)-3-benzylidene-6-isobutylpiperazine-2,5-dione¹³⁹ and albomoursin¹⁴⁰ displayed potent inhibition of the virus and were first time marine isolates.¹⁴¹

Streptomyces sp. (sediment, S. China Sea) yielded the spirotetronate lobophorin G **103**, a potent inhibitor of both *Mycobacterium bovis* Bacillus Calmette-Guerin (BCG) and *B. subtilis* and a moderate inhibitor of *Mycobacterium tuberculosis* (*M. tuberculosis*).¹⁴² Sungsanpin **104** isolated from a *Streptomyces* sp. (deep-sea sediment, Jeju Is., S. Korea) is an example of a so-called lasso peptide, a ribosomally synthesised peptide of between 16 and 23 amino acids with an N-terminal eight- or nine-residue ring with a linear C-terminus threaded through the ring.¹⁴³ Sungsanpin inhibited A549 cells in a cell invasion assay.¹⁴⁴



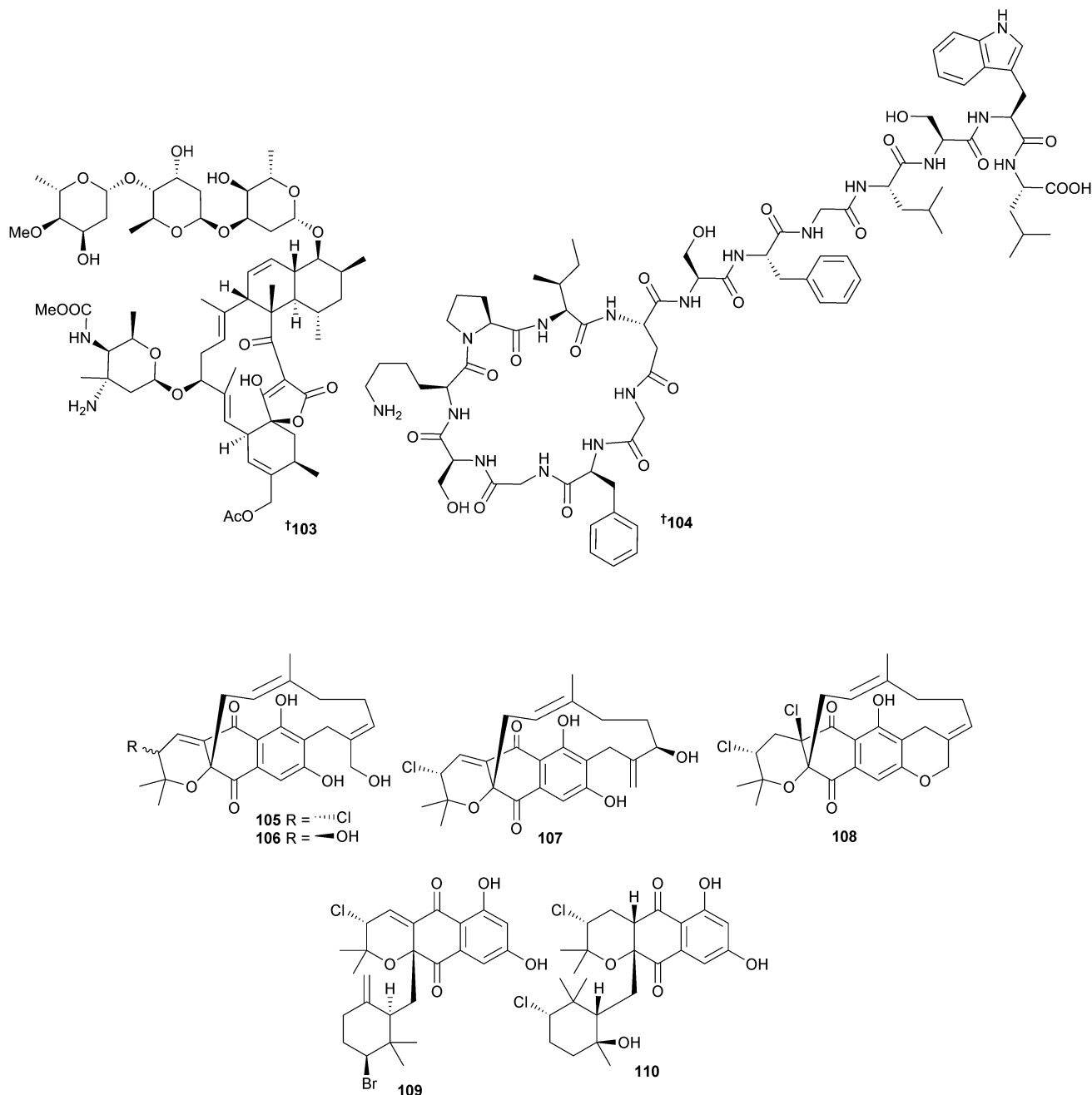


Investigation of two different *Streptomyces* strains identified six new napyradiomycin analogues. The *Streptomyces* strain CNQ-329 (sediment, San Diego, California, U.S.A.) produced napyradiomycins A–E **105–109**, while strain CNH-070 (sediment, San Elijo Lagoon, Encinitas, California, U.S.A.) produced napyradiomycin F **110**.

Four of the napyradiomycins A, D–F were cytotoxic (moderate) to HCT-116 cells whilst napyradiomycins A and B inhibited MRSA (moderate).

Also isolated were napyradiomycins B2–B4; B3 (ref. 145) and B4 (ref. 146) as first time marine isolates.¹⁴⁷ Three napyradiomycins, 4-dehydro-4a-dechloronapyradiomycin A1 **111**, 3-dechloro-3-bromonapyradiomycin A1 **112** and 3-chloro-6,8-



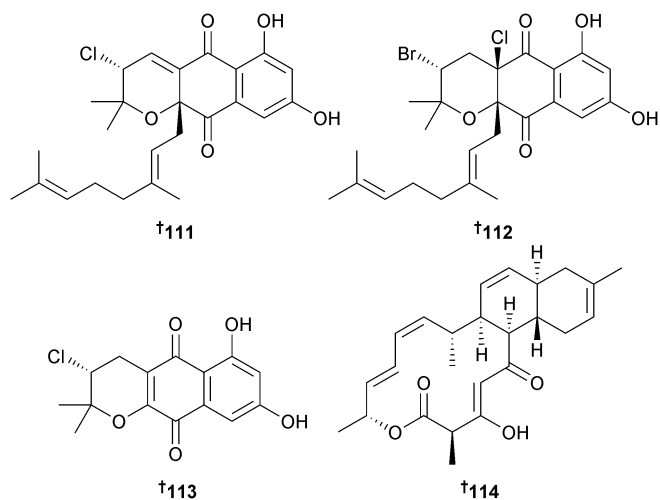


dihydroxy-8- α -lapachone **113** isolated from a *Streptomyces* species (sediment, Xieyang Is., Beihai, Guangxi Province, China) displayed moderate inhibition of several Gram-positive bacteria while 3-dechloro-3-bromonapyradiomycin A1 **112** was moderately active against several HTCLs.¹⁴⁸ A *Streptomyces* sp. (sediment, Santa Barbara, California, U.S.A.) yielded the antibiotic anthracimycin **114**, significantly active against *Bacillus anthracis*. Early *in vivo* results indicated that **114** also provided significant protection against MRSA cell lines. The planar structure of anthracimycin **114** may have been published in a

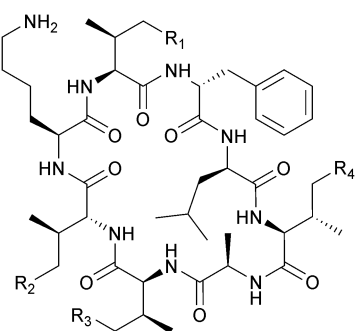
2011 patent¹⁴⁹ but insufficient detail was given to permit a full comparison.¹⁵⁰

Surugamides A–E **115–119**, cyclic octapeptides with four D-amino acid residues, were obtained from *Streptomyces* sp. (deep-sea sediment, Kinko Bay, Japan) and were modest inhibitors of the protease enzyme bovine cathepsin B.¹⁵¹ Three strains of *S. champavatii* (sediment, Gotland Deep and Kiel Bight, Baltic Sea and Urania Basin, Eastern Mediterranean) produced the octapeptide champacyclin **120**, an inhibitor of the bacterium *Erwinia amylovora*, the causative agent of fire blight disease in certain plants. Champacyclin **120** has the same

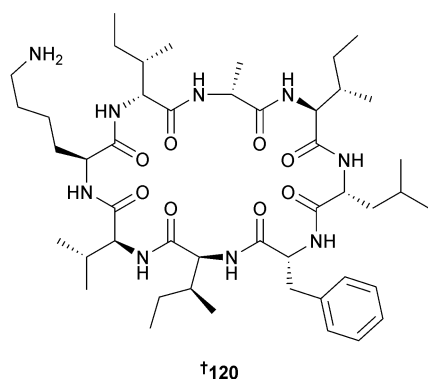




planar structure as surugamide A **115** but different configurations at two amino acid residues. Champacyclin was also prepared by solid-phase peptide synthesis.¹⁵²

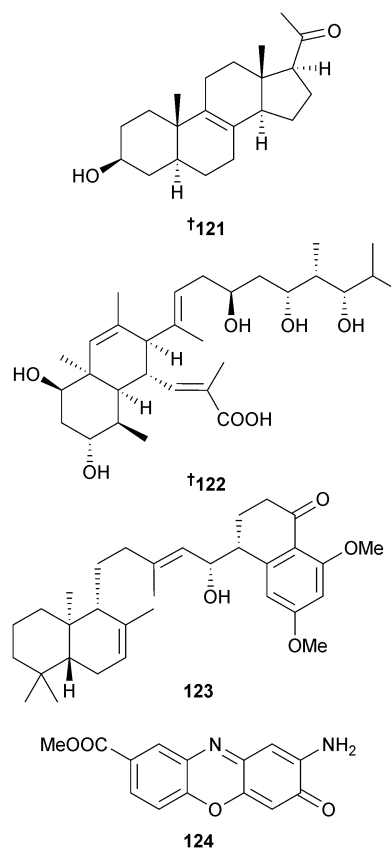


- †115 $R_1 = R_2 = R_3 = R_4 = \text{Me}$
 †116 $R_1 = R_3 = R_4 = \text{Me}, R_2 = \text{H}$
 †117 $R_1 = \text{H}, R_2 = R_3 = R_4 = \text{Me}$
 †118 $R_1 = R_2 = R_4 = \text{Me}, R_3 = \text{H}$
 †119 $R_1 = R_2 = R_3 = \text{Me}, R_4 = \text{H}$

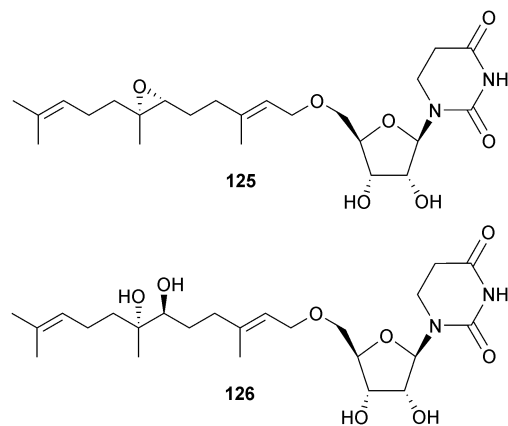


Streptomyces sp. (sediment, S. China Sea) yielded the pregnene steroid 3219A **121** with a rare $\Delta^{8,9}$ -double bond in the skeleton,¹⁵³ and the polyketide nahuic acid A **122** was obtained from a *Streptomyces* sp. (sediment, Padana Nahua, Papua New Guinea) as a selective SAM-competitive inhibitor

of the histone methyltransferase enzyme SETD8.¹⁵⁴ A meroterpenoid actinoranone **123** was isolated from a bacterium, likely a *Streptomyces* species (sediment, San Diego, California, U.S.A.)¹⁵⁵ as a moderate cytotoxin of HCT-116¹⁵⁶ and *Streptomyces* sp. (sediment, Marsa Matruh city, Egypt) was the source of maroxazinone **124**, moderately cytotoxic to several HTCLs.¹⁵⁷

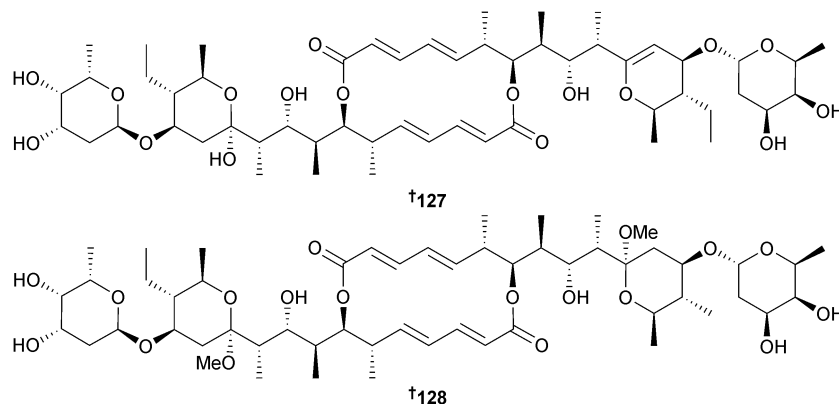


Farnesides A **125** and B **126**, linear sesquiterpenoids connected by ether linkages to a ribose dihydrouracil nucleoside, came from *Streptomyces* sp. (sediment, Nacula Is., Yasawa Is., Fiji) with farneside A modestly active against *Plasmodium falciparum* (*P. falciparum*).¹⁵⁸



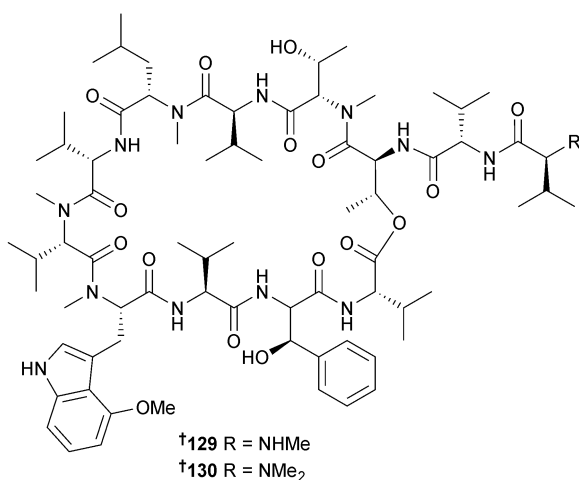
A PCR-based genetic screening experiment targeting the dTDP-glucose-4,6-dehydratase gene was used to identify that





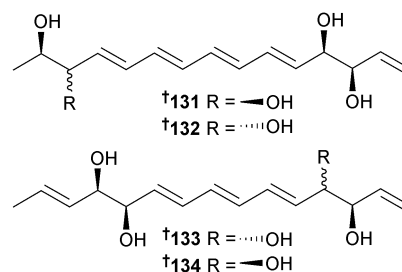
a *Streptomyces* sp. (sediment, Heishijiao Bay, Dalian, China) could potentially produce glycosidic antibiotics. Further investigation of this strain yielded the 6-deoxyhexose-containing antibiotics, 11',12'-dehydroelaiophylin **127** and 11,11'-*O*-dimethyl-14'-deethyl-14'-methylelaiophylin **128**, of which **127** was an inhibitor of MRSA and vancomycin-resistant *Enterococci* pathogens. The elaiophylin derivative **128** might be an artefact resulting from methanolysis during the isolation procedure.¹⁵⁹

The cyclic peptides ohmyungsamycin A **129** and B **130** were isolated from a *Streptomyces* sp. (sand, Shinyang Beach, Jeju Is., S. Korea). During determination of configurations a new method to determine the absolute configuration of *N,N*-dimethylvaline was developed which utilises phenylglycine methyl ester derivatisation coupled with chromatographic analysis and provides a general and convenient method for determination of the configurations of amino acids with fully substituted amine groups. Ohmyungsamycins A **129** and B **130** inhibited growth of several HTCLs and of Gram-positive and Gram-negative bacteria with ohmyungsamycin A **129** being much more potent than B **130**.¹⁶⁰



Separacenes A–D **131–134** are polyene polyols obtained from *Streptomyces* sp. (sediment, Jeju Is., S. Korea).

Separacenes A **131** and B **132** are C-3 epimers whilst separacenes C **133** and D **134** are C-12 epimers. Separacene A **131** was a modest inhibitor of *Candida albicans* (*C. albicans*) isocitrate lyase and two HTCLs.¹⁶¹

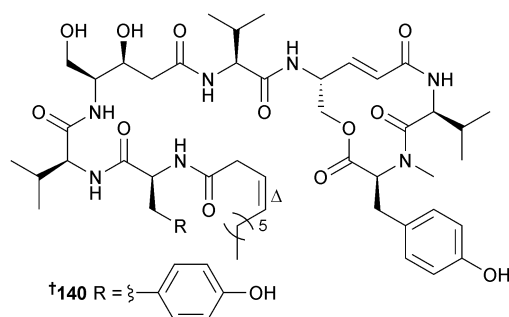
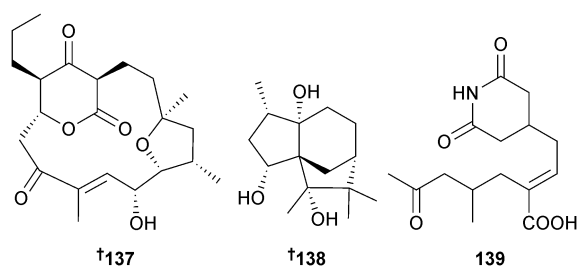
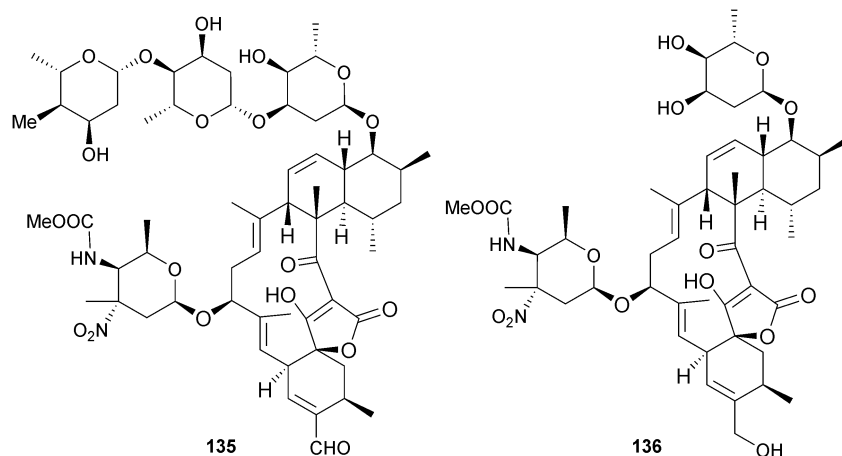


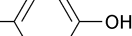
Streptomyces sp. (deep-sea sediment, S. China Sea) was the source of lobophorins H **135** and I **136** of which lobophorin H **135** exhibited significant inhibition of *B. subtilis* and moderate inhibition of *S. aureus* while lobophorin I **136** was much less active.¹⁶²

The polycyclic polyketide akaeolide **137** was isolated from a *Streptomyces* sp. (sediment, Miyazaki Harbour, Japan) as a modest cytotoxin to 3Y1 rat fibroblasts.¹⁶³ Strep-sesquiritriol **138**, a caged sesquiterpene isolated from *Streptomyces* sp. (sediment, Bay of Bengal, Indian Ocean), was a moderate inhibitor of lipopolysaccharide-induced TNF α production in RAW264.7 macrophages,¹⁶⁴ while cycloheximide acid A **139** was obtained from *Streptomyces* sp. (seawater, E. China Sea, Wenzhou, Zhejiang Province, China).¹⁶⁵

The immunosuppressant cyclic lipopeptides thalassospiramides A and B were originally obtained from the α -proteobacterium *Thalassospira* sp.¹⁶⁶ Reinvestigation of the original producer, a second strain of *Thalassospira* (source not given), *Tistrella mobilis* (Red Sea¹⁶⁷) and *Tistrella bauzanensis* (Pacific Ocean¹⁶⁷) led to the isolation of fourteen analogues thalassospiramides A1–A5 **140–144**, C **145** and C1 **146**, E **147** and E1 **148**, B1 **149** and B2 **150**, D **151** and D1 **152** and thalassospiramide F **153** that have been subdivided into six structural classes with variations in the length and composition of the acyl peptide side chain. The planar





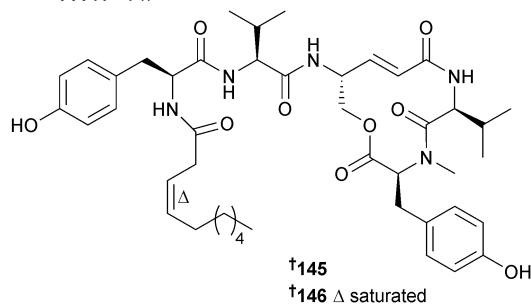
†140 R = ξ -

†141 R = OH, Δ saturated

†142 R = ξ -, Δ saturated

†143 R = *i*-Pr

†144 R = Ph



†145

†146 Δ saturated

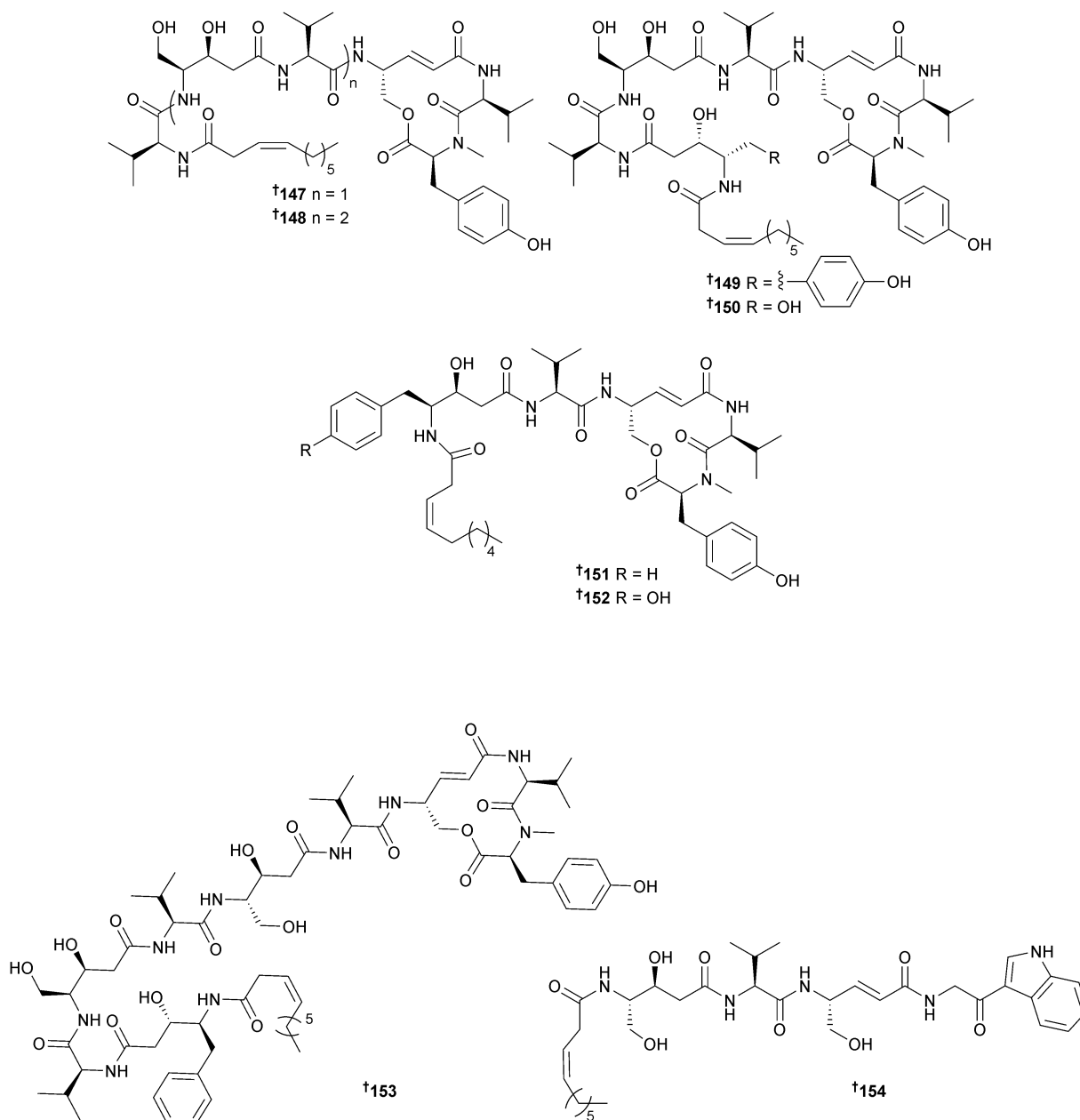
structures of **149** and **152** were described in a patent as metabolites of another α -proteobacterium, *Oceanospirillum* sp.¹⁶⁸ and potent inhibitors of the cysteine protease calpain 1. In the current study selected thalassospiramides (A, A1, B, C, D1 and E1) were tested and all displayed potent activity against calpain 1. Biosynthetic gene clusters for all four bacterial strains were characterised revealing some atypical NRPS biochemical features such as intrasynthetase *trans* A domain activation, module skipping and multimodule interaction which likely yield the structural diversity.¹⁶⁹ *Thalassospira* sp. (brown alga *Rosenvingea* sp., Bahamas) yielded a further member of the thalassospiramide family of peptides, thalassospiramide G **154**. The co-isolated thalassospiramides A¹⁶⁶ and D¹⁶⁹ were moderate inhibitors of NO production in lipopolysaccharide (LPS)-stimulated mouse macrophage RAW 264.7 cells.¹⁷⁰

The 18-membered macrolide macplocimine A **155** was obtained from the filamentous sulfur bacterium *Thioploca* sp. (benthic microbial mat, Chile).¹⁷¹ *Verrucosipora* sp. (deep-sea sediment, S. China Sea) was the source of three further abyssomicin polyketides abyssomicin J–L **156–158**. Abyssomicin C¹⁷² was also isolated and converted to abyssomicin J **156**. *In vitro* and cell-based analytical studies were then used to show that abyssomicin J **156** can act as a prodrug which, upon oxidative

activation, will be selectively transformed to *atrop*-abyssomicin C,¹⁷³ an anti-TB antibiotic.¹⁷⁴

Heronamide A, a polyketide macrolactam originally obtained from an Australian, sediment-derived *Streptomyces* sp.,¹⁷⁵ was reisolated from a *Streptomyces* sp. (sediment, Uranoichi Bay, Kochi Prefecture, Japan). Detailed NMR analysis of heronamide A and derivatives resulted in configurational reassignment of heronamide A to **159** and the suggestion that





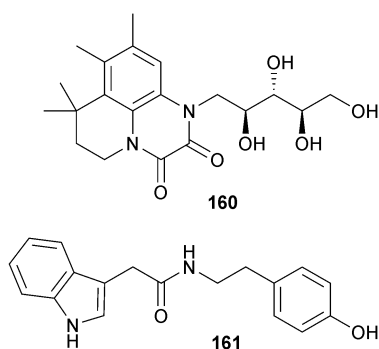
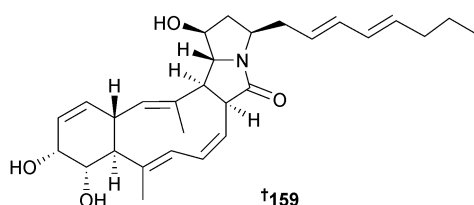
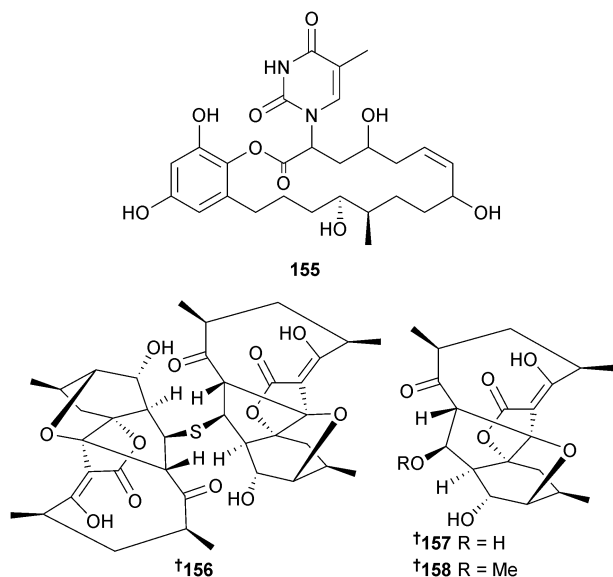
the configurations of heronamides **B**¹⁷⁵ and **C**¹⁷⁵ should be reinvestigated.¹⁷⁶

The configuration of the α -methylserine residue in the tetrapeptides JBIR-34 and JBIR-35 and in the trichostatin analogue JBIR-111, originally obtained from a sponge-derived *Streptomyces* sp.^{177,178} have been corrected from (*R*) to (*S*).^{179,180} *Tenacibaculum mesophilum* (unidentified sponge, Republic of Palau) yielded a siderophore bisucaberin **B**. This is an open form of the known macrocyclic dimer bisucaberin^{181,182} that has been reported as a degradation product of desferrioxamine **B**¹⁸³ but not as a product of *de novo* biosynthesis.¹⁸⁴

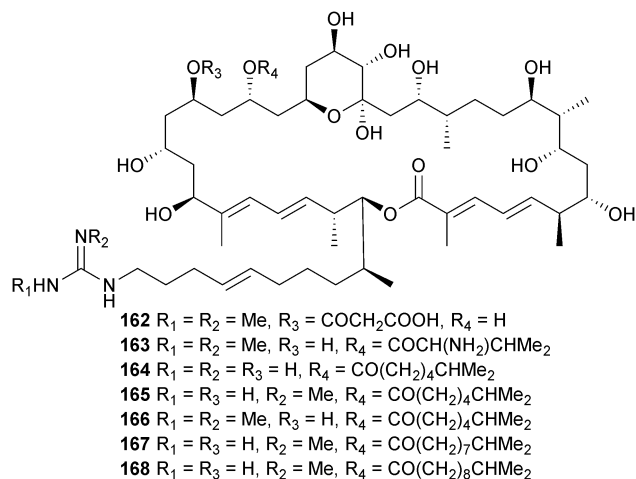
3.2 Bacteria from mangroves

Bacillus hunanensis (sediment, Trinity Bay, Galveston Texas, U.S.A.) yielded hunanamycin **A** **160**, the first NP with a pyrido [1,2,3-*de*]quinoxaline-2,3-dione core, which also displayed modest inhibition of *Salmonella enterica*.¹⁸⁵ Hunanamycin **A** was subsequently synthesised *via* a simple and scalable method from 6,7-dimethyl-1,4-dihydroquinoxaline-2,3-dione.¹⁸⁶ An indole alkaloid **161** was obtained from *Pantoea agglomerans* (mangrove *Ceriops tagal*, Zhanjiang, Guangdong, China) along with two phenylethylamine derivatives, 3-(*p*-hydroxy)benzoyl indole¹⁸⁷ and 1,2-di(1*H*-indol-3-yl)ethane,¹⁸⁸ both known synthetic compounds but now isolated for the first time as MNPs.¹⁸⁹

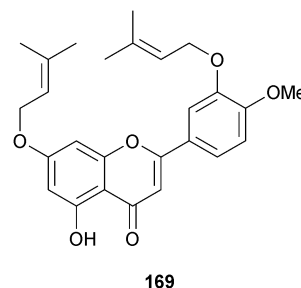




Streptomyces sp. (mangrove rhizosphere soil *Heritiera globosa*, Wenchang, China)¹⁹⁰ was the source of a series of azalomycin F analogues **162–168** which were all broad-spectrum antimicrobials and inhibitors of HCT-116 cells.¹⁹¹ The di-*O*-prenylated flavone **169** was isolated from an endophytic *Streptomyces* sp. (mangrove root *Myoporum bontoides*, Leizhou Peninsula, Guangdong Province, China) and was a moderate inhibitor of the plant pathogenic fungi, *Colletotrichum musae*, *Gibberella zeae* and *Penicillium citrinum*.¹⁹²

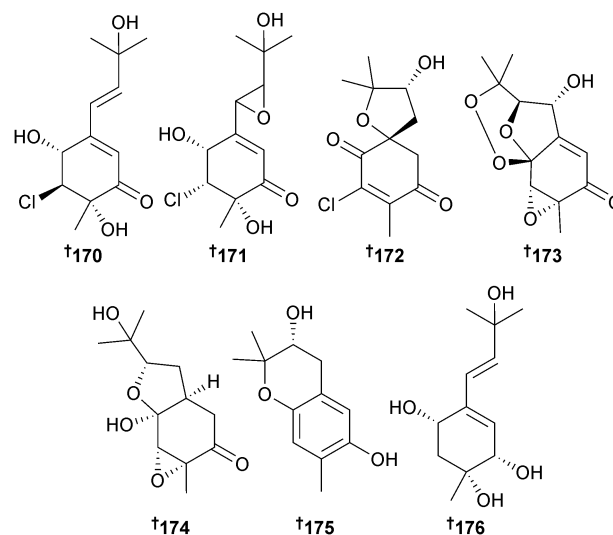


- 162** $R_1 = R_2 = \text{Me}$, $R_3 = \text{COCH}_2\text{COOH}$, $R_4 = \text{H}$
163 $R_1 = R_2 = \text{Me}$, $R_3 = \text{H}$, $R_4 = \text{COCH}(\text{NH}_2)\text{CHMe}_2$
164 $R_1 = R_2 = R_3 = \text{H}$, $R_4 = \text{CO}(\text{CH}_2)_4\text{CHMe}_2$
165 $R_1 = R_3 = \text{H}$, $R_2 = \text{Me}$, $R_4 = \text{CO}(\text{CH}_2)_4\text{CHMe}_2$
166 $R_1 = R_2 = \text{Me}$, $R_3 = \text{H}$, $R_4 = \text{CO}(\text{CH}_2)_4\text{CHMe}_2$
167 $R_1 = R_3 = \text{H}$, $R_2 = \text{Me}$, $R_4 = \text{CO}(\text{CH}_2)_7\text{CHMe}_2$
168 $R_1 = R_3 = \text{H}$, $R_2 = \text{Me}$, $R_4 = \text{CO}(\text{CH}_2)_8\text{CHMe}_2$



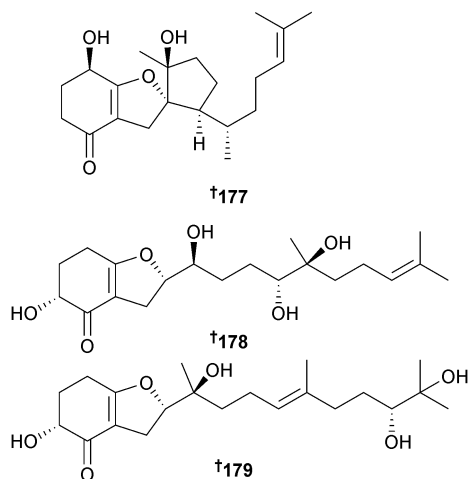
3.3 Marine-sourced fungi (excluding from mangroves)

Several acremine metabolites, 5-chloroacreminine **A 170**, 5-chloroacreminine **H 171** and acremines **O–R 172–175**, together with the known terrestrial fungal metabolite acreminine **F**,¹⁹³ were isolated from *Acremonium persicinum* (sponge *Anomoianthella rubra*, Gneering Reef, S. E. Queensland, Australia). The configuration of acreminine **F** was determined as **176** and this was the first isolation as an MNP.¹⁹⁴

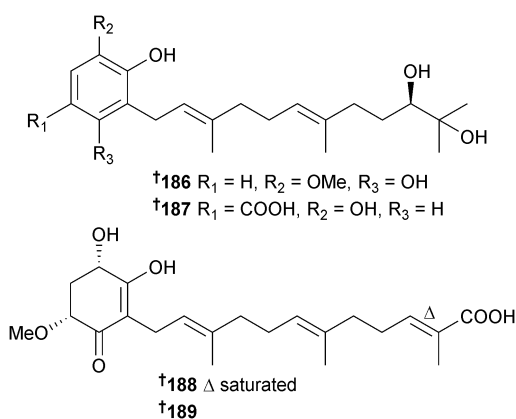
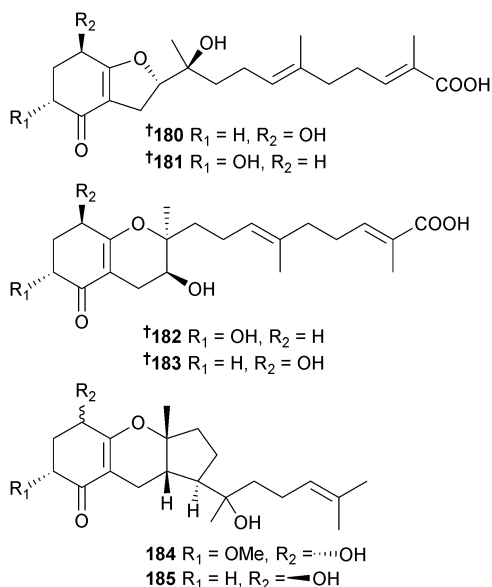


Alternaria sp. (sponge *Callyspongia* sp., Sanya, Hainan Is., China) was the source of a variety of meroterpenoids including tricycloalternarene **A 177**, the hydrogenated benzofurans, bicycloalternarene **A–D 178–181**, the hydrogenated chromans,



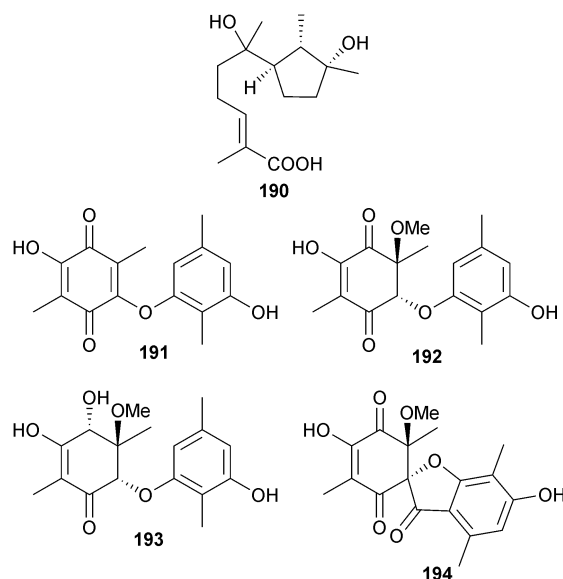


bicycloalternarene E **182** and F **183**, and the hydrogenated cyclopenta-[*b*]-chromans, tricycloalternarene B **184** and C **185**. Four additional monocyclic meroterpenoids monocycloalternarene A¹⁹⁵ **186** and monocycloalternarene B-D **187**–

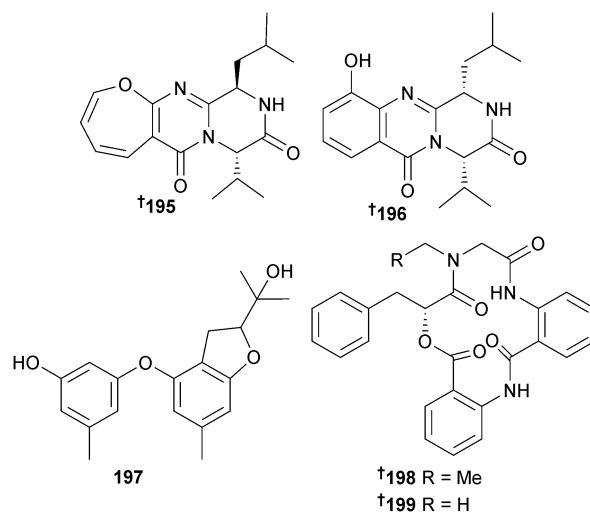


189 were obtained when the putative precursors sodium 3,4-dihydroxybenzoic acid or shikimic acid were fed to the fungus, reinforcing the proposed shikimate-isoprenoid hybrid biosynthetic pathway. All the metabolites except bicycloalternarenes E **182** and F **183** were weak to moderate inhibitors of NF- κ B in RAW264.7 cells.¹⁹⁶

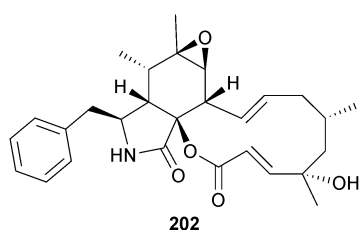
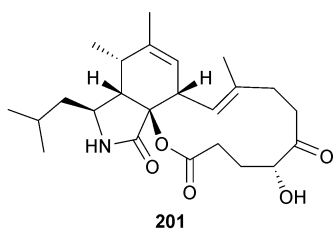
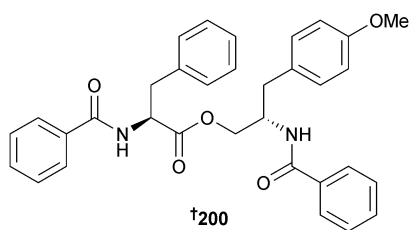
The sesquiterpene ascotrichic acid **190** was isolated from *Ascotricha* sp. (coastal mud, Fenghua County, Zhejiang, China).¹⁹⁷ The benzoquinone derivatives aculeatusquinone A-D **191**–**194** were isolated from *Aspergillus aculeatus* (sediment, Langqi Is., Fujian, China) and of these aculeatusquinones B and D were moderately cytotoxic to several HTCLs.¹⁹⁸



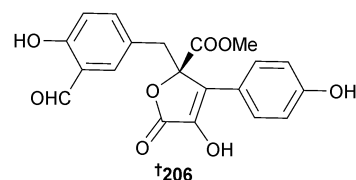
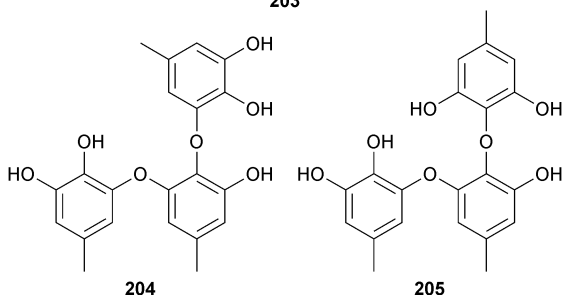
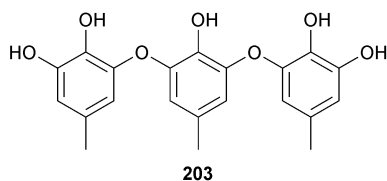
An oxepin-containing alkaloid **195**, a quinazolinone-containing alkaloid **196** and a dihydrobenzofuran derivative **197** were obtained from *A. carneus* (brown alga *Laminaria sachalinensis*, Kunachir Is., Russia).¹⁹⁹ Clavatusides A **198** and B **199**, cyclodepsipeptides with an unusual anthranilic acid dimer and a *D*-phenyllactic acid residue, were isolated from *A. clavatus* (hydrothermal vent crab *Xenograpsus testudinatus*, Kueishantao, Taiwan) and suppressed proliferation of HTCLs.²⁰⁰



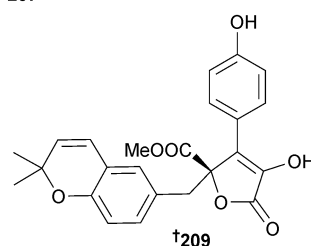
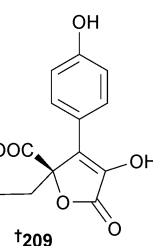
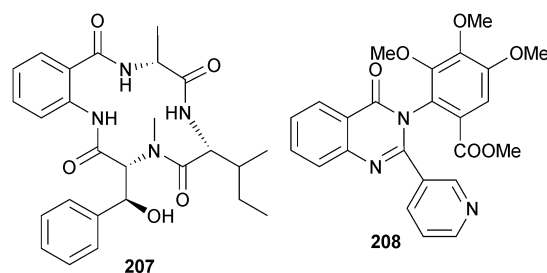
A. elegans (soft coral *Sarcophyton* sp., Weizhou coral reef, S. China Sea) produced the phenylalanine derivative 4'-methoxyasperphenamate **200** and the cytochalasins aspochalasin A1 **201** and cytochalasin Z24 **202**, in addition to a number of known cytochalasin analogues. 4'-Methoxyasperphenamate **200** was modestly active against *Staphylococcus epidermidis* while the known cytochalasins aspochalasin I,²⁰¹ J,²⁰¹ D^{202,203} and H²⁰⁴ displayed strong antifouling activity against larval settlement of the barnacle *Balanus amphitrite* (*B. amphitrite*). Aspochalasins I, J and H, previously isolated from terrestrial *Aspergillus* species, are first time MNPs.²⁰⁵



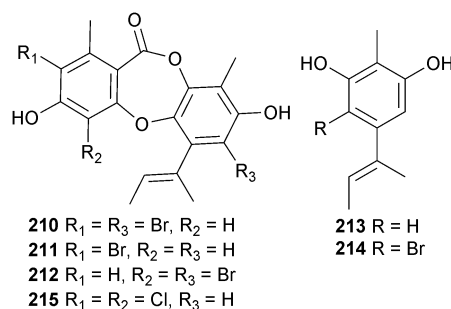
Of the tris-pyrogallol ethers sydowniol A-C **203–205** from *A. sydowii* (sediment, E. China Sea), sydowniols A **203** and C **205** inhibited *M. tuberculosis* protein tyrosine phosphatase A (PTPA).²⁰⁶ *A. terreus*, var. *boedijnii* (Blochwitz) (red alga *Laurencia ceylanica*, Arugam Bay, Sri Lanka) produced a new butyrolactone **206** which was a strong inhibitor of the enzyme β -glucuronidase.



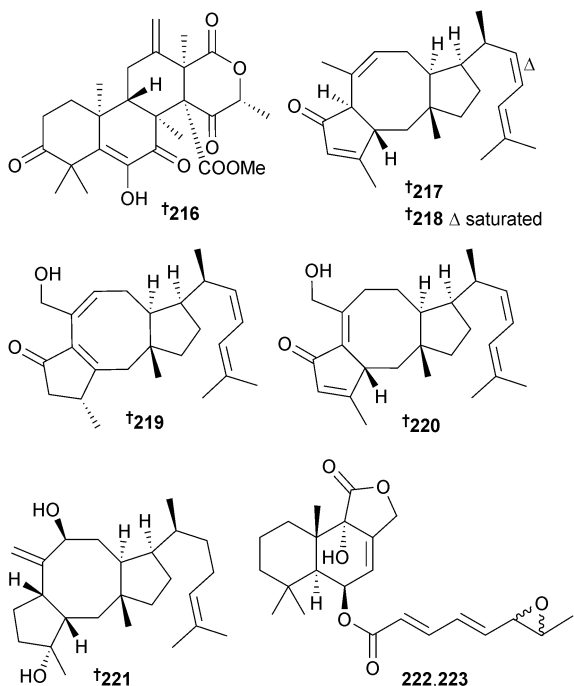
A number of known compounds were also isolated which included (+)-asterrelenin,²⁰⁷ a moderate inhibitor of β -glucuronidase, (3*R*,4*R*)-6,7-dimethoxy-4-hydroxymellin²⁰⁸ and (+)-territonin A,²⁰⁷ all reported as first time MNPs.²⁰⁹ The cyclic tetrapeptide asperterrestide A **207**, the alkaloid terremide C **208** and an aromatic butenolide aspernolide E **209** were obtained from *A. terreus* (gorgonian *Echinogorgia aurantiaca*, Sanya, Hainan Province, China). Asperterrestide A **207** inhibited influenza virus strains H1N1 and H3N2 and was cytotoxic to HTCLs.²¹⁰



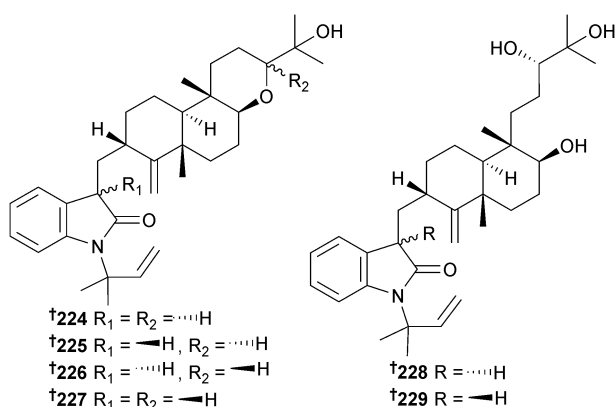
Cultivation of *A. unguis* (unidentified sponge, Tub-La-Mu Bay, Pang-nga Province, Thailand) in media containing different halogen salts led to the production of “unnatural natural” depsidones. Growth in media containing KBr produced the brominated depsidones aspergillusidone D-F **210–212** and the orcinol derivatives aspergillusidone A **213** and B **214**, whilst culture in KI produced another new depsidone 2,4-dichlorounguinol **215**. Of these, aspergillusidones D-F **210–212** inhibited aromatase, a therapeutic target for breast cancer treatment.²¹¹



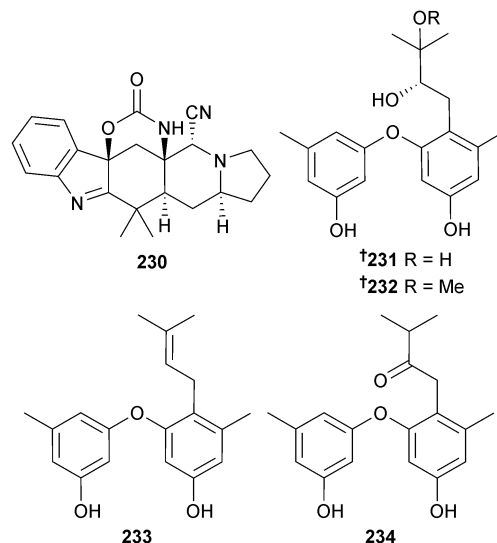
A large number of terpenes were sourced from *A. ustus* (green alga *Codium fragile*, Zhoushan Is., Zhejiang Province, China) and included the meroterpene 1,2-dihydroterretonin F **216**, the sesterterpenes (6 α)-21-deoxyophiobolin G **217**, (6 α)-16,17-dihydro-21-deoxyophiobolin G **218**, ophiobolins U–W **219–221** and the diastereoisomeric sesquiterpenes, (6-strobilactone-B) esters of (*E,E*)-6,7-epoxy-2,4-octadienoic acids **222** and **223** as new compounds. Ophiobolin F²¹² was obtained from the marine environment for the first time. Ophiobolin U **219** and the co-isolated known (5 α ,6 α)-ophiobolin H²¹³ moderately inhibited growth of *E. coli*.²¹⁴



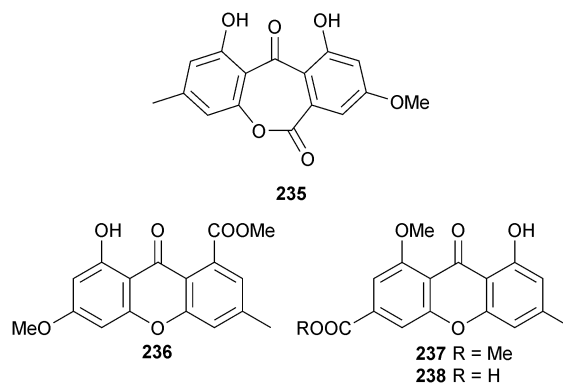
Anthcolorins A–F **224–229**, tetrahydropyran diterpene metabolites containing an oxoindoline moiety were isolated from *A. versicolor* (sea urchin *Anthocardia crassispina*, Tanabe Bay, Wakayama, Japan), as three sets of epimeric pairs with moderate growth inhibition (P388) noted for anthcolorins B–D **225–227**.^{215,216}



Aspeverin **230** isolated from *A. versicolor* (green alga *Codium fragile*, Dalian, China) was a moderate growth inhibitor of the phytoplankton *Heterosima akashiwo*.²¹⁷ Four prenylated diphenyl ethers diorcinol B–E **231–234** were obtained from *A. versicolor* (mud, Yellow Sea),²¹⁸ of which two, diorcinols D and E were toxic to HTCLs.²¹⁹

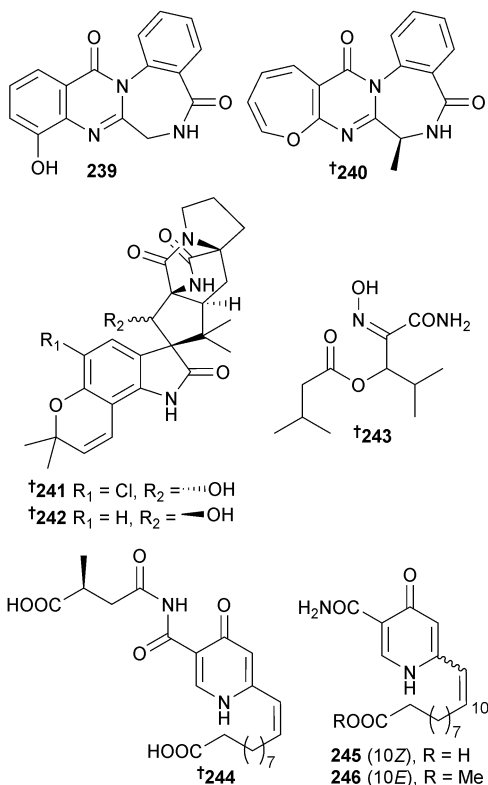


Endophytic *A. wentii* (brown alga *Sargassum* sp., no location specified) produced wentiquinone A **235**, along with another secoanthraquinone derivative which was claimed as new and named wentiquinone B. A compound of this structure had already been isolated as guepinone from the terrestrial fungus *Pestalotiopsis guepinii*,²²⁰ but this was the first isolation from the marine environment.²²¹ The xanthone derivatives yicathin A–C **236–238** were isolated from endophytic *A. wentii* (red alga *Gymnogongrus flabelliformis*, Pingtan Is., China). Yicathins B and C had antimicrobial activities.²²²

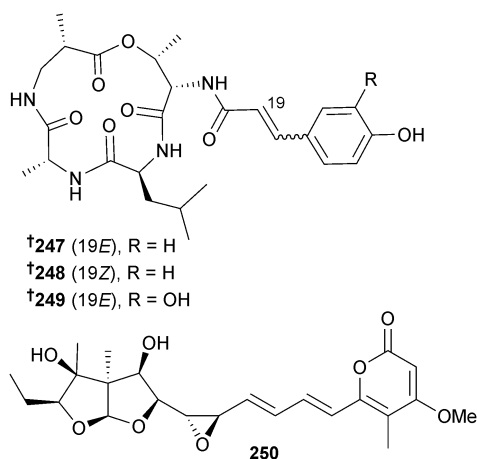


A. westerdijkiae (deep-sea sediment, S. China Sea) was the source of the benzodiazepine alkaloids circumdatin K **239** and L **240**, the prenylated indole alkaloids 5-chlorosclerotiamide **241** and 10-*epi*-sclerotiamide **242** and the amide aspergilliamide B **243** (ref. 223) whilst *Aspergillus* sp. (mussel *Mytilus edulis*, Toyama Bay, Japan Sea)²²⁴ produced himeic acids E–G **244–246**.²²⁵





The cyclic tetrapeptides aspergillipeptide A–C **247–249** and asteltoxin B **250** were isolated from *Aspergillus* sp. (gorgonian *Melitodes squamata*, Sanya, Hainan province, China) with aspergillipeptide C **249** showing strong antifouling activity against *Bugula neritina* (*B. neritina*) larvae settlement.²²⁶



Aspergillus sp. (sponge *Tethya aurantium*, Limski canal, N. Adriatic Sea, Croatia) produced seven new alkaloids, tryptovaline K **251** and fumiquinazolines K–P **252–257**, the latter group containing the rare 1-aminocyclopropane-1-carboxylic acid residue.²²⁷

The prenylated indole alkaloids 17-*epi*-notoamide Q **258** and M **259** and the phenyl ether derivative cordylol D **260** were obtained from *Aspergillus* sp. (gorgonian *Dichotella gemmacea*, Xisha Is., S. China Sea). A further phenyl ether was isolated and claimed as new but had already been reported from the

mangrove-associated fungus *Penicillium expansum*.²²⁸ The synthetic compound dehydronotoamide C²²⁹ was obtained for the first time as an NP and the fungal metabolite notoamide C²³⁰ was also reisolated and the absolute configuration previously proposed²³¹ for this metabolite proven as **261**.²³² As a consequence the configurations of the *Aspergillus*-derived notoamides J,²³³ Q²³⁴ and M,²³⁵ have been corrected from (3*S*) to (3*R*) for notoamide J^{235,236} and from (3*R*) to (3*S*) for notoamides Q and M.^{237,238}

Aspergillide D **262**, a 16-membered macrolide, was isolated from *Aspergillus* sp. (gorgonian *Melitodes squamata*, Sanya, Hainan Province, China).²³⁹ Co-isolated were two known sesquiterpenoid nitrobenzoyl esters, 9 α ,14-dihydroxy-6 β -*p*-nitrobenzoylcinnamamide²⁴⁰ and 7 α ,14-dihydroxy-6 β -*p*-nitrobenzoylconferifolin,²⁴⁰ moderate inhibitors of H1N1.²³⁹ Two aspergillidic acid group toxins aspergilliamide **263** and ochratoxin A butyl ester **264** were obtained from *Aspergillus* sp. (gorgonian *Melitodes squamata*, Sanya, Hainan Province, China), both modestly toxic to brine shrimp (*Artemia salina*). Co-isolated was the known neoaspergillidic acid²⁴¹ and, surprisingly, the aluminium and zirconium salts of the acid.²⁴²

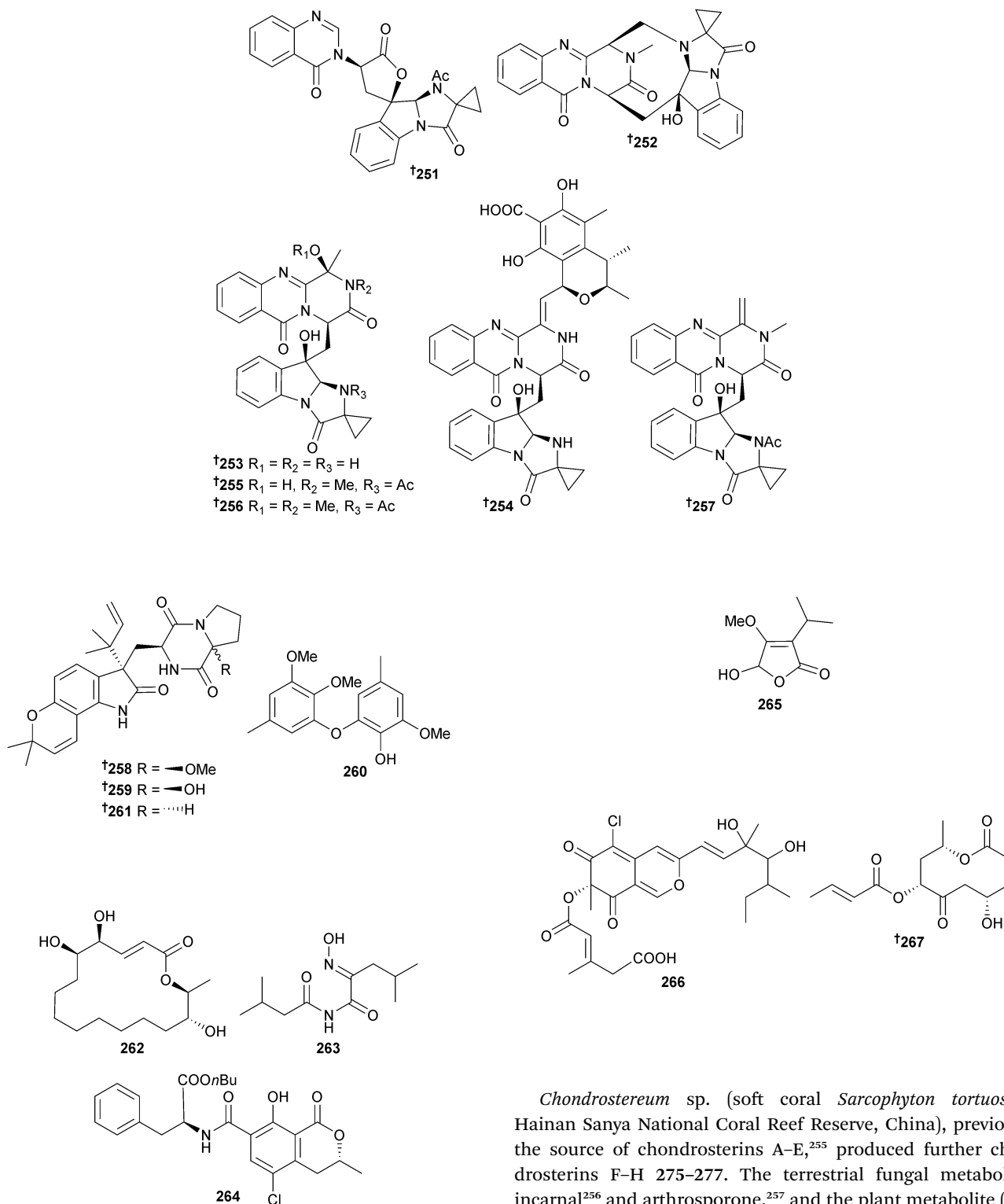
A racemic mixture of a γ -lactone derivative **265** was isolated from *Aspergillus* sp. (gorgonian *Melitodes squamata*, Sanya, Hainan Province, China) with significant toxicity to brine shrimp.²⁴³ A lactam derivative was also obtained and the structure proposed as a dehydrated pyrrolol 1-isoquinoline alkaloid,²⁴³ a structure originally proposed for marinamide, but which was subsequently revised to that of the dehydrated quinoline alkaloid penicoline (in section 3.4 below this same problem is addressed with respect to two unidentified micro-organisms grown in co-culture).^{244,245} While it might be possible that these two compounds have very similar NMR data, X-ray crystallography of this new marinamide is required to resolve the doubt.

Bartalinia robillardoides (sponge *Tethya aurantium*, Limsky Channel, Croatia) was the source of the chloroazaphilone heliscus E **266** and the pentaketide bartanolide **267**. Isochromophilones X²⁴⁶ and XI²⁴⁶ were also isolated and claimed as new but are known terrestrial fungal metabolites. Isochromophilone XI,²⁴⁶ along with other known fungal metabolites heliscus A²⁴⁷ and deacetylsclerotiorin,²⁴⁸ had a variety of moderate to weak antimicrobial activities.²⁴⁹

Calcarisporium sp. (seawater, Wadden Sea, Germany) generated macrocyclic and linear polyesters including calcarides A–E **268–272**, out of which calcarides A–C **268–270** and the co-isolated analogues 15G256 α and 15G256 β , previously obtained from the marine fungus *Hypoxylon oceanicum*,²⁵⁰ inhibited growth of *Staphylococcus epidermidis* and *Xanthomonas campestris* while the linear ester 15G256 π inhibited growth of *Propionibacterium acnes*.²⁵¹

Two lanostanes **273** and **274**, with the latter previously reported in the patent literature as a metabolite of the mushroom *Fomitopsis pinicola*,²⁵² were obtained from endophytic *Ceriporia lacerate* (starfish *Acanthaster planci*, Hainan Sanya National Coral Reef Reserve, China).²⁵³ Although a further lanostane, 3 β -acetoxy-15 α -hydroxylanosta-8,24-dien-21-oic acid

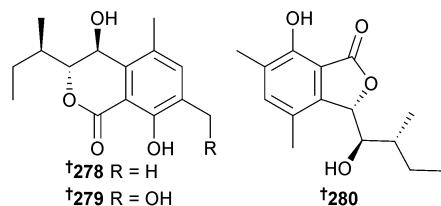
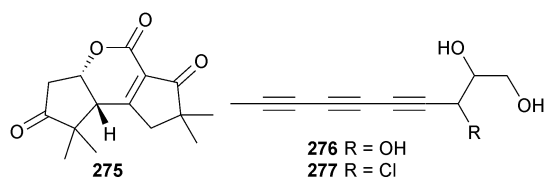
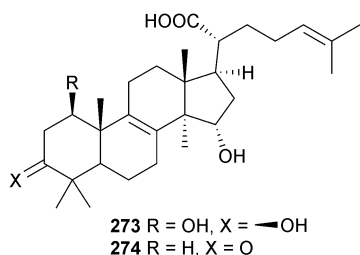
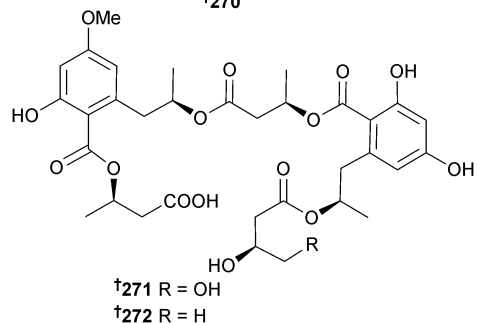
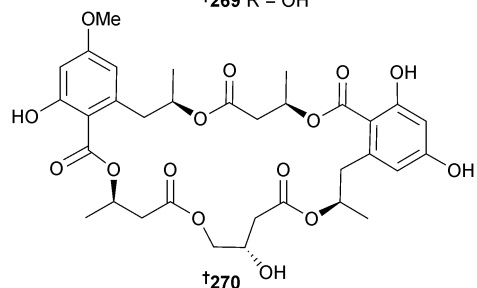
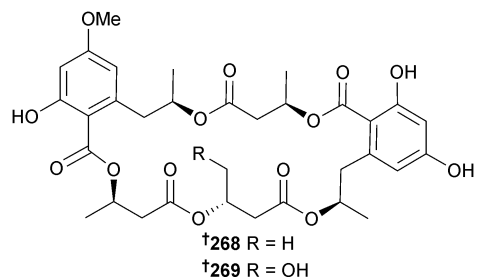




was also claimed as new, it had previously been isolated from a fungal endophyte of a traditional Chinese medicinal plant *Huperzia serrata*.²⁵⁴

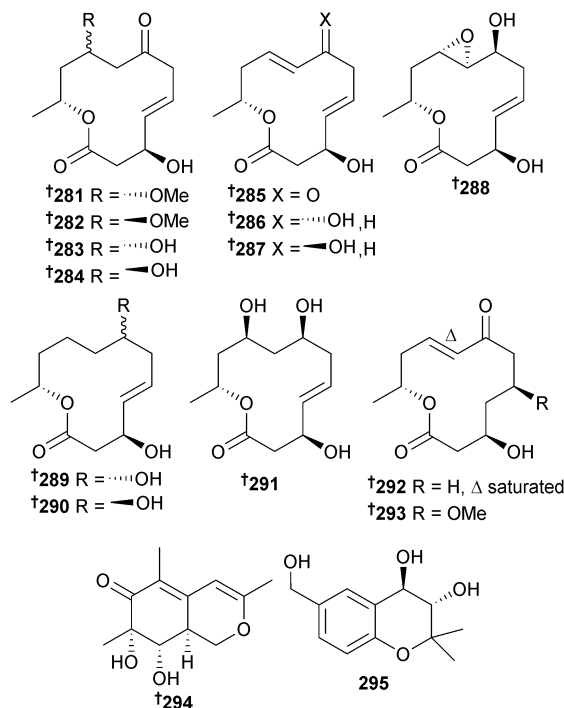
Chondrostereum sp. (soft coral *Sarcophyton tortuosum*, Hainan Sanya National Coral Reef Reserve, China), previously the source of chondrosterins A–E,²⁵⁵ produced further chondrosterins F–H 275–277. The terrestrial fungal metabolites incarnal²⁵⁶ and arthrosponone,²⁵⁷ and the plant metabolite (2*E*)-decene-4,6,8-triyn-1-ol,²⁵⁸ were also all isolated for the first time as MNPs.²⁵⁹ The benzolactone metabolites chrysoarticulin A–C 278–280 were isolated from *Chrysosporium articulatum*, (unidentified dictyoceratid sponge, Gagu-do, S. Korea) with chrysoarticulin C 280 active against the bacterial transpeptidase enzyme sortase A.²⁶⁰



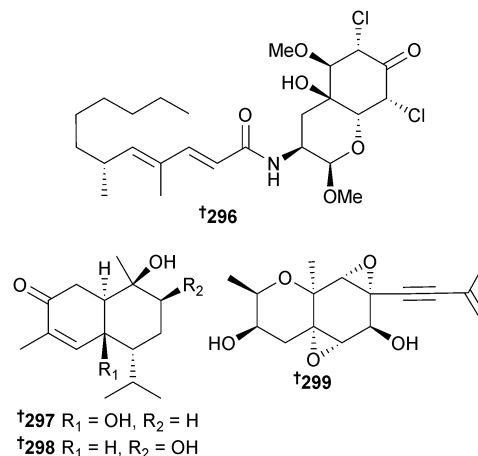


Dendrodochium sp. (sea cucumber *Holothuria nobilis*, S. China Sea) produced the 12-membered macrolides dendrolide A–M **281–293** (dendrolides A–E, G–I, K and L had

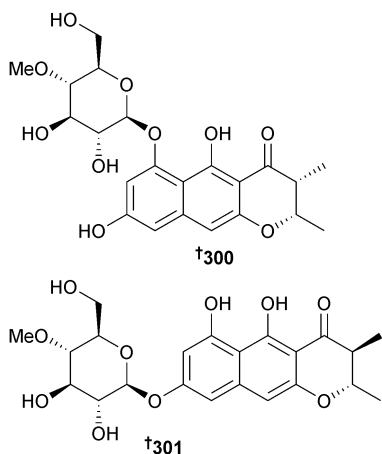
modest inhibitory activity against two HTCLs),²⁶¹ while the polyketides **294** and **295** were obtained from *Eutypella scoparia* (sediment, S. China Sea).²⁶²



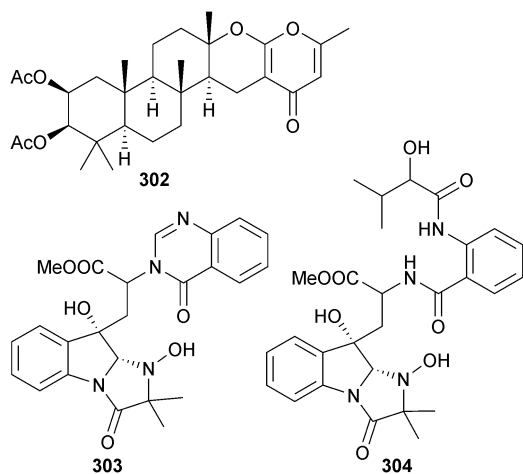
Gymnascella dankaliensis (sponge *Halichondria japonica*, Osaka Bay, Japan)²⁶³ provided dankastatin C **296**, a polyketide tyrosine derivative with potent growth inhibition of P388 cells.²⁶⁴ *Hypocreales* sp. (sponge *Gelliodes carnosa*, S. China Sea) was the source of the cadinane-type sesquiterpenes hypocreterpene A **297** and B **298**. The known terrestrial plant metabolites, (1*R*,6*R*,7*R*,10*S*)-10-hydroxy-4(5)-cadinen-3-one²⁶⁵ and (*R*)-5,6-dihydro-6-pentyl-2*H*-pyran-2-one²⁶⁶ were also isolated for the first time as MNPs and both had moderate anti-inflammatory activity (inhibition of NO production).²⁶⁷ Oxirapentyn E **299**, a highly oxidised chromene was isolated from *Isaria felina* (sediment, Vietnam) as a growth stimulant of corn (*Zea mays* L.) and barley (*Hordeum vulgare* L.) rootlets.²⁶⁸



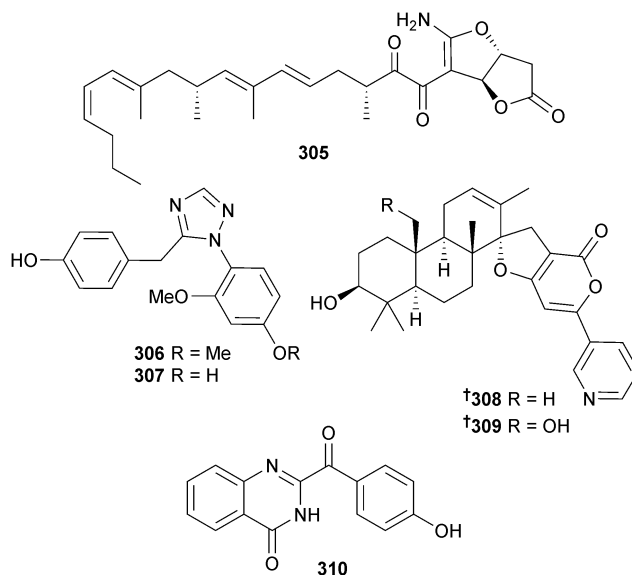
Metarhizium anisopliae (unidentified sponge, Naozhou Is., Guangxi, China) generated two naphtho- γ -pyrone glycosides indigotide G **300** and H **301**. The known compounds iso-chaeochromin B2 (ref. 269) and ustilaginoidin D²⁷⁰ were obtained for the first time from a marine source and displayed modest inhibition of *Mycobacterium phlei*.²⁷¹



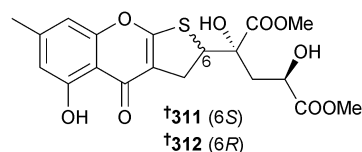
Sartorypyrone B **302**, a moderate inhibitor of HTCLs, was obtained from *Neosartorya tsunodae* (sponge *Aka coralliphaga*, Similan Is., Phagna Province, Thailand),²⁷² while tryptoquivalines R **303** and S **304** are indole alkaloids obtained from *Neosartorya* sp. (intertidal mud, Hainan Province, China),²⁷³ previously the producer of tryptoquivalines P and Q.²⁷⁴



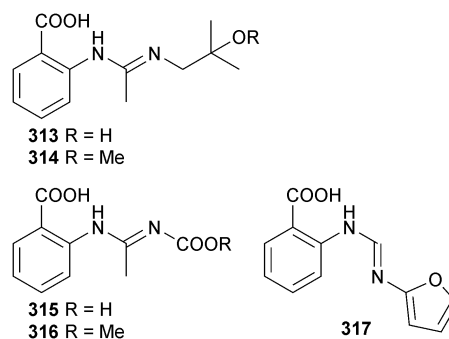
Paecilomyces sp., (unspecified sponge, Tinggi Is., Malaysia) was the source of the dione **305**,²⁷⁵ while the chrysotriazoles A **306** and B **307** were obtained from endophytic *Penicillium chrysogenum* (brown alga *Sargassum palladium*, Fujian, China).²⁷⁶ *P. oxalicum* (sediment, Bohai Bay, Liaoning Province, China) produced decaturins E **308** and F **309**,²⁷⁷ and 2-(4-hydroxybenzoyl) quinazolin-4(3H)-one **310** was isolated from *P. oxalicum* (strain 0312F1, Genbank accession no. EU926977) as a moderate inhibitor of tobacco mosaic virus (TMV) and the human gastric cancer cell line SGC-7901.²⁷⁸



The dihydrothiophene-condensed chromones oxalicumone A **311** and B **312** were obtained from *P. oxalicum* (gorgonian *Muricea flexuosa*, Sanya, China) with oxalicumone A **311** moderately cytotoxic to HTCLs.²⁷⁹ A further chromone was also claimed as new and named as oxalicumone C but while isolated from a natural source for the first time, is a known reaction product of chloromonilicin, a metabolite of the cherry rot fungus *Monilinia fructicola*.²⁸⁰



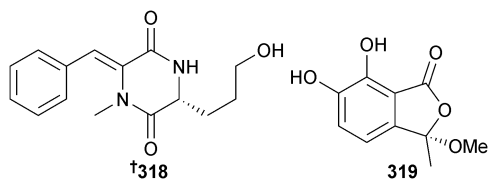
The anthranilic acid derivatives penipacid A-C **313**–**315**, E **316** and G **317** were isolated from *P. paneum* (sediment, S. China Sea) together with a known analogue, 2-[(1-methyl-2-oxopropylidene)aminobenzoic acid],²⁸¹ previously synthesised but now isolated as an NP. Penipacids A **313** and E **316** inhibited human colon cancer RKO cells and 2-[(1-methyl-2-oxopropylidene)aminobenzoic acid] was cytotoxic to HeLa cells.²⁸²



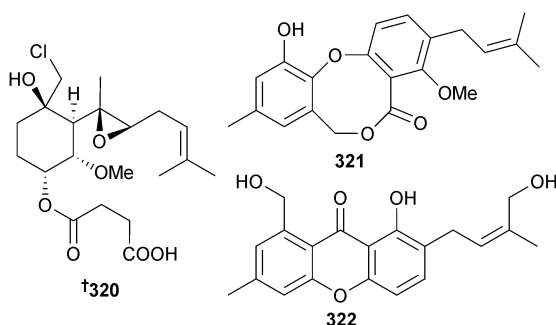
P. pinophilum (sediment, Pearl River Estuary, S. China Sea) yielded pinodiketopiperazine A **318** and 6,7-dihydroxy-3-methoxy-3-methylphthalide **319** and the known synthetic



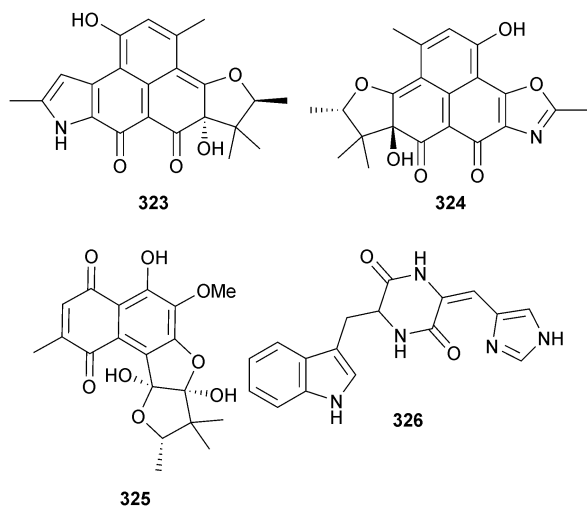
compounds, alternariol 2,4-dimethyl ether^{283,284} and L-5-oxo-proline methyl ester²⁸⁵ as first time NPs. The phthalide **319** displayed potent cytotoxicity to brine shrimp and pinodiketo-piperazine **A 318**, alternariol 2,4-dimethyl ether^{283,284} and the co-isolated known metabolites *N*-methylphenyldehydroalanyl-L-proline-anhydride²⁸⁶ and rubralide **C**²⁸⁷ all exhibited moderate inhibition of *E. coli* growth.²⁸⁸



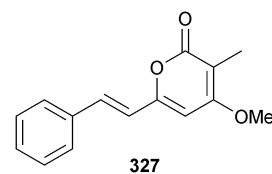
The chlorinated sesquiterpenoid ligerin **320** came from a *Penicillium* strain (seawater, La Prée, Loire Atlantique, France) and strongly inhibited the osteosarcoma cell line POS1,²⁸⁹ while another *Penicillium* sp. (sediment, Jiaozhou Bay, China) yielded prenenicillide **321** and prenxanthone **322**.²⁹⁰



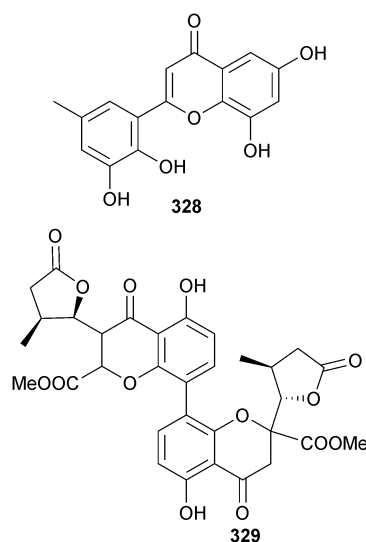
The polyaromatic metabolites herqueiazole **323**, herqueioazole **324** and herqueidiketal **325** were obtained from *Penicillium* sp. (sediment, Gagu-do, S. Korea). Herqueidiketal **325** was moderately cytotoxic to A549 cells and significantly inhibitory against sortase A.²⁹¹ *Penicillium* sp. (gorgonian *Dichotella gemmacea*, Sanya, Hainan Province, China) produced the indolyl diketopiperazine penilloid **A 326** in addition to a number of known indole alkaloids.



Aspergillus sydowii (gorgonian *Verrucella umbraculum*, Sanya, Hainan Province, China) also yielded additional known indole alkaloids including fumiquinazoline **D**,²⁹² cyclotryptostatin **B**²⁹³ and fumiquinazoline **G**,²⁹⁴ which in addition to (*E*)-3-(1*H*-imidazol-4-ylmethylene)-6-(1*H*-indol-3-ylmethyl)-2,5-piperazinedione,²⁹⁵ meleagrin,²⁹⁶ roquefortine **C**,²⁹⁷ and 11 α -methoxy roquefortine **C**²⁹⁸ from the *Penicillium* sp. exhibited significant antifouling activity towards *B. amphitrite* and/or *B. neritina* larvae. Meleagrin also exhibited moderate activity against the larvae settlement-inducing bacterium *Micrococcus luteus*.²⁹⁹ Penstyrylpyrone **327** and the known terrestrial fungal metabolite anhydrofulvic acid (first time MNP)³⁰⁰ were obtained from *Penicillium* sp. (unidentified sponge, Jeju Is., S. Korea) as inhibitors of protein tyrosine phosphatase 1B (PTP1B) activity. Furthermore, penstyrylpyrone **327** suppressed production of pro-inflammatory mediators *via* the NF- κ B pathway through expression of the anti-inflammatory enzyme, heme oxygenase.³⁰¹

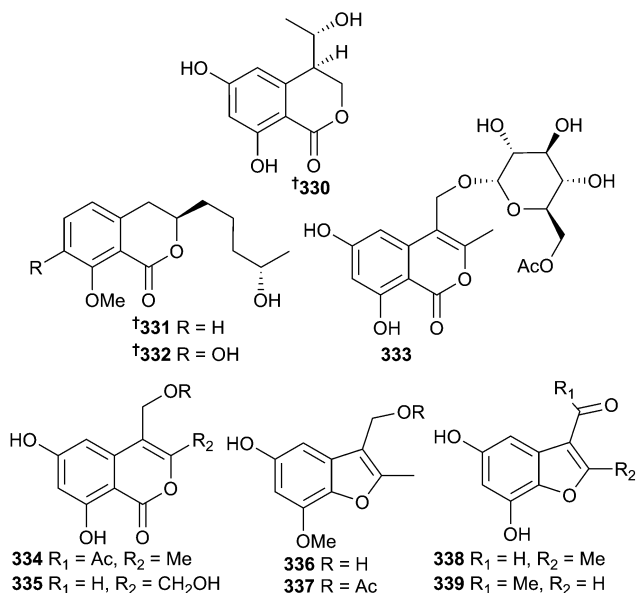


Penicillium sp. (gorgonian coral *Dichotella gemmacea*, Sanya, Hainan, China) was the source of the polyketides **328** and paecilin **C 329**, and some known analogues. 6,8,5',6'-Tetrahydroxy-3'-methylflavone **328**, emodin,³⁰² citreorosein³⁰² and isorhodoptilometrin³⁰³ exhibited significant antifouling activity against *B. amphitrite* larvae settlement while penicillixanthone **A**³⁰⁴ was moderately antibacterial.³⁰⁵

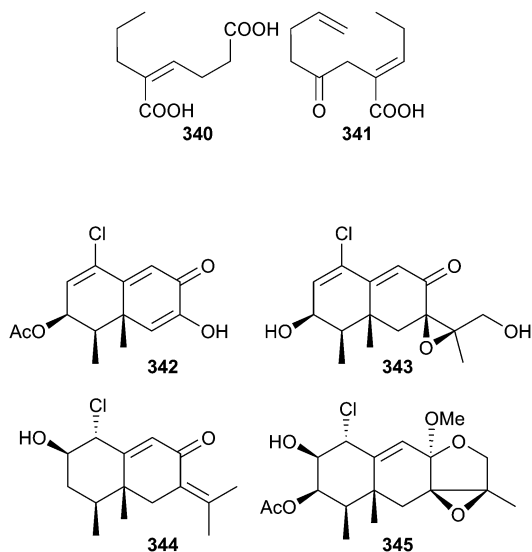


Endophytic *Penicillium* sp. (unidentified sponge, Weizhou, S. China Sea) was the source of the hydroisocoumarins penicimarins **A–C 330–332**, the isocoumarins penicimarins **D–F 333–335** and the benzofurans penicifurans **A–D 336–339**, out of which only penicifuran **A 336** was cytotoxic to *Staphylococcus albus* (moderate).³⁰⁶



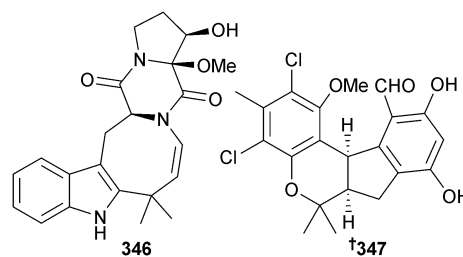


Co-cultivation of *Penicillium* sp. (sponge *Mycale angulosa*, Toque-Toque Is., Brazil)³⁰⁷ and *Trichoderma* sp. (sponge *Geodia corticostylifera*, same location)³⁰⁷ led to the unusual polyketides, (*Z*)-2-ethylhex-2-enedioic acid **340** and (*E*)-4-oxo-2-propylideneoct-7-enoic acid **341**.³⁰⁸ A chloro-trinoreremophilane sesquiterpene **342** and three chlorinated eremophilane sesquiterpenes **343**–**345** were isolated from *Penicillium* sp. (deep-sea sediment, Prydz Bay, Antarctica). Just **342** was cytotoxic to HTCLs (moderate).³⁰⁹

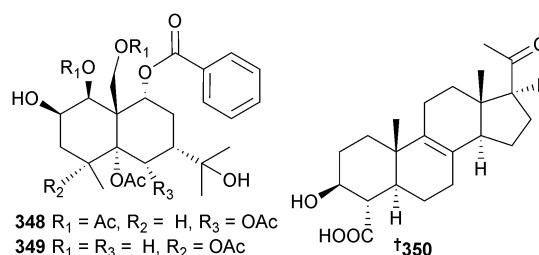


The isoastamide alkaloid **346** was obtained from *Penicillium* sp. (unidentified sponge, Jeju Is., S. Korea). Also isolated for the first time as an NP was deoxydihydroisoastamide, previously reported as an intermediate in the total synthesis of (+)-deoxyisoastamide.^{310,311} *Pestalotiopsis* sp. (soft coral *Sarcophyton* sp., Yongxing Is., S. China Sea) was the source of the chlorinated benzophenone derivative (\pm)-pestalachloride D **347** (moderate antibacterial activity against several Gram-positive strains). Co-isolated was (\pm)-pestalachloride C, known as a

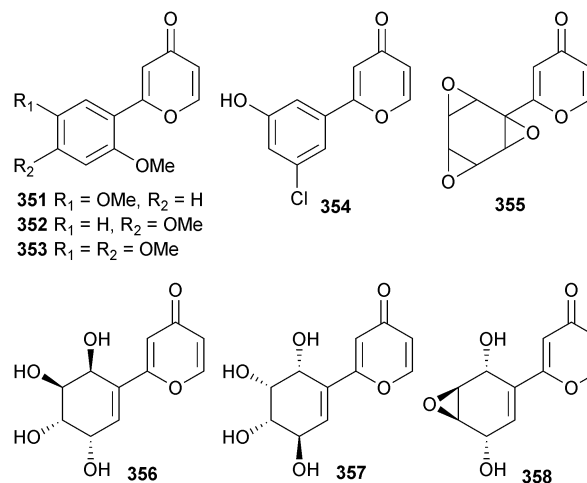
metabolite of terrestrial endophytic *Pestalotiopsis adusta*³¹² but now a first time MNP.³¹³

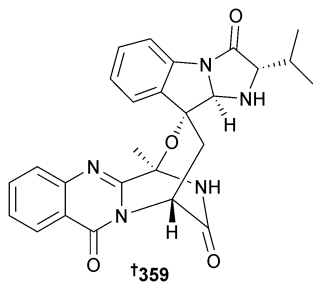


The eudesmane sesquiterpenes **348** and **349** were produced by *Pestalotiopsis* sp. (brown alga *Sargassum horneri*, Wenzhou, China) in response to abiotic stress elicitation by addition of CuCl₂ to the growth media and both were both potent inhibitors of tyrosinase.³¹⁴ Endophytic *Phaeosphaeria spartinae* (red alga *Ceramium* sp., North Sea, Büsum, Germany) was the source of spartopregnenolone **350**.³¹⁵

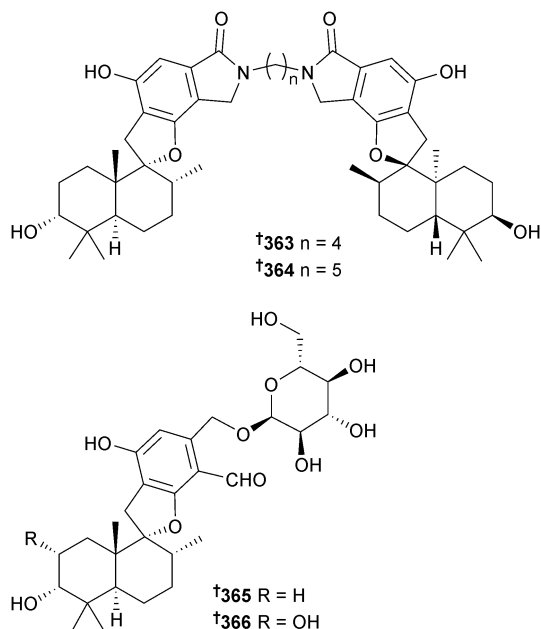
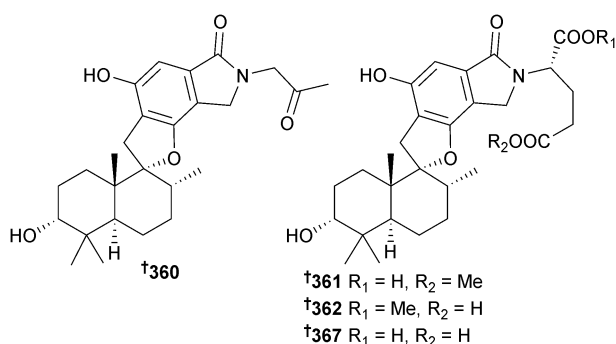


Polyporapyranones A–H **351**–**358** were isolated from two *Polyporales* species (seagrass *Thalassia hemprichii*, location unspecified, presumably Thailand). Polyporapyranones A **351** and D **354** exhibited moderate and weak inhibition of the Vero cell line respectively.³¹⁶ *Scopulariopsis* sp. (gorgonian *Carijoa* sp., Weizhou, S. China Sea) was the source of fumiquinazoline L **359**, an alkaloid with a heptacyclic skeleton.³¹⁷



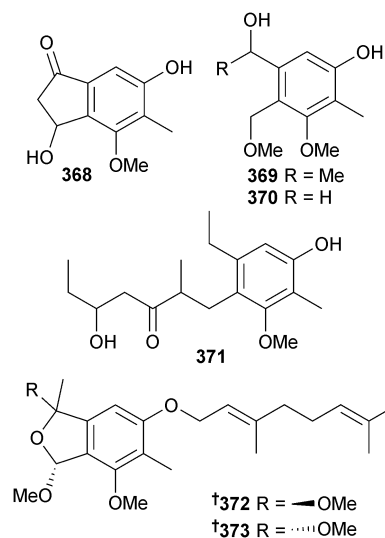


Stachybotrys chartarum (sponge *Xestospongia testudinaria*, Xisha Is., China) yielded new phenylspirodrimanes stachybotrin D–F **360–362**, stachybocin E **363** and F **364** and stachyboside A **365** and B **366**, of which stachybotrin D **360** inhibited replication of HIV-1 by targeting reverse transcriptase and blocked non-nucleoside reverse transcriptase inhibitors-resistant strains as well. The absolute configuration of a co-isolated known terrestrial sesquiterpenoid **367** (*S. chartarum*³¹⁸) was determined.³¹⁹

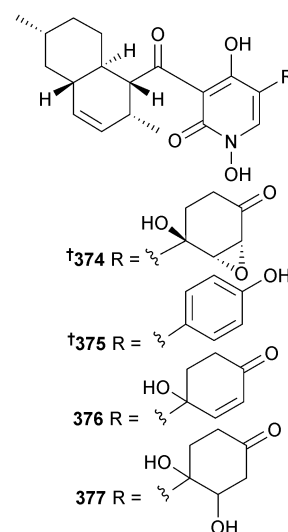


Several polyketides were obtained from *Stachylidium* sp. (sponge, *Callyspongia* sp. cf. *C. flammea*, Bear Is., Sydney, Australia) including cyclomarinone **368**, maristachone A–E **369–373**

and marilactone.³²⁰ Due to rotation values being close to zero, racemic mixtures were assumed for cyclomarinone **368**, maristachone A **369** and the epimers **372** and **373**. Marilactone³²⁰ is a known synthetic compound but now a first time NP. From a biosynthetic perspective, all of the isolated compounds are unusual due to the presence of an additional carbon atom over the basic polyketide skeleton.³²¹

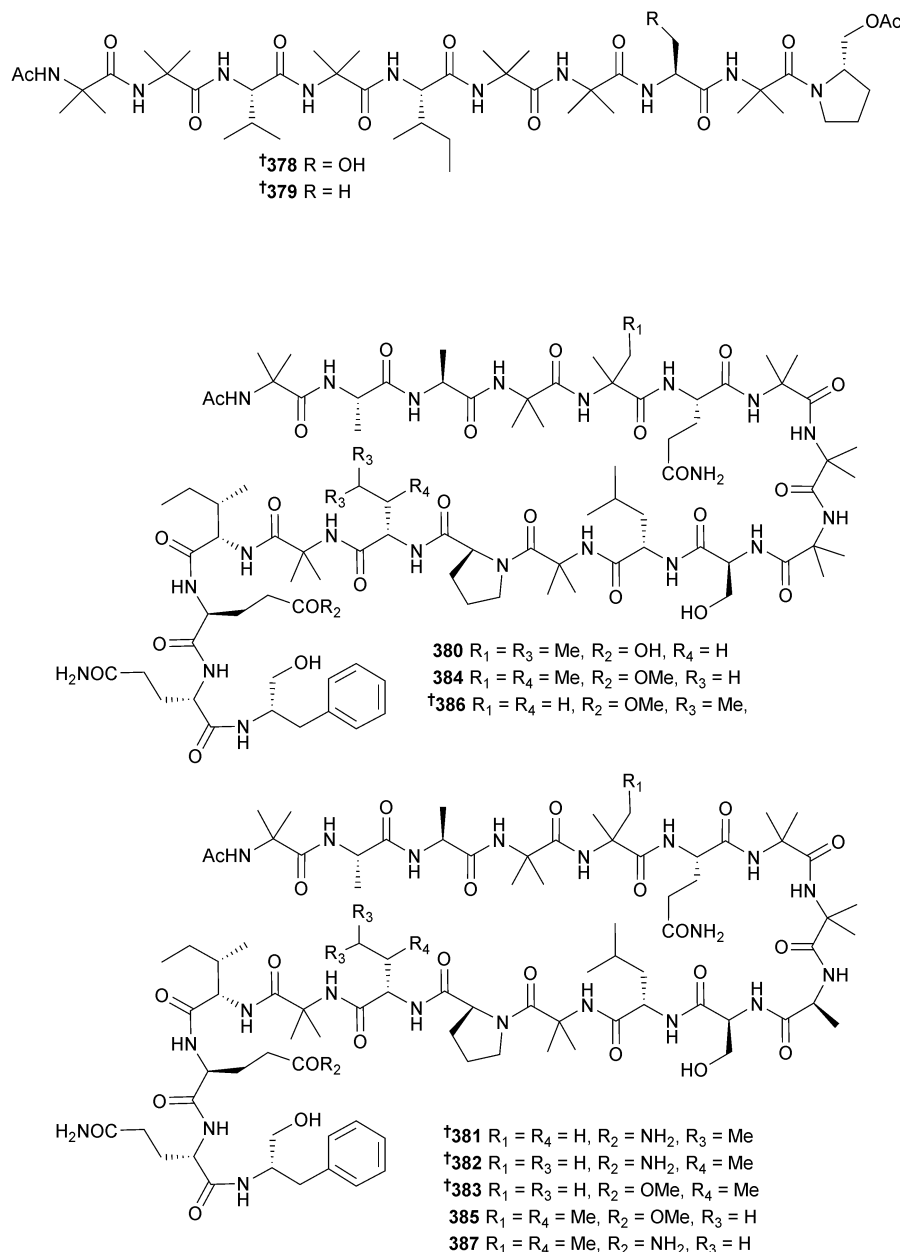


Stagonosporopsis cucurbitacearum (unidentified sponge, Atami-shi, Shizuoka Prefecture, Japan) yielded the alkaloids didymellamides A–D **374–377**. Didymellamide A **374** inhibited growth of several pathogenic fungi including azole-resistant *C. albicans*.³²²



The peptaibols aspereline G **378** and H **379** were obtained from *Trichoderma asperellum* (sediment, Langqi Is., Fujian, China),³²³ while asperelines G–Z₁₃ are thirty-two new short peptaibols detected from *T. asperellum* (sediment, Penguin Is., Antarctica) by ultrahigh pressure liquid chromatography in combination with electrospray-ionisation tandem mass





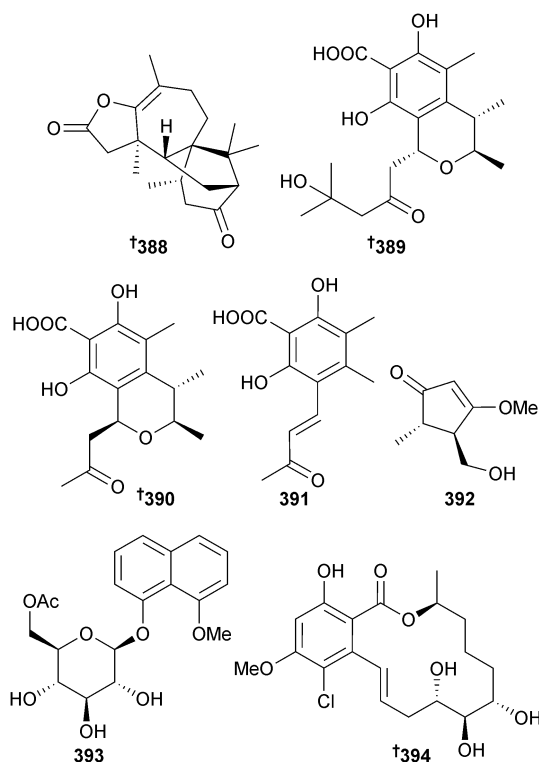
spectrometry (UHPLC-ESIMS/MS).³²⁴ Several strains of marine-derived *T. atroviride* (University of Nantes culture collection) produced two series of 17-residue peptaibiotics with a common C-terminus³²⁵ and eight new peptaibols **380–387**, trichorhizanine 1938, 1909, 1895, 1896, 1924, 1910, 1924A and 1909A, linear 19-residue hydrophobic peptides were obtained from *T. atroviride* (Axiellid sponge, Akhziv, Mediterranean coast, Israel).³²⁶

The diterpenoid lactone trichodermaerin **388** was isolated from endophytic *T. erinaceum* (sea star *Acanthaster planci*, Hainan Sanya National Coral Reef Reserve, China).³²⁷ A *Xylariaceae* sp. (gorgonian coral *Melitodes squamata*, S. China Sea) produced a number of polyketides including penicitrinol F **389**, 7-carboxypenicitrinol C **390** and **391–393**. Several known polyketides were also isolated and of these, dihydrocitrinin³²⁸ and

phenol acid A³²⁸ strongly inhibited settlement of *B. neritina* larvae with dihydrocitrinin³²⁸ also an inhibitor of the enzymes SHP2 and IMPDH. Phenol acid A³²⁸ and dihydrocitrininone³²⁹ inhibited cathepsin B and (3*R*,4*S*)-(+)-4-hydroxy-6-deoxycytalone³³⁰ inhibited the enzymes SHP2, PTP1B and IMPDH and is a first time MNP.³³¹ There is considerable confusion surrounding this report: the name penicitrinol F has been given previously to a citrinin derivative obtained from a *Penicillium* sp.³³² so **389** should be renamed. Also, for 7-carboxypenicitrinol C **390** there is a discrepancy between the configuration in the diagram and in the text. The text gives (1*R*) but the diagram gives (1*S*). If the diagram is correct, this is a known compound from both terrestrial³³³ and marine^{334,335} fungi. The configuration of cochliomycin C, a resorcylic acid lactone obtained from



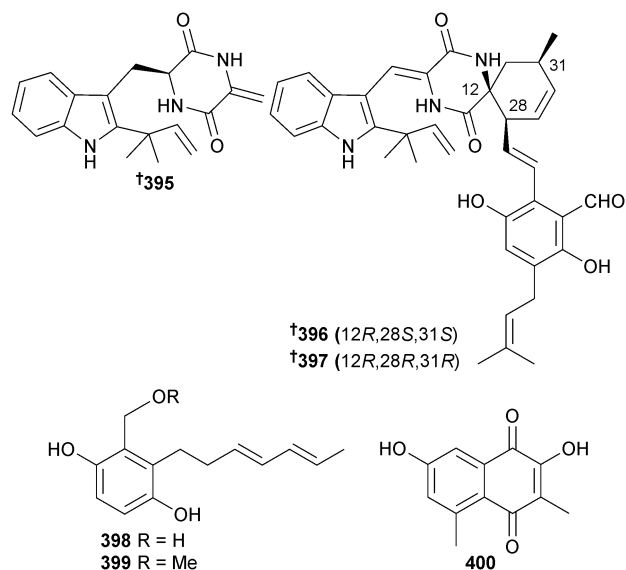
the gorgonian-derived fungus *Cochliobolus lunatus*³³⁶ has been corrected to **394**.³³⁷



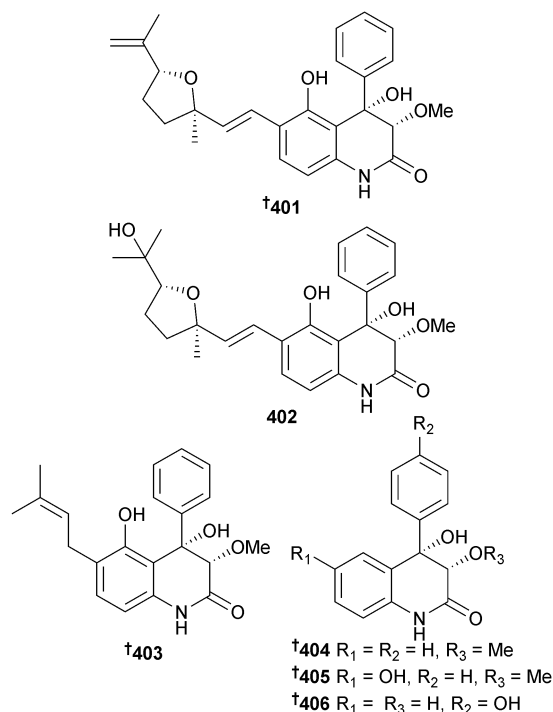
Addition of sodium bromide to a culture of *Aspergillus ochraceus* (red alga *Chondria crassicalis*, Yokji Is., Kyeongnam Province, S. Korea) resulted in medium-induced production of (*R*)-(-)-5-bromomellein as a modest radical scavenger (against 1,1-diphenyl-2-picrylhydrazyl (DPPH)). Both the racemate³³⁸ and antipode³³⁹ have been previously synthesised but this is the first report of their isolation as NPs.³⁴⁰ The sesquiterpene helminthosporic acid has been reported previously as a semi-synthetic derivative of the fungal metabolite helminthosporol aldehyde³⁴¹ but has been isolated for the first time as an NP from *Drechslera* sp. (green alga *Ulva* sp., Tönning, North Sea).³⁴² Also as a first time MNP was the terrestrial fungal metabolite epiepoformin³⁴³ isolated from an endophytic *Penicillium* sp. (brown alga *Fucus spiralis*, Bridge End, Shetland Is., U.K.).³⁴⁴

3.4 Fungi from mangroves

Aspergillus effusus (rhizosphere soil, unidentified mangrove, Fujian Province, China) produced the prenylated indole diketopiperazine alkaloid dihydroneochinulin B **395** and the enantiomeric spiro-polyketide-diketopiperazine hybrids cryptoechinuline D **396** and **397**. The latter compound has been isolated previously from terrestrial³⁴⁵ and marine³⁴⁶ fungi but in this study was resolved into enantiomers and absolute configurations assigned.³⁴⁷ The benzyl derivatives aspergentisyl A **398** and aspergentisyl B **399** and a naphthoquinone derivative aspergiodiquinone **400** were isolated from *A. glaucus* (mangrove sediment, unspecified species, Fujian Province, China). Aspergentisyls A **398** and B **399** were strong radical-scavengers (DPPH).³⁴⁸

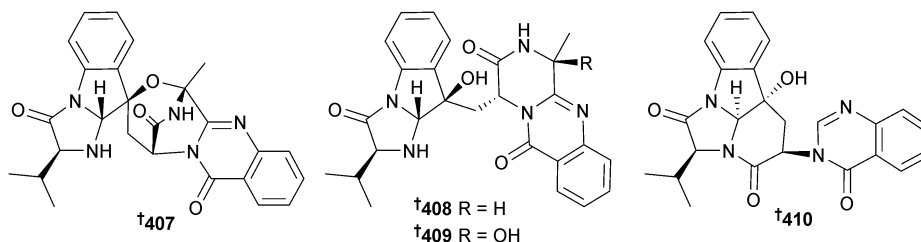


Some 4-phenyl-3,4-dihydroquinolone derivatives were obtained from *A. nidulans* (mangrove leaves *Rhizophora stylosa*, source not given, presumably China), namely aniduquinolone A–C **401**–**403**, 6-deoxyaflaquinolone E **404**, isoafilaquinolone E **405** and 14-hydroxyaflaquinolone F **406**. Of these, aniduquinolones B **402** and C **403** and the co-isolated aflaquinolone A³⁴⁹ were moderately toxic to brine shrimp. Aflaquinolone A, previously obtained from a terrestrial *Aspergillus* sp., was obtained for the first time as an MNP.³⁵⁰

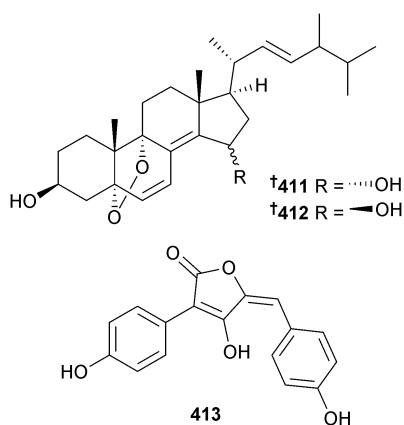


Aniquinazolines A–D **407**–**410** are quinazolinone alkaloids from the endophytic *A. nidulans* (mangrove leaves *Rhizophora stylosa*, unspecified location, presumably China) and were all strongly cytotoxic to brine shrimp.³⁵¹ The nigerasterols A **411** and B **412** were obtained from endophytic *A. niger* (mangrove

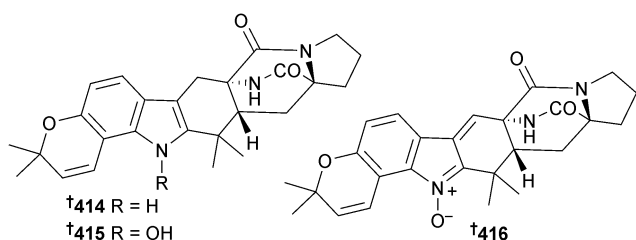




Avicennia marina, Hainan, China) as relatively potent inhibitors of the HTCLs HL60 and A549.³⁵² The butenolide isoaspulvinone E **413** came from *A. terreus* (mangrove rhizosphere soil, Fujian Province, China) along with the known butenolides aspulvinone E³⁵³ and pulvic acid.³⁵⁴ All exhibited significant H1N1 virus inhibition but only isoaspulvinone E inhibited H1N1 viral neuraminidase. Pulvic acid was a first time MNP.³⁵⁵

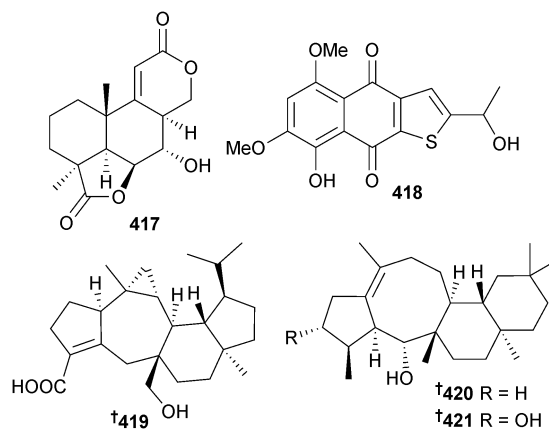


A. taichungensis (mangrove root soil *Acrostichum aureum*, no location given)³⁵⁶ was the source of the prenylated indole alkaloids 6-*epi*-stephacidin A **414**, *N*-hydroxy-6-*epi*-stephacidin A **415** and 6-*epi*-avrainillanide **416**, and of these **415** and **416** were cytotoxic to two HTCLs. On exposure to light and air **415** converted to a complex mixture of analogues, including (+)-versicolamide B,³⁵⁷ a mixture of two compounds (here named versicolamide C) and **416**, which suggested that **416** may be an artefact. 6-*Epi*-stephacidin A **414** was stable under the same conditions.³⁵⁸



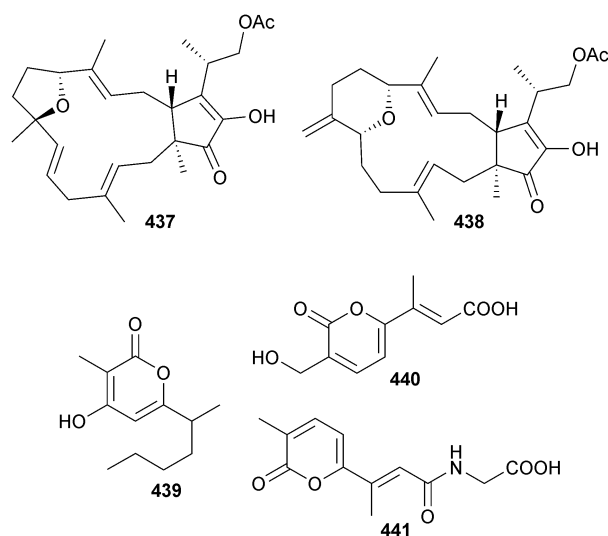
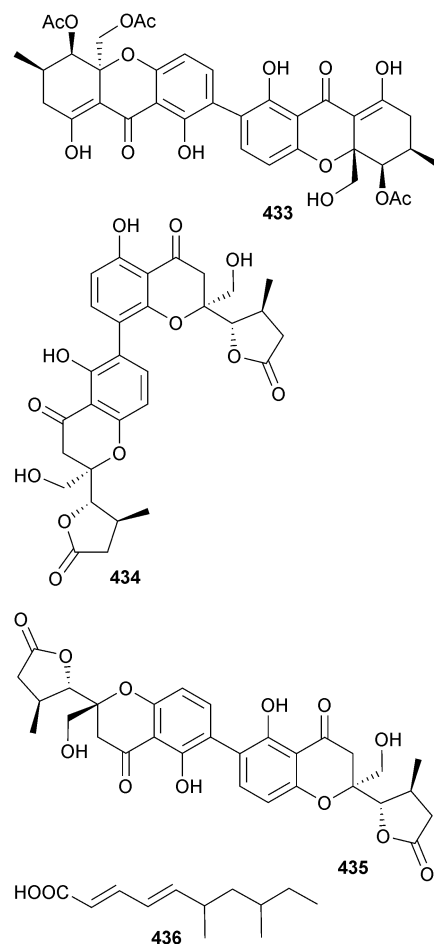
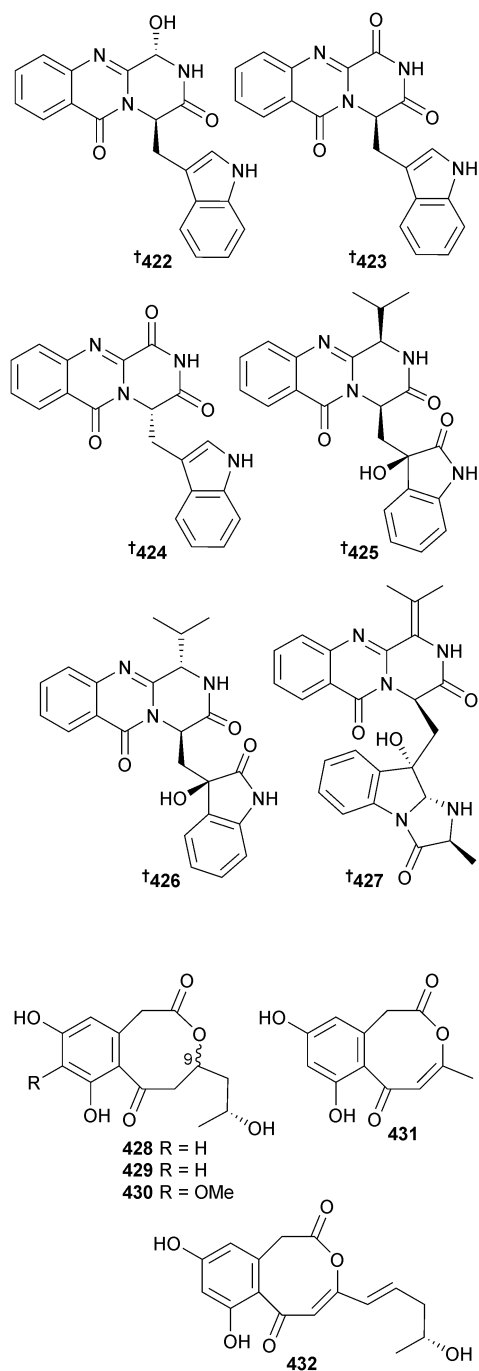
Botryosphaerin F **417** was obtained from endophytic *A. terreus* (mangrove branch *Bruguiera gymnorhiza*, Guangxi, China) and inhibited growth of HTCLs.³⁵⁹ Several known compounds were also isolated including LL-Z1271 β ,³⁶⁰ which

although reported as active against the HL60 cell line used here, had previously been reported as being inactive against a number of other HTCLs.^{361,362} Endophytic *A. terreus* (mangrove branch *Bruguiera gymnorhiza*, Guangxi province, China) was the source of a thiophene compound **418**. The co-isolated 6-ethyl-5-hydroxy-3,7-dimethoxynaphthoquinone,³⁶³ a known synthetic compound, was a first time NP.³⁶⁴ Asperterpenoid A **419**, a sesterterpenoid with a new carbon skeleton, was isolated from endophytic *Aspergillus* sp. (mangrove species not specified, no location given) and displayed inhibitory activity against *M. tuberculosis* protein tyrosine phosphatase B (mPTPB).³⁶⁵ Asperterpenols A **420** and B **421** are sesterterpenoids with an unusual 5/8/6/6 tetracyclic ring skeleton. Both were acetylcholinesterase inhibitors and were obtained from endophytic *Aspergillus* sp. (mangrove, S. China Sea).³⁶⁶



Cladosporium sp. (mangrove soil, Guangzhou, China) was the source of a number of indole alkaloids including five glyantrypine derivatives; 3-hydroxyglyantrypine **422**, oxoglyantrypine **423**, **424**, cladoquinazoline **425** and *epi*-cladoquinazoline **426** and a pyrazinoquinazoline derivative norquinadoline A **427**. Of these alkaloids, oxoglyantrypine **424** and norquinadoline A **427**, together with the co-isolated known terrestrial *Aspergillus* alkaloid metabolites, deoxynortryptoquivaline,³⁶⁷ deoxytryptoquivaline,³⁶⁷ tryptoquivaline³⁶⁸ and quinadoline B³⁶⁹ had significant activities against H1N1. The latter four were also obtained for the first time as MNPs. Over time, a solution of oxoglyantrypine **423** partially converted into **424**, leading to the proposal that **424** was an artefact.³⁷⁰





Further investigation of endophytic *Corynespora cassicola* (mangrove leaf *Laguncularia racemosa*, Hainan Is., China), which originally yielded some decalactone derivatives,³⁷¹ yielded some minor metabolites coryoctalactone A–E **428–432**, of which coryoctalactones A **428** and B **429** were assumed to be C-9 epimers.³⁷²

As part of a screening programme for new antimalarial compounds, four metabolites were obtained from several species of Chinese mangrove endophytic fungi from either Mai Po Nature Reserve, Hong Kong or Hainan Is., Taiwan. Despite lack of a tight correlation between location and source micro-organism, this study described the isolation of a dimeric

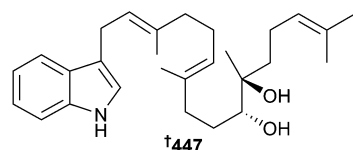
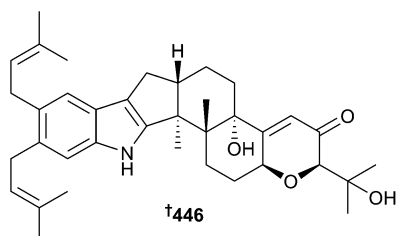
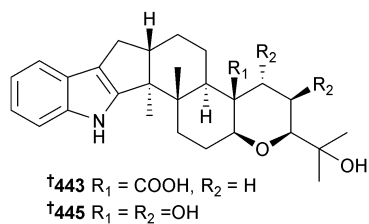
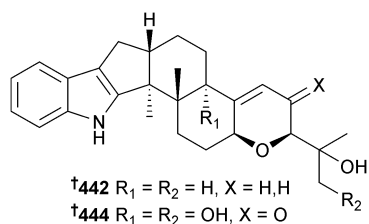
tetrahydroxanthone dicerandrol D **433** from a *Diaporthe* sp., diaporthochromes A **434** and B **435** from another *Diaporthe* sp. and the lipid **436** was obtained from *Xylaria* sp. Dicerandrol D **433** exhibited potent activity against *P. falciparum* with relatively low toxicity to A549 cells.³⁷³

Endophytic *Fusarium proliferatum* (mangrove *Bruguiera sexangula*, Hainan Is., China) produced the tricyclic

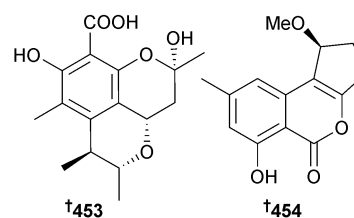
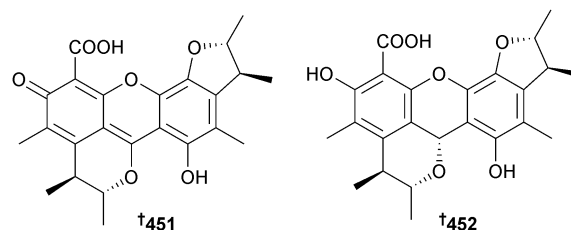
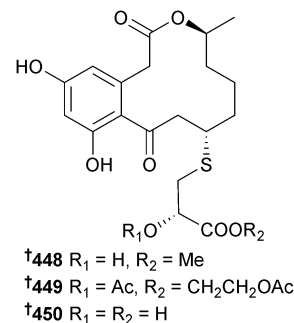


sesterterpenes fusaprolifin A **437** and B **438** and the 2H-pyran-2-one derivatives prolipyron A–C **439–441**. Fusaprolifins A and B had modest activity against brine shrimp.³⁷⁴

Penicillium camemberti (mangrove soil *Rhizophora apiculata*, Wenchang, Hainan Province, China) produced the indole diterpenoids **442–447**, as well as some known analogues. Of these, emindole SB,³⁷⁵ 21-isopentenylpaxilline,³⁷⁶ paspaline,^{377,378} and paxilline³⁷⁹ displayed significant activity against H1N1 as did indole diterpenoids **442–444**, **446** and **447**. 21-Isopentenylpaxilline³⁷⁶ and dehydroxypaxilline³⁸⁰ were obtained for the first time as MNPs.³⁸¹



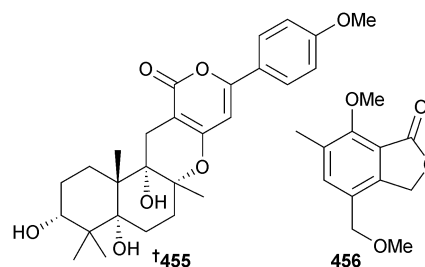
Penicillium sumatrense (mangrove rhizosphere *Lumnitzera racemosa*, WenChang, Hainan Is., China) yielded sumalarins A–C **448–450**, sulfur-containing curvularin derivatives which were cytotoxic to several HTCLs.³⁸² The planar structure of sumalarin C **450** had previously been reported as part of several compound libraries.^{383–385} The citrinin dimers penicitrinone E **451** and penicitrinol J **452** and the citrinin monomers penicitrinol K **453** and citrinolactone D **454** were isolated from *Penicillium* sp. (mangrove sediment, Fu Gong, Long Hai, Taiwan Strait, China).³⁸⁶

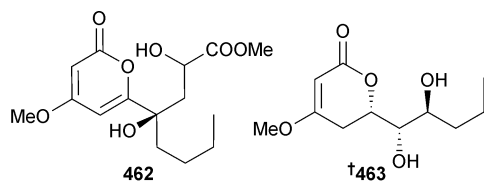
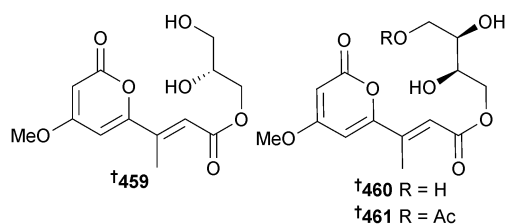
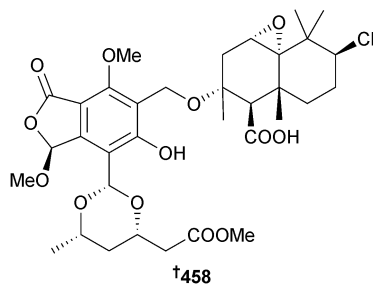
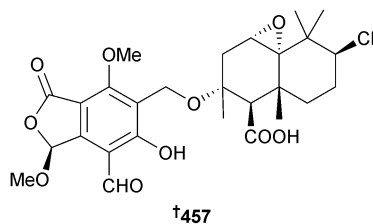


Arisugacin I **455**, an α -pyrone meroterpene, was obtained from endophytic *Penicillium* sp. (mangrove leaves *Kandelia candel*, Shankou, Guangxi Province, China) as an inhibitor of acetylcholinesterase.³⁸⁷ The known fungal metabolite arisugacin F³⁸⁸ was also obtained for the first time from the marine environment.³⁸⁷ Endophytic *Penicillium* sp. (mangrove leaves *Avicennia* sp., Dong Sai, Hainan, China) yielded the iso-benzofuranone **456** which was moderately cytotoxic to KB and KB_{V200} cells.³⁸⁹

Pestaliopins A **457** and B **458**, hybrid sesquiterpene–cyclopaldic acid metabolites with an unusual carbon skeleton, were isolated from endophytic *Pestalotiopsis* sp. (mangrove leaves *Rhizophora mucronata*, Hainan Is. China). Pestaliopin A **457** exhibited modest inhibition of *E. faecalis*.³⁹⁰

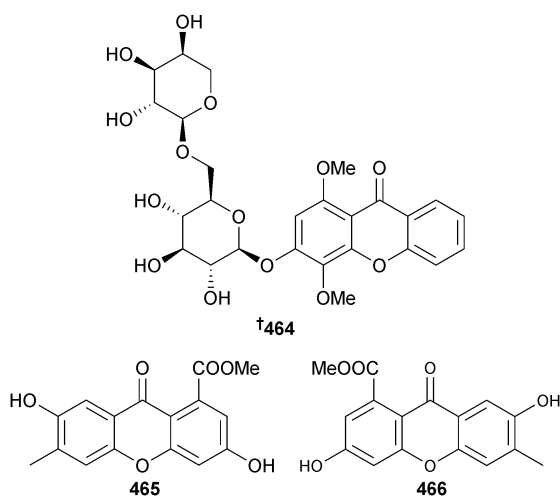
P. virgatula (mangrove leaf *Sonneratia caseolaris*, Dong Zhai Gang mangrove garden, Hainan Is., China) yielded the α -pyrone derivatives pestalotiopyrone I–L **459–462** as well as (6*S*,1'*S*,2'*S*)–



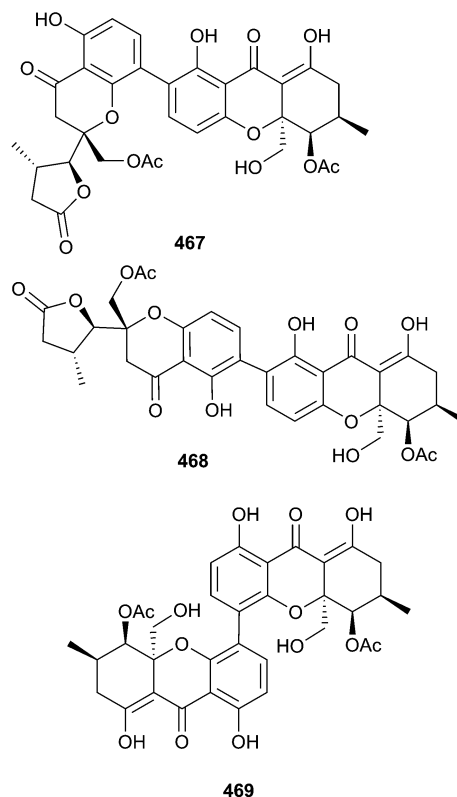


hydroxypestalotin **463**,³⁹¹ a diastereoisomer of a metabolite isolated from a plant associated *Penicillium* sp.³⁹²

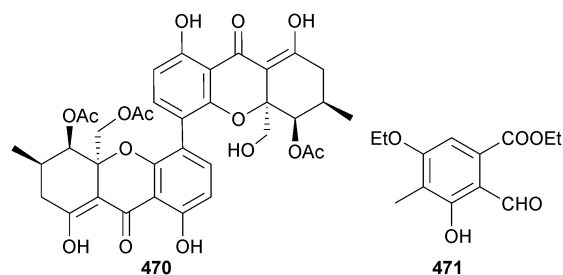
The xanthenes *O*-glycoside **464** isolated from endophytic *Phomopsis* sp. (mangrove stem *Excoecaria agallocha*, Dong Zai, Hainan, China)³⁹³ and **465** and **466** isolated from *Phomopsis* sp. (mangrove sediment, Shankou, Hainan, China)^{394,395} were moderate inhibitors of HEP-2 and HepG2 cells.



Three new phomoxanthone compounds phomolactonexanthone A **467**, B **468** and deacetyl-phomoxanthone C **469** were obtained from *Phomopsis* sp. (mangrove branch *Acanthus ilicifolius*, Hainan, S. China Sea) along with five phomoxanthenes known as endophytic metabolites of terrestrial fungi, namely dicerandrol A,³⁹⁶ dicerandrol B,³⁹⁶ dicerandrol C,³⁹⁶ deacetylphomoxanthone B³⁹⁷ and penexanthone A,³⁹⁸ all isolated as first time MNPs.³⁹⁹



Phomopsis sp. (mangrove plant *Rhizophora mucronata*, Muara Angke, Jakarta, Indonesia) was the producer of the dimeric tetrahydroxanthone 12-*O*-deacetyl-phomoxanthone A **470** which exhibited moderate inhibition of several Gram-positive bacteria.⁴⁰⁰ A polysubstituted benzaldehyde derivative **471** was isolated from co-culture of two unidentified mangrove fungi (S. China Sea coast).⁴⁰¹



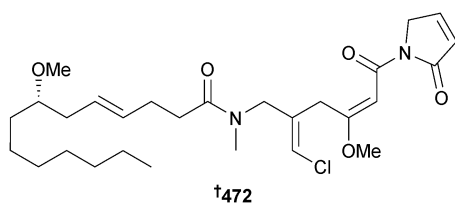
Marinamide and the methyl ester, methyl-marinamide were originally isolated from a co-culture of two mangrove



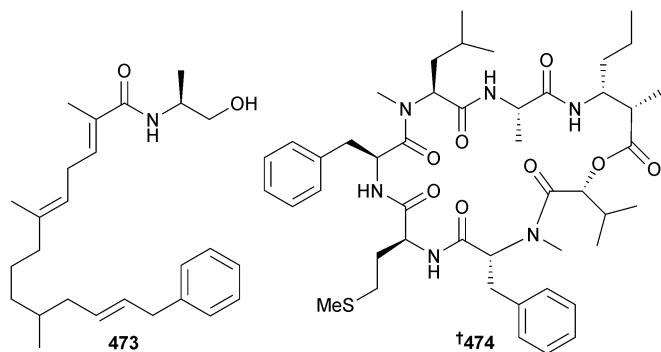
endophytic fungi from the S. China Sea Coast and assigned as pyrrol-1-isoquinoline alkaloids.⁴⁰² Subsequently, the fungus *Auxarthron reticulatum* (sponge *Ircinia variabilis*) yielded the quinolinone methyl-penicinoline, shown to be identical to methyl-marinamide requiring structural revision.²⁴⁴ The revised structure of marinamide is identical to that of penicinoline, previously obtained from a mangrove endophytic fungus.⁴⁰³ This problem has already been addressed above in Section 3.3. Both marinamide/penicinoline⁴⁰³ and its methyl ester²⁴⁵ displayed potent cytotoxicity to several HTCLs.

3.5 Cyanobacteria

There has been a marked drop in the number of new metabolites reported from cyanobacteria, continuing the downward trend from 2012. The lipopeptide malyngamide 472 was isolated from *Moorea producens* (Red Sea, Jeddah, Saudi Arabia) as a moderate inhibitor of several HTCLs.⁴⁰⁴

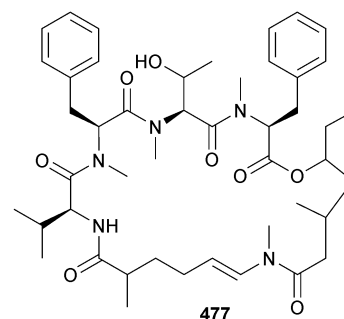
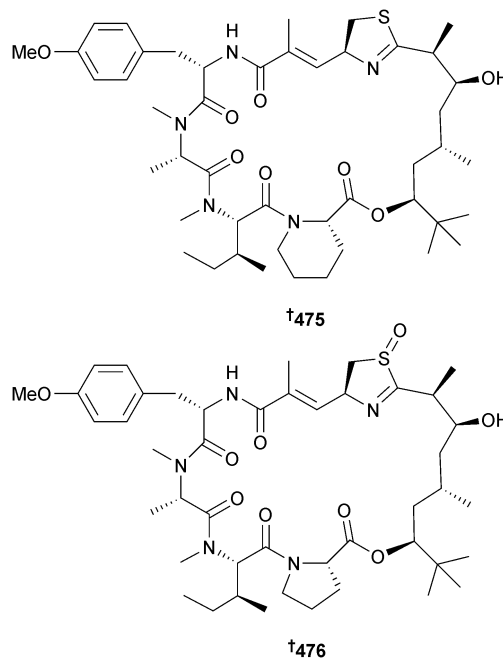


M. producens (La Parguera, Puerto Rico) was the source of the lipopeptides parguerene 473 and precarriebowmide 474. Studies of the stability of precarriebowmide 474 to atmospheric oxygen indicated that carriebowmide⁴⁰⁵ and carriebowmide sulfone,⁴⁰⁶ previously isolated from *Lyngbya polychroa* and *Lyngbya majuscula* respectively, may in fact be isolation artefacts of precarriebowmide 474.⁴⁰⁷

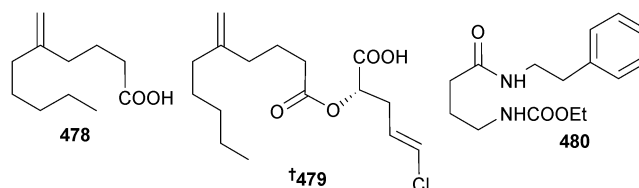


Two new aprataoxin analogues, aprataoxin H 475 and aprataoxin A sulfoxide 476, were obtained from *M. producens*, (Nabq Mangroves, Gulf of Aqaba, Red Sea) and both exhibited cytotoxicity to NCI-H460 lung cancer cells, but aprataoxin H 475 was much more potent than aprataoxin A sulfoxide 476.⁴⁰⁸

M. bouillonii (New Britain, Papua New Guinea) was the source of bouillonamide 477, a cyclic depsipeptide which contained two unique polyketide-derived moieties, a 2-methyl-6-methylamino-hex-5-enoic acid residue and a unit of 3-methyl-5-hydroxy-heptanoic acid. Bouillonamide 477 displayed moderate toxicity to neuron 2a mouse neuroblastoma cells.⁴⁰⁹



A cyanobacterium of similar morphology to *Lyngbya* sp. (Piti Bay, Guam) produced the lipids pitinoic acid A 478 and B 479. Pitinoic acid A 478 inhibited quorum sensing in *Pseudomonas aeruginosa* and pitinoic acid B 479 exhibited anti-inflammatory activity, inhibiting production of pro-inflammatory cytokine expression. Pitinoic acid B 479 has been synthesised.⁴¹⁰ A species resembling the genus *Symploca* (Santa Cruz Is., Coiba National Park, Panama) yielded santacruzamate A 480, a potent and specific inhibitor of histone deacetylase 4 and cytotoxic to several HTCLs. Santacruzamate A 480 was synthesised from γ -aminobutyric acid.⁴¹¹

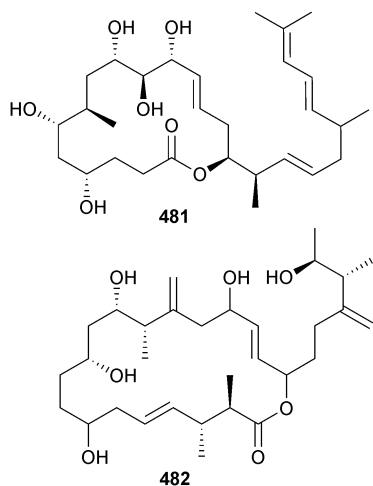


3.6 Dinoflagellates

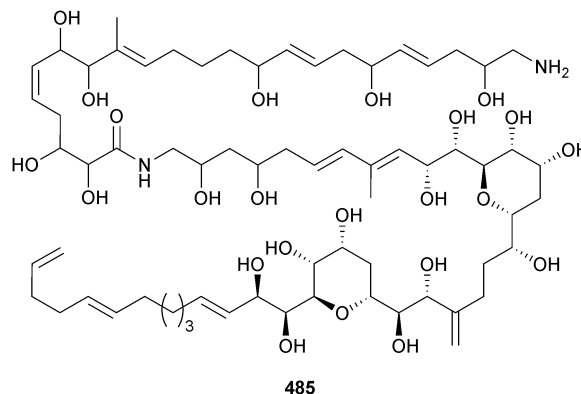
An *Amphidinium* sp. (sediment, Iriomote Is., Japan) was the producer of iriomoteolides-4a 481 and -5a 482, which displayed



moderate cytotoxicity against human B lymphocyte DG-75 cells.⁴¹²



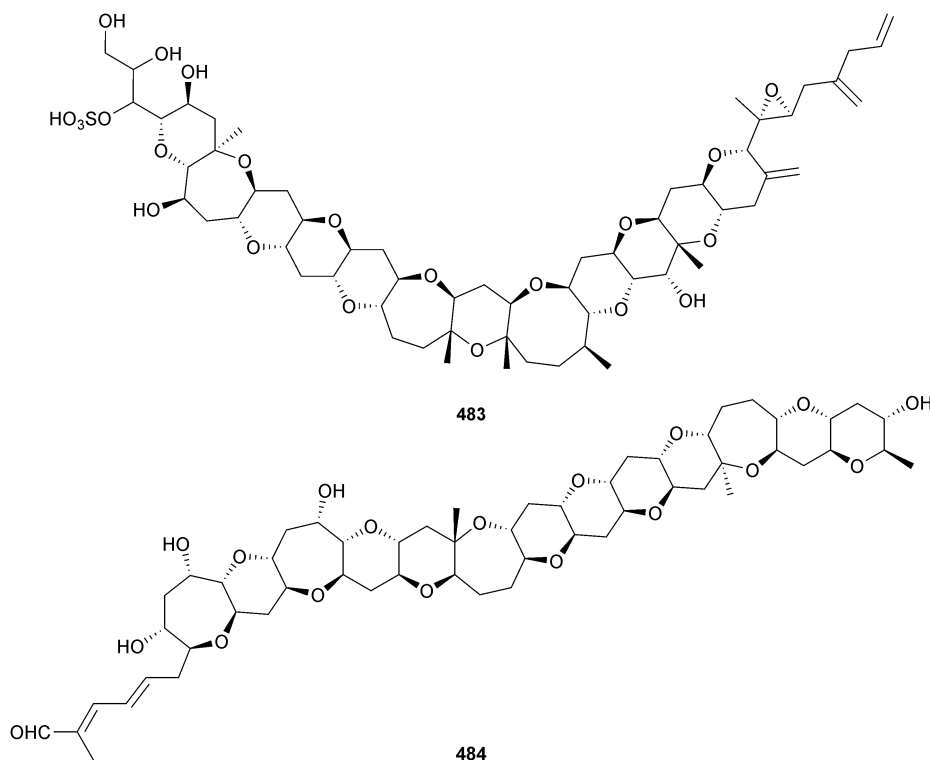
(Ikei Is., Okinawa, Japan) produced ovatoxins-a, -d and -e, each tentatively assigned by negative fast-atom bombardment collision-induced tandem mass spectrometry (FAB CID MS/MS).⁴¹⁷

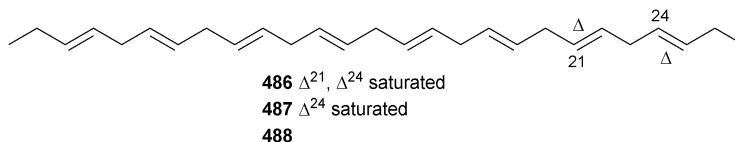


An epoxy polyether with twelve contiguous *trans*-fused ether rings, gambieroxide **483** was obtained from *Gambierdiscus toxicus* (Papeete, Tahiti, French Polynesia).⁴¹³ Gymnocin-A2 **484** was isolated from *Karenia* (formerly *Gymnodinium*) *mikimotoi* (Kushimoto Bay, Wakayama, Japan) as a moderate cytotoxin to P388 cells, along with the known synthetic analogue, gymnocin-A carboxylic acid⁴¹⁴ (first isolation from a natural source).⁴¹⁵

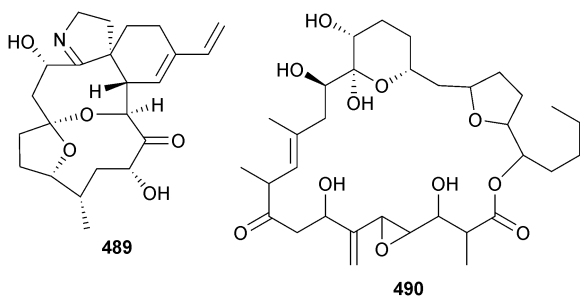
The epiphytic, benthic dinoflagellate *Ostreopsis cf. ovata* (Jeju Is., S. Korea) was the source of ostreol A **485**, significantly cytotoxic to brine shrimp,⁴¹⁶ whilst the IK2 strain of *O. ovata*

Pyrocystis lunula (University of Texas Culture Collection) yielded three polyunsaturated C27 hydrocarbons; *n*-heptacos-3,6,9,12,15,18-hexaene (C27:6) **486**, (approx. 0.7 ng per sheathed cell), *n*-heptacos-3,6,9,12,15,18,21-heptaene (C27:7) **487** and *n*-heptacos-3,6,9,12,15,18,21,24-octaene (C27:8) **488**.⁴¹⁸ The benthic dinoflagellate *Vulcanodinium rugosum* (Northland, New Zealand) yielded portimine **489**, a polycyclic ether toxin containing a five-membered imine ring, which exhibited potent toxicity to P388 cells, in addition to activation of caspases, as an indication of apoptotic activity.⁴¹⁹



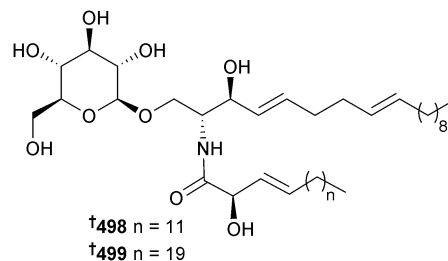
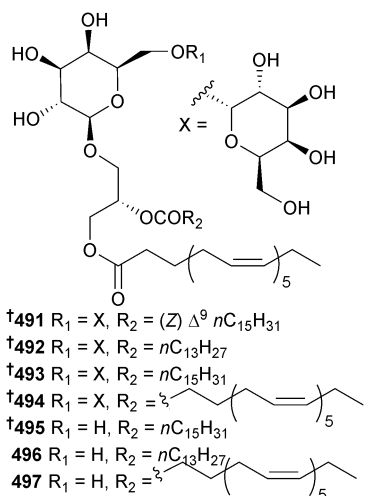


The structure of amphidinolide N, the most potent cytotoxic macrolide isolated from *Amphidinium* sp. to date⁴²⁰ has been revised to **490** (and the relative configuration has been assigned).⁴²¹



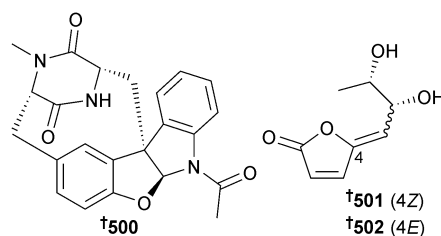
3.7 Microalgae

The microalga *Nannochloropsis granulata* (Provasoli-Guillard National Centre for Culture of Marine Phytoplankton, West Boothbay Harbour, Maine) was the source of the digalactosyldiacylglycerols **491**, **492** and the known **493** (ref. 422) and **494**,⁴²² whose configurations were determined. Also isolated were the monogalactosyl analogues **495**,⁴²² **496** (ref. 423) (first time as an NP) and **497**.⁴²³ All of the isolated metabolites exhibited strong NO inhibitory activity against LPS-induced NO production in RAW264.7 macrophage cells suggesting potential as anti-inflammatory agents.⁴²⁴ The green microalga *Tetraselmis* sp. (National Institute of Technology and Evaluation Biological Resource Centre, Chiba, Japan) was a producer of the glycosylceramides GT1 **498** and GT2 **499**.⁴²⁵



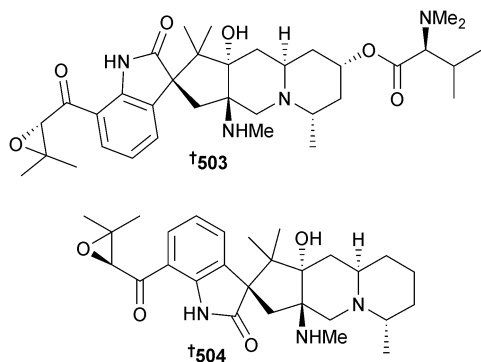
3.8 Synthetic aspects

Synthesis of acremolins, originally isolated from sponge-associated *Acremonium strictum* and assigned as containing a 1*H*-aziridine moiety⁴²⁶ proved that the alternative structure independently proposed (an isomeric, substituted $N^2,3$ -ethenoguanine)⁴²⁷ was indeed correct.⁴²⁸ Total synthesis of *ent*-(-)-azonazine utilising a hypervalent iodine-mediated biomimetic oxidative cyclisation to construct the core, has resulted in revision of the absolute configuration of natural (+)-azonazine, originally obtained from Hawaiian *Aspergillus insulicola*⁴²⁹ to **500**,⁴³⁰ while syntheses of versicolactones A and B, lactones originally isolated from coral-associated *Aspergillus versicolor*,⁴³¹ have resulted in revision of the absolute configurations of the NPs to (4*Z*,6*R*,7*S*)-**501** and (4*E*,6*R*,7*S*)-**502** respectively.⁴³² It should be noted that the names versicolactones A and B have also been used to refer to unrelated sesquiterpene lactones isolated from the plant *Aristolochia versicolor*.^{433,434}

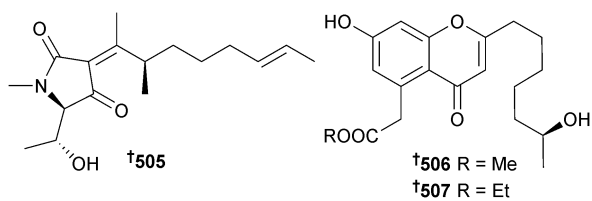


Citrinadins A and B are pentacyclic alkaloids, originally obtained from a red alga-associated strain of *Penicillium citrinum*.^{435,436} An enantioselective total synthesis of (-)-citrinadin A has been achieved in twenty steps from commercially available materials which featured an asymmetric vinylogous Mannich addition of a dienolate to a chiral pyridinium salt to set the initial chiral centre. The synthesis led to revision of the core stereochemistry of the citrinadins and thus of citrinadin A to **503**.⁴³⁷ An enantioselective total synthesis of (+)-citrinadin B featuring a stereoselective intermolecular nitron cycloaddition reaction as a key step, similarly led to revision of the configuration of citrinadin B to (+)-**504**.⁴³⁸

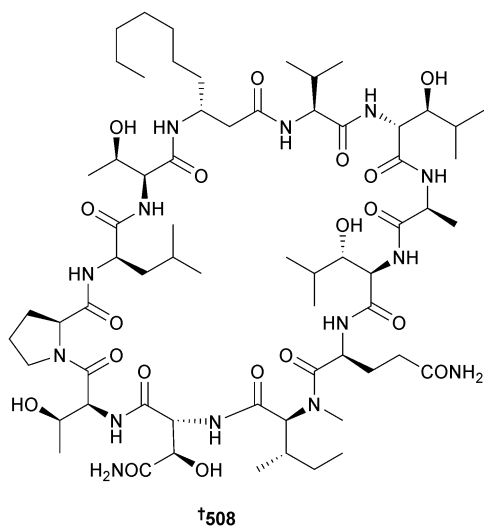




Trichodermatide A, a polyketide isolated from the fungus *Trichoderma reesei*,⁴³⁹ has been synthesised from L-tartaric acid utilising an intramolecular ketal formation reaction to construct the core of the molecule.⁴⁴⁰ The total syntheses of the putative structures of (±)-trichodermatides B and C featuring the oxa-[3 + 3] annulation strategy have also been accomplished but mismatch of spectroscopic data between the synthetic and NP samples has indicated that the structural assignments of these metabolites may need revision.⁴⁴¹ Syntheses of two diastereoisomers of penicillenol C1, originally obtained from an endophytic, mangrove-associated *Penicillium* species,⁴⁴² have led to reassignment of the absolute configuration as 505 (5*S*,6*R*,9*S*).⁴⁴³ The absolute configurations of the endophytic mangrove *Pestalotiopsis* sp. metabolites, pestalotiopsone D and E⁴⁴⁴ were determined through total syntheses as 506 and 507 respectively.⁴⁴⁵



Synthesis of the reported structure of xylopyridine A, a DNA-binding agent originally obtained from a mangrove-associated *Xylaria* sp.,⁴⁴⁶ has indicated that the reported structure is incorrect and requires revision.⁴⁴⁷ Total synthesis of laxaphycin



B, a metabolite of terrestrial *Anabaena laxa*⁴⁴⁸ and of marine *L. majuscula*,⁴⁴⁹ was achieved through stepwise automated solid-phase peptide synthesis, which led to revision of configuration to 508. The related *L. majuscula* metabolite lyngbyacyclamide A⁴⁵⁰ was also synthesised by a similar procedure.⁴⁵¹

The dolastatin 14 analogue, malevamide E, was originally obtained from the cyanobacterium *Symploca laete-viridis* and the stereochemistry of the peptidic portion assigned.⁴⁵² Convergent synthesis of (2*S*,3*S*)-malevamide E involving Julia-Kocienski olefination, Urpi acetal aldol and Shiina macro-lactonisation reactions has been achieved but a mismatch of the NMR data between the synthetic and natural samples indicated that the originally assigned configurations of some of the amino acids need revision.⁴⁵³ A stereoselective synthesis of the C-43–C-67 fragment of amphidinol 3, originally obtained from the dinoflagellate *Amphidinium klebsii*,⁴⁵⁴ revised the originally assigned configuration at C-51 from (*R*) to (*S*).⁴⁵⁵ Ieodomycins A and B are antimicrobial fatty acids originally obtained from a *Bacillus* sp.⁴⁵⁶ The first⁴⁵⁷ of several total syntheses of these published in 2013,^{458–460} has been achieved in fifteen steps *via* the chiral pool approach from D-glucose.⁴⁵⁷ Syntheses of the glycolipopeptides ieodoglucomide A and B, originally obtained from *Bacillus licheniformis*,⁴⁶¹ have been accomplished *via* a method involving β-glycosylation and Grubbs olefin cross-metathesis as key steps. The syntheses highlighted that the optical rotation values were originally misreported as being of opposite sign to their actual values and the authors of the isolation paper had noted this also.^{462,463} Syntheses of marinacarboline A–D, antimalarial β-carboline alkaloids originally obtained from *Marinactinospora thermotolerans*⁴⁶⁴ were achieved in four steps from methyl 1-chloro-β-carboline-3-carboxylate⁴⁶⁵ and the cyclic peptide urukthapelstatin A, originally isolated from the bacterium *Mechercharimyces asporophorigenens*^{466,467} has been synthesised *via* a convergent strategy.⁴⁶⁸ Trioxacarcin A, a structurally complex glycosidic metabolite of terrestrial⁴⁶⁹ and marine⁴⁷⁰ *Streptomyces* species, has been synthesised *via* a method which utilised late-stage stereoselective glycosylation reactions of aglycon substrates.⁴⁷¹ Indoxamycins A, C, and F, cytotoxic tricyclic polypropionates originally obtained from a *Streptomyces* sp.⁴⁷² and whose stereochemistry has also been revised as a result of a synthesis of indoxamycin B,⁴⁷³ have been synthesised *via* a divergent approach with an Ireland-Claisen rearrangement, a stereodivergent reductive 1,6-enyne cyclisation and a tandem 1,2-addition/oxa-Michael/methylenation reaction sequence as key steps.⁴⁷⁴ Cytosporin D, an epoxyquinone metabolite of *Eutypella scoparia*,⁴⁷⁵ has been prepared from the Diels–Alder adduct of cyclopentadiene and 2-prenyl-*p*-benzoquinone,⁴⁷⁶ while helicascolide B, a lactone originally obtained from the fungus *Helicascus kanaloanus*,⁴⁷⁷ has been synthesised in seven steps from commercially available tiglic aldehyde.⁴⁷⁸ Leptosin D, originally obtained from a *Leptosphaeria* sp. associated with a brown alga⁴⁷⁹ has been synthesised *via* a strategy which first prepared the known terrestrial⁴⁸⁰ and marine⁴⁸¹ fungal metabolite gliocladine C, which was then manipulated to access various tryptophan-derived epidithiodioxopiperazine NPs.⁴⁸² Enantioselective total synthesis of (–)-penicipyron, a polycyclic



4-hydroxy-2-pyrone metabolite of a *Penicillium* species associated with a Thai sea fan *Annella* sp.,⁴⁸³ was achieved in twelve steps by a biomimetic bimolecular cascade cyclisation featuring an intermolecular Michael addition/cyclo-(spiro-) ketalisation sequence⁴⁸⁴ and total syntheses of plectosphaeroic acids A–C (indoleamine 2,3-dioxygenase inhibitors from the fungus *Plectosphaerella cucumerina*⁴⁸⁵) have been accomplished.^{486,487} The quinoline alkaloid, 4,8-dimethyl-6-*O*-(2',4'-di-*O*-methyl- β -D-xylopyranosyl)hydroxyquinoline, originally obtained from a Caribbean collection of *Lyngbya majuscula*,⁴⁸⁸ has been synthesised by a method which utilises unusual silyl group migrations⁴⁸⁹ and synthesis of nhatrangin A, an aplysiatoxin-related metabolite isolated from Vietnamese *Lyngbya majuscula*,⁴⁹⁰ has been accomplished and confirmed the absolute configuration originally proposed.⁴⁹¹ (+)-Serinolamide A, a cannabinomimetic lipid metabolite of Panamanian *Lyngbya majuscula*⁴⁹² has been synthesised from L-serine in nine steps with 30% overall yield⁴⁹³ and total synthesis of viequeamide A, a cyclic depsipeptide metabolite of the Puerto Rican “button” cyanobacterium *Rivularia* sp.,⁴⁹⁴ was achieved in ten linear steps based on three retrosynthetic fragments.⁴⁹⁵ Amphidinolide C, a macrocyclic lactone metabolite of the dinoflagellate *Amphidinium* sp.,⁴⁹⁶ has been synthesised through the use of a common intermediate to access both the C-1–C-8 and the C-18–C-25 sections.⁴⁹⁷

3.9 Assorted bioactivities

The sesterterpenes ophiobolin K,^{498,499} 6-*epi*-ophiobolin K^{498,499} and 6-*epi*-ophiobolin G,⁴⁹⁹ known metabolites of both terrestrial⁴⁹⁸ and marine⁴⁹⁹ fungi were isolated from *Emericella varicolor* (sediment, Gokasyo Gulf, Mie Prefecture, Japan) as inhibitors of biofilm formation of *Mycobacterium smegmatis* and of *M. bovis* BCG at concentrations below those required for antimicrobial activity.⁵⁰⁰ Toluquinol, a methylhydroquinone known as a metabolite of the soil fungus *Nectria erubescens*⁵⁰¹ was isolated from a *Penicillium* sp. (Instituto Biomar, León, Spain) as an antiangiogenesis agent, inhibiting the growth of endothelial and tumour cells *via* apoptosis after a cell cycle block and caspase activation.⁵⁰² Several known fungal metabolites were isolated as selective inhibitors of PTP1B, a potential target for the treatment of type 2 diabetes and obesity.⁵⁰³ *Penicillium* sp. (sediment, Wan Is., S. Korea) yielded fructigenine A⁵⁰⁴ and cyclopenol,⁵⁰⁵ *Eurotium* sp. (sediment, Wan Is., Korea) yielded echinulin⁵⁰⁶ and flavoglucin⁵⁰⁷ and a further *Penicillium* sp. (unidentified sponge, Jeju Is., S. Korea) was the source of viridicatol.⁵⁰⁵ Bis-*N*-norgliovictin, a known terrestrial⁵⁰⁸ and marine^{509,510} metabolite was isolated from a marine-derived endophytic fungus (no other details given), as an anti-inflammatory agent that inhibited LPS-induced TNF- α production in RAW264.7 cells.⁵¹¹

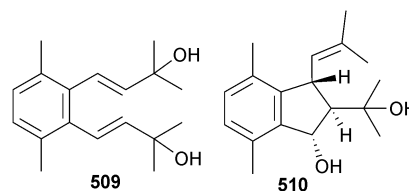
3.10 Biosynthesis

The gene cluster responsible for the biosynthesis of the glycosylated diazofluorene polyketides lomaiviticins A–E,^{512,517} originally isolated from *Salinispora pacifica* (formerly *Micromonospora lomaivitiensis*), was identified in wild-type *Salinispora tropica* and several mutant strains through bioactivity-guided genome mining.⁵¹³ An investigation of 163 strains of actinomycetes isolated

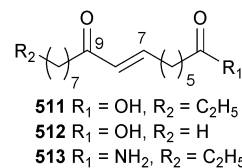
from mangrove sediments *via* homologous screening of the biosynthetic genes and bioassay identified 16% of the strains as possessing the potential to produce halogenated NPs.⁵¹⁴ The stephacidin and notoamide families of NPs occur in various *Aspergillus* species, both terrestrial⁵¹⁵ and marine.⁵¹⁶ In a further elaboration of the biosynthesis of these metabolites, notoamide T was identified as the likely precursor to stephacidin A and synthesised along with the C-6-epimer, 6-*epi*-notoamide T. Stephacidin A was chemically converted to notoamide T by reductive ring opening while notoamide T also underwent oxidative conversion to stephacidin A. [¹³C]₂-Notoamide T was synthesised and fed to two *Aspergillus* strains resulting in significant incorporation into the advanced metabolite notoamide B.⁵¹⁷ Analysis of transcriptome data of a number of saxitoxin (STX)-producing dinoflagellates, especially *Alexandrium tamarense* strains, identified 265 putative homologues of 13 cyanobacterial STX synthesis genes, including all of the genes directly involved in toxin synthesis. Putative homologues of four proteins group closely in phylogenies with cyanobacteria but the phylogenies do not support transfer of these genes directly between toxic cyanobacteria and dinoflagellates, suggesting that the STX synthesis pathway was likely to have been assembled independently in cyanobacteria and dinoflagellates, but using some evolutionarily related proteins.⁵¹⁸

4 Green algae

Interest in green alga chemistry continued at a low ebb in 2013. Further work on *Caulerpa racemosa* (Zhanjiang coastline, China), previously the source of caulerpin and two related caulerpin derivatives,⁵¹⁹ led to the discovery of two prenylated *para*-xylenes caulerprenylol A **509** and B **510** that were each weakly antifungal.⁵²⁰



Interesting results were uncovered from the screening and careful bioassay-guided analysis of a collection of Floridian marine eukaryotic algae using an ARE-luciferase reporter gene assay that led to the detection and isolation of three mono-unsaturated fatty acids **511–513** from *Ulva lactuca* as activators of the ARE response. Each contained the identical $\Delta^7,9$ -keto motif.⁵²¹



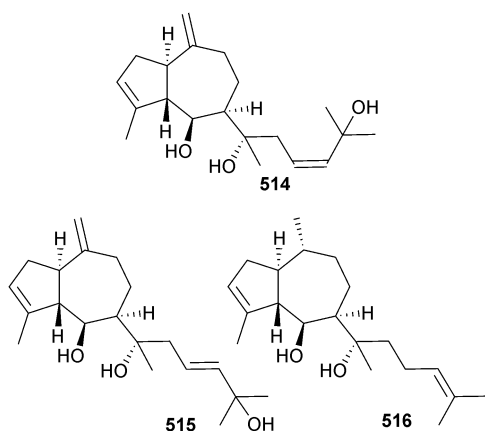
A stereoselective synthesis of the C-8'–O–C-6'' ether of the antimetabolic agent nigricanoside A⁵²² was successfully applied in model systems.⁵²³ Included in the green algal literature for 2013



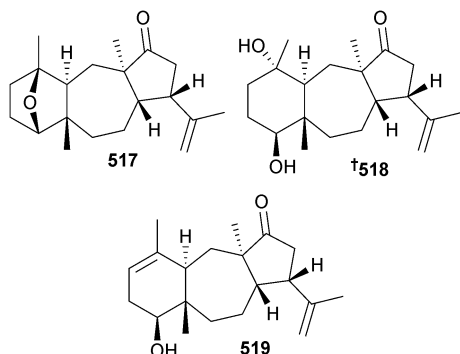
were reports on the cytotoxic effects of clerosterol from *Codium fragile*⁵²⁴ on HTCLs⁵²⁵ and the spasmolytic effects of caulerpine⁵²⁶ on guinea pig ileum.⁵²⁷

5 Brown algae

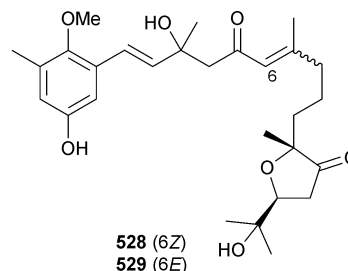
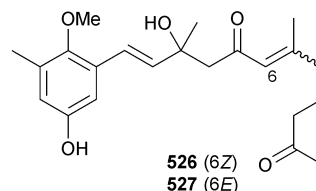
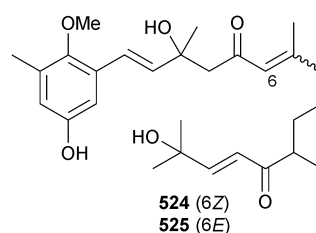
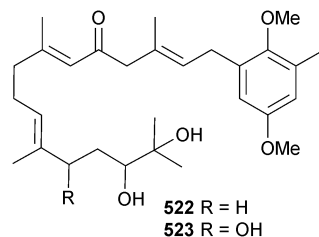
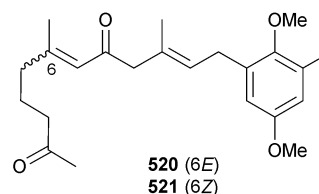
The number of new compounds characterised in 2013 from the Ochrophyta was again relatively low and was dominated by terpenoid chemistry. Based on the *in vitro* cytotoxicity of a crude *Dictyota dichotoma* (Abu-Bakr, Red Sea, Egypt) extract an investigation was mounted and three new diterpenoids (*Z*)-pachydictyol B **514**, (*E*)-pachydictyol B **515** and pachydictyol C **516** were characterised along with the known pachydictyol A⁵²⁸ and several other well-known brown algal metabolites.⁵²⁹



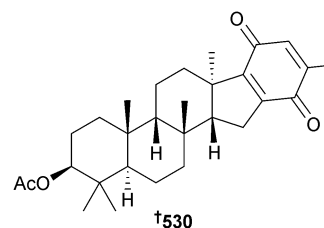
Re-investigation of *Dilophus spiralis* (Elafonissos Is., Greece) resulted in the isolation of three new dolastanes **517–519** and five previously reported perhydroazulenes. The relative configurations were established for all three dolastanes and the absolute configuration of **518** established by conversion to a compound of known absolute configuration. The absolute configurations of **517** and **519** were assumed on the basis of biogenetic considerations.⁵³⁰



The cytotoxic meronorsesquiterpenoids cystoazorone A **520** and B **521** and meroditerpenoids cystoazorol A **522** and B **523** were isolated from *Cystoseira abies-marina* (Mosteiros, Sao Miguel Is., Azores)⁵³¹ while a series of meroditerpenoids cystodione A–F **524–529**, all with strong antioxidant properties in the ABTS assay, were isolated from *Cystoseira usneoides* (Gibraltar Strait).⁵³²

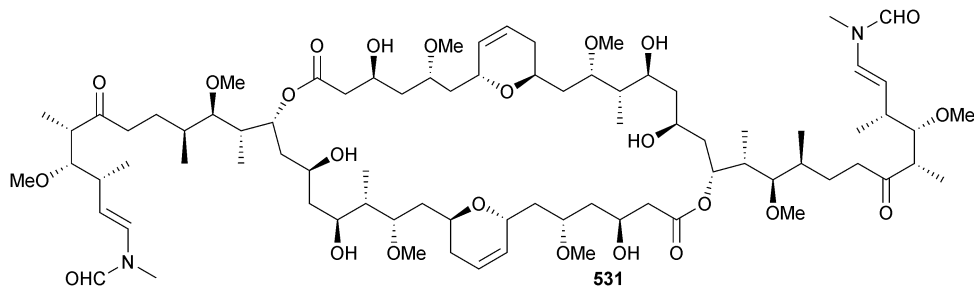


The mildly antiproliferative meroditerpenoid zonaquinone acetate **530** was obtained from a Jamaican *Stypopodium zonale*.⁵³³ Other known brown algal metabolites were co-isolated and these included flabellinone,⁵³⁴ not previously identified in *S. zonale*, stypoldione,⁵³⁵ and sargaol.⁵³⁶ The absolute configuration of **530** was determined by vibrational circular dichroism (VCD) calculations at several levels of theory.⁵³³



The synthesis of the core framework of the proposed structure of sargaol⁵³⁷ was achieved but the ¹H and ¹³C NMR

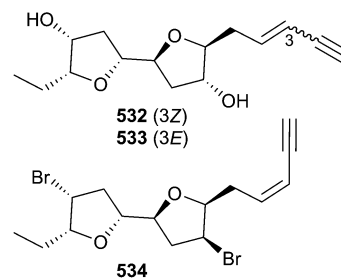




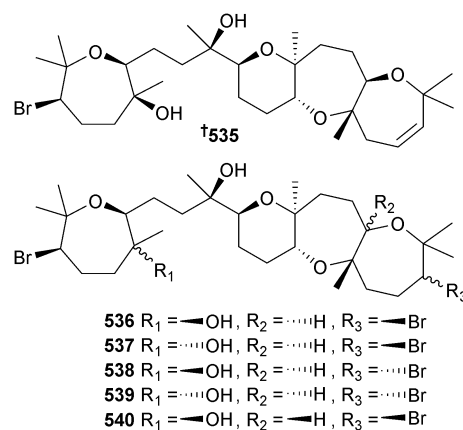
spectral data of the synthetic analogue did not match suggesting that the originally proposed structure of sargafuran is incorrect.⁵³⁸ The data matched better with the known sargachromenol.⁵³⁹ Another total synthesis of (–)-ecklonialactone B,⁵⁴⁰ as well as the non-natural (+)-9,10-dihydro-ecklonialactone B, was reported.⁵⁴¹ In papers covering biological properties of brown algal metabolites, four papers were published on the eckol group of phlorotannins describing anti-inflammatory properties,^{542,543} induction of apoptosis in carcinoma cells⁵⁴⁴ and potential as SARS inhibitors.⁵⁴⁵ Two surveys were published on the antioxidant potential of brown algal extracts which included an excellent summary from species across the phylum as well as the properties of individual brown algal metabolites.^{546,547} The antiviral properties of sulfoquinovosyldiacylglycerols from *Sargassum vulgare* (Ilha de Itacuruçá, S.E. Brazil) were evaluated⁵⁴⁸ and the antiviral activity of *Dictyota* diterpenes assessed in docking studies against HIV-1 reverse transcriptases.⁵⁴⁹ A putative inhibitory mechanism for RANK-induced osteoclast formation by sargachromanol G from *Sargassum siliquastrum*⁵⁵⁰ has been proposed⁵⁵¹ and the antiplatelet and antithrombotic effects of sargahydroquinolic and sargaquinolic acids determined.⁵⁵² In other reports of biological testing, the strong antimelanogenic properties of an extract from *Dictyota coriacea* (Jeju Is., S. Korea) were attributed to 1,9-dihydroxycrenulide⁵⁵³ and epiloliolide,⁵⁵⁴ known compounds.⁵⁵⁵ Seven known meroditerpenoids were isolated from *Sargassum siliquastrum* (Jeju Is., S. Korea) and evaluated for cytotoxicity against a range of HTCLs,⁵⁵⁶ while the cytotoxic sterol (24*R*)-hydroperoxy-24-vinylcholesterol⁵⁵⁷ was reported for the first time from *Nizamuddiniana zanardinii* (Oman Sea).⁵⁵⁸ In a comprehensive study the anticancer effects of fucoxanthin were examined from a mechanistic perspective.⁵⁵⁹ In another wide-ranging study, 20 green and brown algal extracts from the French coast were evaluated against *Trypanosoma brucei rhodesiense* (*T. b. rhodesiense*).⁵⁶⁰ The *Bifurcaria bifurcata* extract showed the strongest trypanocidal activity which was tracked to eleanolone.⁵⁶¹ The potential of the HPLC/NMR technique for chemical profiling and dereplication was illustrated with the characterisation of nine known compounds from *Cystophora torulosa* (Pt. Lonsdale, Victoria, Australia).⁵⁶²

year (47). The relative configurations of the 30 stereogenic centres in the macrodiolide luminaolide **531** (*Hydrolithon reinbodii*)⁵⁶³ were assigned from NMR data, although the relationships of the two side chains to the macrolide ring are still to be established.⁵⁶⁴

The structures of laurefurenynes A **532** and B **533** (*Laurencia* sp.)⁵⁶⁵ were reassigned following syntheses of **532**⁵⁶⁶ and **533**,⁵⁶⁷ respectively, and density functional theory (DFT) calculations of NMR chemical shift data.⁵⁶⁷ There is still doubt about the configuration of the closely related elatenyne (*L. elata*).⁵⁶⁸ Computational⁵⁶⁹ and synthetic⁵⁷⁰ efforts suggested a revised structure. However, recent more extensive NMR and chemical derivatisation studies proposed a further revision **534** but were unable to establish the absolute configuration.⁵⁷¹



Various aspects of the configurations of armatols A–F (*Chondria armata*)⁵⁷² have now been clarified through the total synthesis of armatol A **535** and hence by analogy to the structures for armatols B–F **536–540**.⁵⁷³ This paper also reported the first total synthesis of dioxepandehydrothyriferol (*Laurencia viridis*)⁵⁷⁴ as the enantiomer.

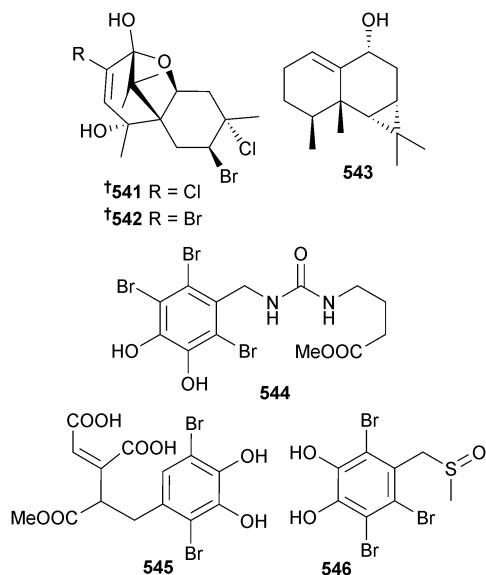


6 Red algae

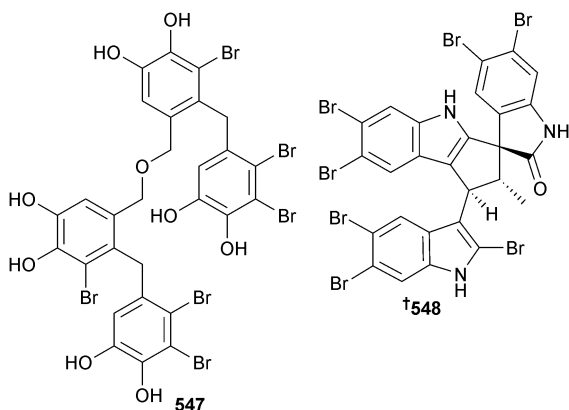
The nine new compounds reported from red algae in 2013 is a marked reduction in the number reported from the previous



The chamigrane sesquiterpenes yicterpene A **541** and B **542** were isolated from *L. composita* (Pingtan Is., China).⁵⁷⁵ Of the 7 compounds isolated from *L. similis* (Sepanggar Is., Kota Kinabalu, Sabah), *ent*-1(10)-aristolen-9 β -ol **543** was claimed as an enantiomer of a known compound.^{576,577} Two bromophenols **544** and **545** with radical scavenging activity were obtained from *Symphyocladia latiuscula* (Qingdao, Shandong Province, China).⁵⁷⁸ This same collection of *S. latiuscula* also provided the weakly antifungal bromophenol sulfoxide **546**.⁵⁷⁹



One new (**547**) and three known bromophenols isolated from *Vertebrata lanosa* (Oldervik, Ullsfjorden, Norway) had cellular antioxidant activities, the first time this activity has been reported for this class of compounds.⁵⁸⁰ The unprecedented polybrominated spiro-trisindole similisine A **548** and its enantiomer similisine B were obtained from *Laurencia similis* (S. China Sea).⁵⁸¹

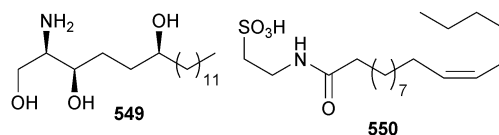


Synthesis of the two proposed diastereomers of prevezol C (*L. obtusa*)⁵⁸² showed that neither is the structure of the NP.⁵⁸³ Parguerenes (*L. filiformis*)⁵⁸⁴ were identified as inhibitors of P-glycoprotein (ABCB1) in multidrug resistant human cancer cells.⁵⁸⁵ Five known bromophenols from a variety of red algae had inhibitory activity against glucose 6-phosphate

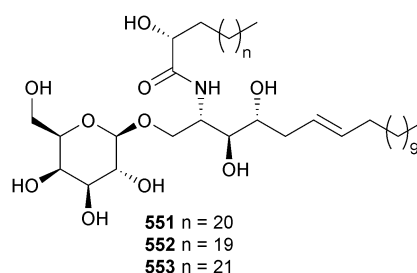
dehydrogenase, this being the first report of such inhibitors from red algae.⁵⁸⁶ Analysis of the metabolite compositions of seasonal collections of *Gracilaria gracilis* (Lesina Lagoon, S. Adriatic Sea, Italy) led to the proposition for using *G. gracilis* as a multi products source for biotechnological, nutraceutical and pharmaceutical applications.⁵⁸⁷ Bioactive metabolites isolated from *Asparagopsis taxiformis* were found to have little potential for therapy services to fish infected with *Streptococcus iniae*.⁵⁸⁸

7 Sponges

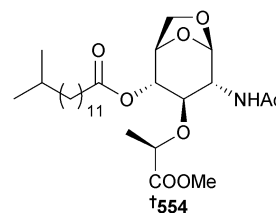
Even with only 243 new compounds reported in 2013, a significant decrease in relation to previous years (19% and 33% down on 2011 and 2012, respectively),^{589,2} sponges remain the dominant phylum for the discovery of new marine-derived bioactives (see section 15 Conclusion). The modified sphingoid base halisphingosine B **549** was isolated from *Haliclona tubifera* (Santa Catarina, Brazil)⁵⁹⁰ while taurinated fatty acid **550** was isolated from *Axinella* sp. (Hainan Is., S. China Sea).⁵⁹¹



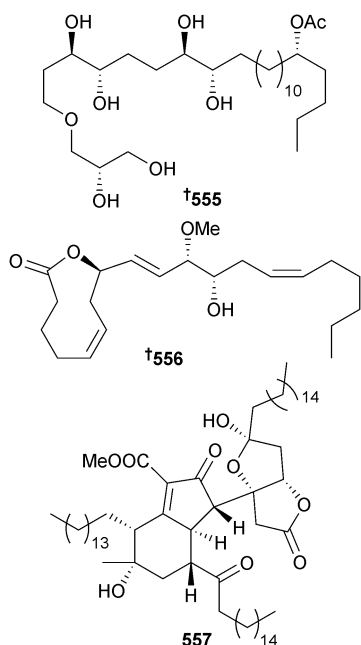
The asymmetric total synthesis of the “two-headed” sphingoid base rhizochalin C (*Rhizochalina incrustata*)⁵⁹² has been completed.⁵⁹³ An *Axinyssa djiferi* found attached to mangrove tree roots (Djifer, Senegal) yielded axidjiferosides A–C **551–553**, a mixture of which inhibited chloroquine-resistant *P. falciparum*.⁵⁹⁴



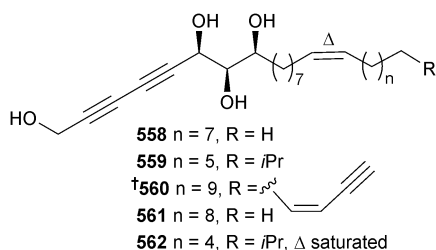
An acetylated nitrogenous glycolipid **554** was isolated from *Plakinastrella clathrata* (Gneerings Reef, Queensland, Australia), with the absolute configuration confirmed by synthesis of lipid-chain analogues. The compound was claimed to be a moderate anti-inflammatory by inhibition of PGE₂ but no data was provided.⁵⁹⁵



Mycalol 555 is a glycerol ether isolated from *Mycale acerata* (Terra Nova Bay, Antarctica). A combination of chiroptical and Mosher's methods were used to assign the absolute configuration of this specific inhibitor of human anaplastic thyroid carcinomas, the most aggressive and currently untreatable thyroid gland malignancies, but inactive against other solid tumours.⁵⁹⁶ The absolute configuration of topsentolide C₂ 556 (*Topsentia* sp.)⁵⁹⁷ was established by total synthesis of four possible diastereomers.⁵⁹⁸ The moderately antimicrobial fatty acid trimer manzamenone O 557 was isolated from *Plakortis* sp. (Manzamo, Okinawa).⁵⁹⁹

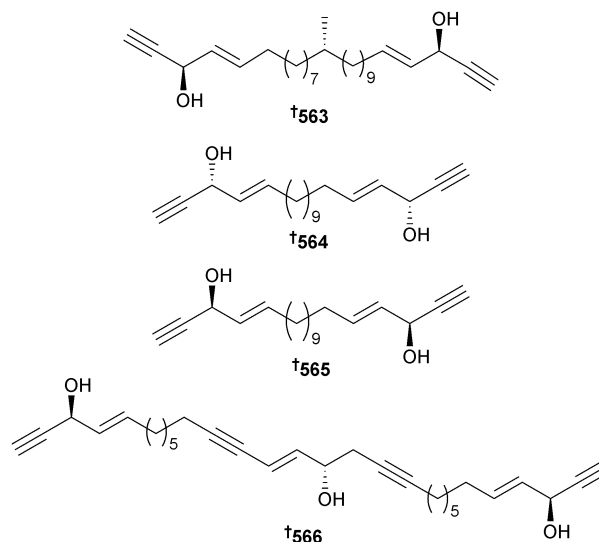


Sponges from the genus *Petrosia* continue to be a rich source of new polyacetylenes. The report of petrosiols A–E 558–562 from *Petrosia strongylata* (Ishigakijima Is., Okinawa) as inducers of nerve growth factor-like neuronal differentiation in PC12 cells was followed rapidly by reports of the total synthesis and absolute configuration of petrosiol D 560,^{600,601} and the discovery that 558 inhibits proliferation and migration of platelet derived growth factor-induced vascular smooth muscle cells and hence could be used as a lead for vascular disorders.⁶⁰²

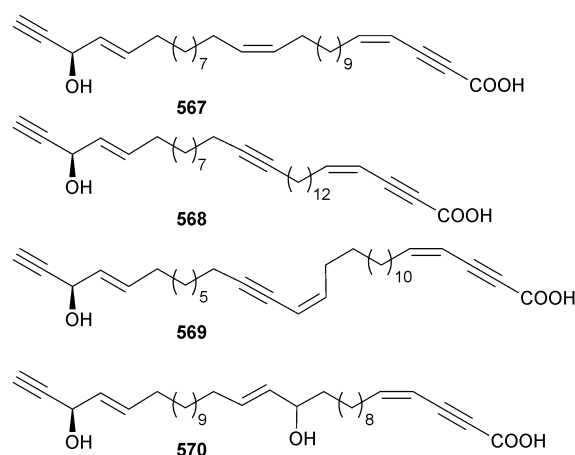


The absolute configuration of the isolated methyl group of miyakosyne A 563 (*Petrosia* sp.)⁶⁰³ was established by chemical degradation and subsequent esterification with Ohruis's

acid,⁶⁰⁴ thus correcting an earlier tentative assignment made from an analysis by X-ray crystallography of miyakosyne absorbed in a porous metal complex.^{71,605} A racemic mixture of C₂₀ bisacetylenic alcohols 564 and 565 has been isolated from *Callyspongia* sp. (Iriomote Is., Okinawa), and separated by chiral HPLC. Total synthesis of both enantiomers and detailed biological evaluation showed 564 was more active than its enantiomer against HeLa and temperature sensitive rat lymphatic endothelial cells, thus defining the 1-yne-3-ol moiety as an essential pharmacophore.⁶⁰⁶ Petrosiacetylene E 566 (*Petrosia* sp. Dokdo Is., S. Korea) was a low μM inhibitor of multiple HTCLs.⁶⁰⁷

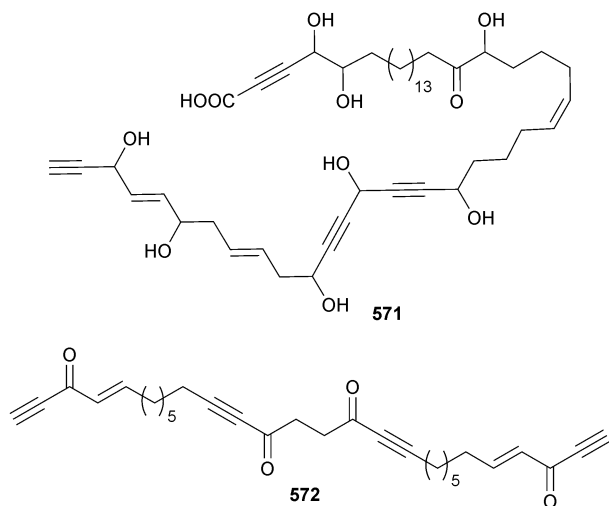


Petrosynic acids A–D 567–570 (*Petrosia* sp., Tutuila, American Samoa) all displayed similar activity versus various HTCLs and non-proliferative human fibroblasts and hence no therapeutic window is available.⁶⁰⁸

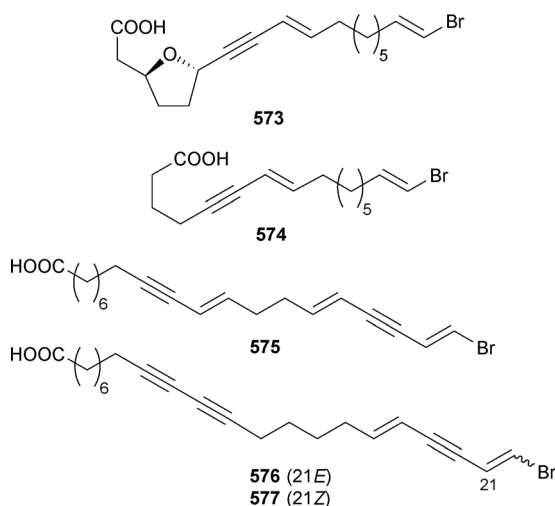


A New Caledonian *Niphat* sp. was the source of nepheliosyne B 571.⁶⁰⁹ Examination of *Petrosia solida* (Amami-Oshima, Japan) yielded petrosiacetylene 572 that inhibited starfish embryo blastulation.⁶¹⁰

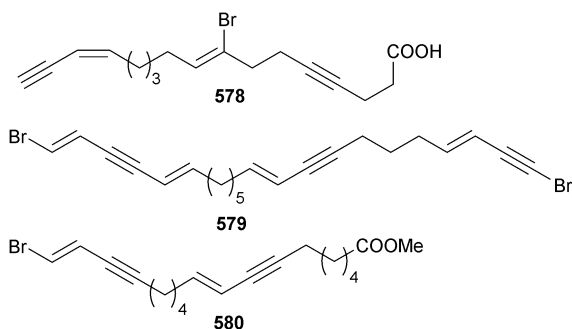




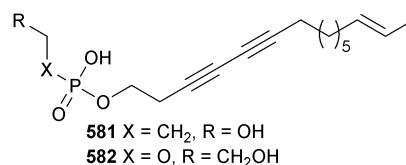
Bromoacetylene testafuran A **573** was isolated from *Xestospongia testudinaria* (Iwo Is., Kagoshima, Japan) along with four other polyacetylenes **574–577**, all five of which induced adipogenesis (stimulation of the differentiation of preadipocytes to adipocytes), and hence may act as leads for treatment of cardiovascular disorders.⁶¹¹



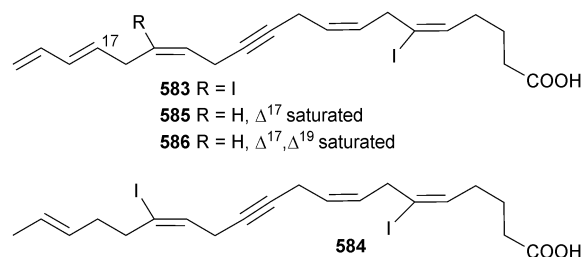
An inhibitor of starfish egg maturation, bromotheoynic acid **578**, was reported from *Theonella swinhoei* (Tanegashima, Kagoshima, Japan),⁶¹² while two further bromopolyacetylenes **579** and **580** were obtained from *Haliclona* sp. (Sharm Obhur, Jeddah, Saudi Arabia).⁶¹³



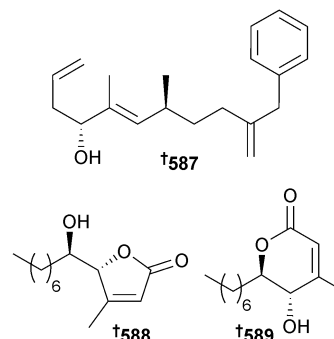
Phosphoiodyns A **581** and B **582** are iodinated and phosphate containing alkynes from *Placospongia* sp. (Tong-Young City, S. Korea). Phosphoiodyn B was inactive, but **581** was a potent inhibitor of human peroxisome proliferator-activated receptor delta (hPPAR δ) with 200-fold selectivity over other PPARs, and therefore a potent regulator of lipid and glucose metabolism, and potentially a lead for treating type 2 diabetes or metabolic disorders.^{614,615}

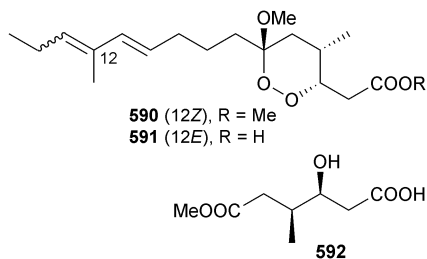


Four mono- or di-iodinated polyacetylene acids were isolated from *Suberites mammilaris* (**583** and **584**) and *S. japonicus* (**585** and **586**) (Gageo Is., S. Korea). Anti-inflammatory bioactivity profiling of the methyl esters indicated that pre-treatment with the *S. mammilaris* metabolites inhibited nitrite production in LPS-stimulated RAW 267.4 macrophages while the *S. japonicus* metabolites inhibited NO production in BV2 microglial cells, with each pair being inactive in the other assay.⁶¹⁶

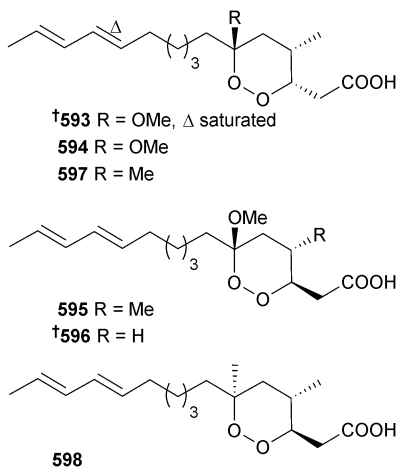


A mixed extract from *Smenospongia aurea*, *S. cerebriformis* and *Verongula rigida* (Key Largo, Florida) yielded a linear phenyl alkene **587** with activity against HL-60 cells. Molecular modelling docking studies suggested that **587** had a pharmacophore similar to that of eribulin and hence potential to interfere with microtubule dynamics.⁶¹⁷ Dysideolides A **588** and B **589** are methyl-branched lactones from *Dysidea cinerea* (Lang Co Beach, Vietnam),⁶¹⁸ while 12-manadoperoxide B **590**, manadoperoxidic acid B **591** and monoester **592** were reported from *Plakortia lita* (Bunaken Is., Manado, Indonesia). Both **591** and the likely oxidative breakdown product **592** showed potent anti-trypanocidal activity against *T. b. rhodesiense*.⁶¹⁹

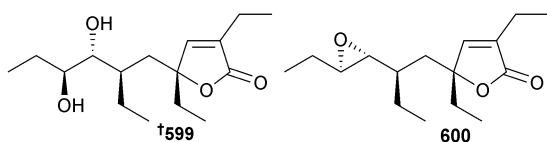




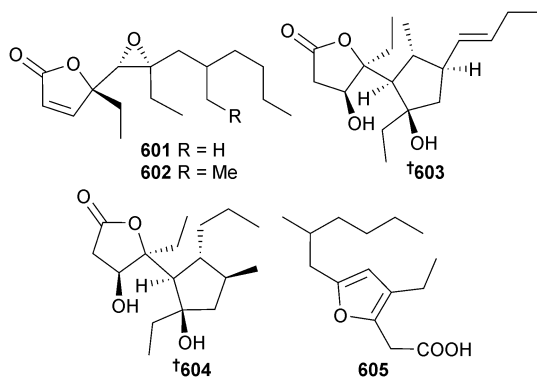
Six new methylated peroxidic acids **593–598** were isolated from *Plakortis simplex* (Keomun Is., West Sea, S. Korea). All showed low moderate cytotoxic activity against RAW264.7 cells.⁶²⁰



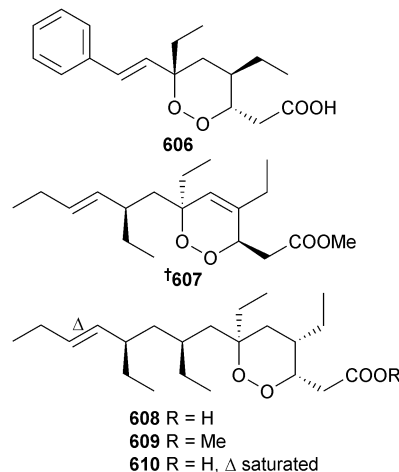
A chemical ecological study of *Discodermia dissoluta* held in Santa Marta, Colombia has shown that <40 kg of sponge could be sufficient to sustainably produce 1 g of discodermolide⁶²¹ over six months for clinical trials.⁶²² A comprehensive study combining computation, chemical derivatisation and NMR studies was used to assign both the relative and absolute configurations of plakilactones G **599** and H **600** from a Fijian *Plakinastrella mamillaris*.⁶²³



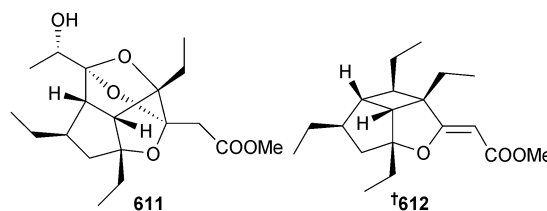
Plakortoxides A **601** and B **602**, simplexones C **603** and D **604** and plakorsin D **605** were all isolated from *Plakortis simplex* (Yongxing Is., S. China Sea) although only **603** showed activity.⁶²⁴



A two-sponge association between *Plakortis communis* and *Agelas mauritiana* (Mooloolaba, Queensland, Australia) yielded a new peroxy acid **606**.⁶²⁵ *Plakinastrella mamillaris* (Fiji Is.) produced plakortides R–U **607–610**. Congener **610** was a potent antimalarial agent against chloroquine-resistant *P. falciparum*. The remaining compounds were less active and none of the compounds were cytotoxic against Vero cells at much higher concentrations.⁶²⁶



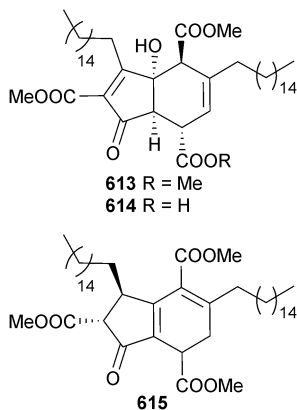
Gracilioether K **611** is a Pregnane X-Receptor (PXR) agonist with no activity against the Farnesoid X-Receptor isolated from *Plakinastrella mamillaris* (Fiji Is.). *In silico* docking studies suggested a similar binding motif to other gracilioether congeners.⁶²⁷ The sponge *Hippospongia lachne* (Xisha Is., S. China Sea) provided hippolachnin A **612**, a compound with an unprecedented carbon skeleton, that was potently antifungal, but had no activity against three cancer cell lines. The absolute configuration of **612** was determined from comparison of calculated and experimental electronic circular dichroism (ECD) spectra.⁶²⁸



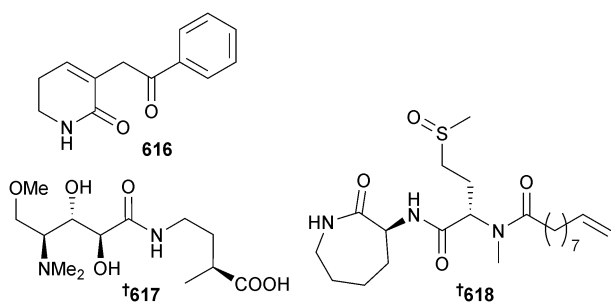
Manzamenones L–N **613–615** were isolated from *Plakortis* sp. (Manzamo, Okinawa). Manzamenones M and N showed some antimicrobial activity against *E. coli*, *S. aureus* and *Cryptococcus neoformans* (*C. neoformans*), while manzamenone L (isolated as a racemate) was inactive.⁶²⁹

Callylactam A **616** was isolated from *Callyspongia* sp. (Hainan Is., China),⁶³⁰ while allos-hemicalculin **617** was reported from *Discodermia calyx* (Shikine-Jima Is., Japan). Photo-oxidative cleavage of the oxazole moiety of calyculin A was suggested as a route to the formation of **617**.⁶³¹ The lipopeptide ciliatamide D **618** was found from a dredged *Stelletta* sp. (170 m, Oshima-shinson seamount, Japan).⁶³² This study also reaffirmed the absolute configuration of ciliatamide A (*Aaptos ciliata*) as that

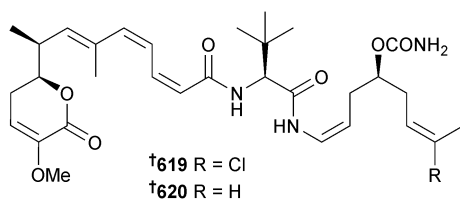




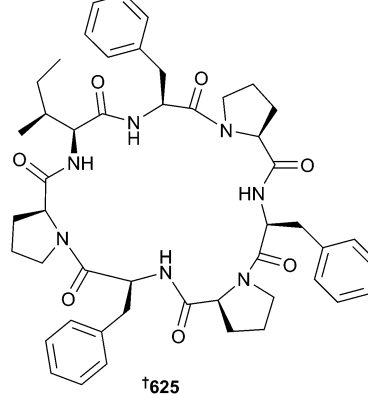
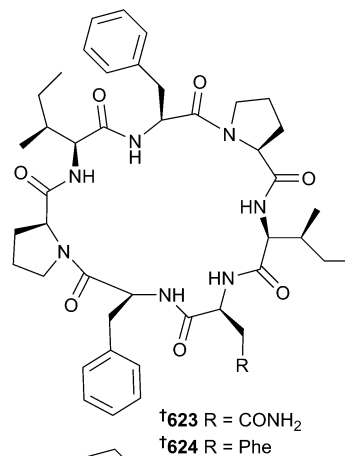
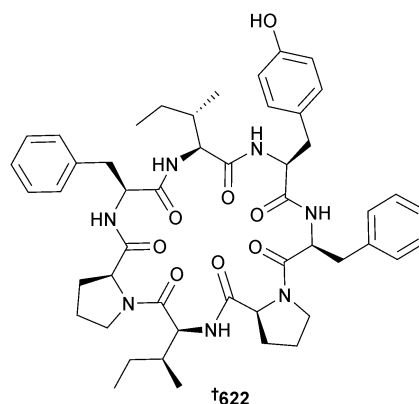
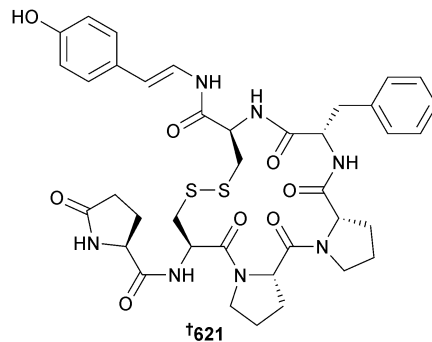
assigned during the original isolation,⁶³³ and subsequently incorrectly reassigned by synthesis.⁶³⁴



The sponge *Lithoplocamia lithistoides* (Madagascar) produced PM050489 **619** and PM060184 **620**, polyketide amides that differ only in the presence of a chlorine atom. Both are active at sub-nanomolar levels against several cancer cell lines. The gram-scale total syntheses of each compound were also reported. PM060184 **620** has undergone a remarkably rapid development from the source sponge collection in 2005 through isolation, characterisation and synthesis in 2006, to the commencement of phase I clinical trials in 2011.⁶³⁵



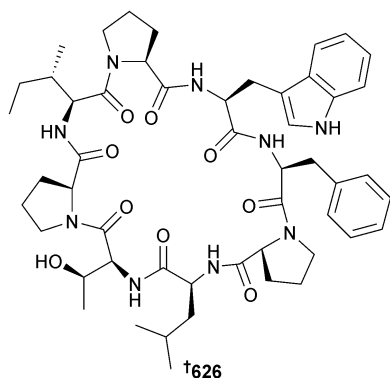
A detailed study of the terrestrial myxobacterial genera *Sorangium* and *Jahnella* has delineated the biosynthesis of the microsclerodermins, unusual peptides isolated from *Microscleroderma* and *Theonella* sponges,^{636,637} hence suggesting the likely microbial origin of these NPs.⁶³⁸ Gombamide A **621**, a disulfide linked hexapeptide, was isolated from *Clathria gombawuiensis* (Gageo-Do, S. Korea).⁶³⁹ Stylissatin A **622**, a cyclic heptapeptide from *Stylissa massa* (Loloata Is., Papua New Guinea), inhibited NO production in LPS-stimulated macrophages,⁶⁴⁰ while euryjanicins E–G **623–625** are phenylalanine- and proline-rich heptapeptides from *Prosuberites laughlini* (Puerto Rico).⁶⁴¹



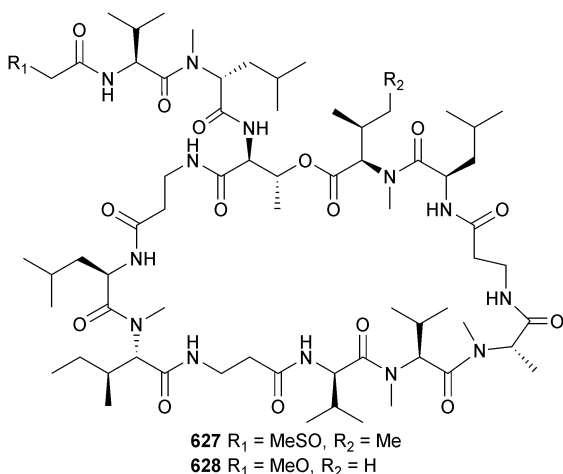
Although the structure of the NP is yet to be reported, the proline-rich octapeptide phakellistatin-19 **626** has been synthesised. Interestingly, the bioactivity of the natural (GI₅₀ =



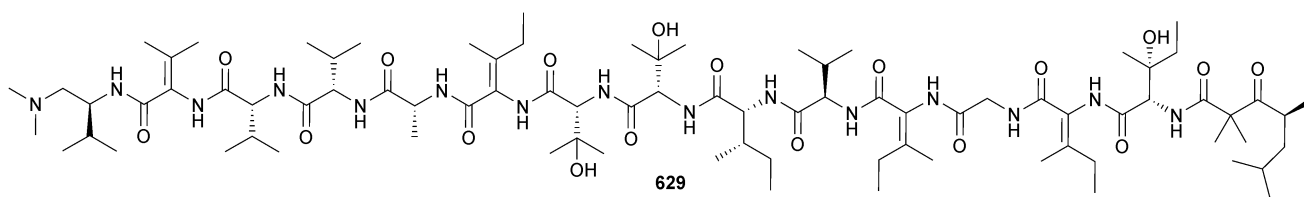
440–515 nM vs. three cell lines) and synthetic (not active) versions differ significantly, a puzzling discrepancy that has been noted previously.^{642,643}



The antifungal activity of the theonellamides (*Theonella* sp.)⁶⁴⁴ has been linked to their ability to bind to the β -OH of sterols in lipid bilayers. This was established using solid state ^2H -NMR and surface plasmon resonance spectroscopies.⁶⁴⁵ Sulfanyltheonellaepetolide **627** and theonellaepetolide If **628** were isolated from *Theonella swinhoei* (N. Sulawesi, Indonesia), both with similar activities against HepG2 hepatic carcinoma cells.⁶⁴⁶



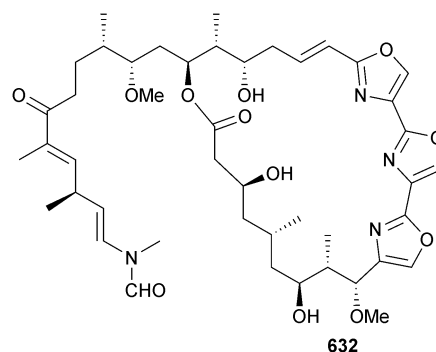
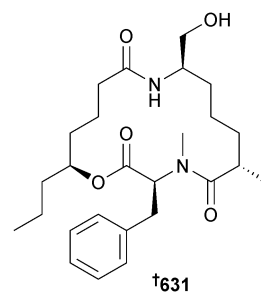
The total synthesis of yaku'amide A **629** (*Ceratopsion* sp.)⁶⁴⁷ established the configuration of the C-terminal methyl. Altering the configuration of the methyl had no significant effect on



bioactivity.⁶⁴⁸ Asteropsin A **630** (*Asteropus* sp., Geoje Is., S. Korea) is a cysteine-knot peptide with an unusual *N*-terminal pyroglutamate residue that enhanced neuronal Ca^{2+} influx in murine cerebrocortical neuron cells and therefore may be useful for the treatment of topical pain or hypertension.⁶⁴⁹



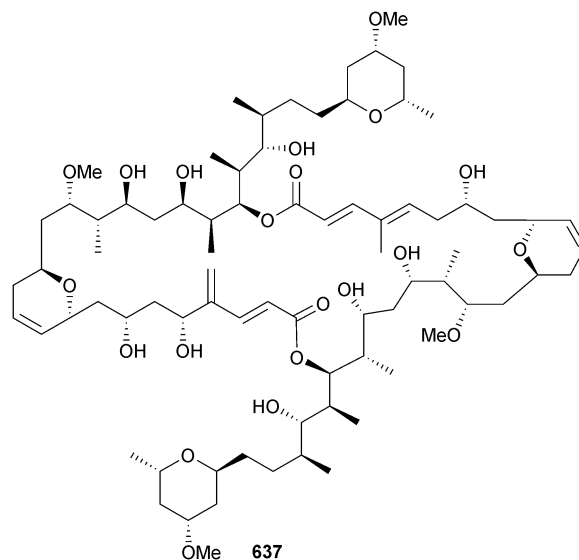
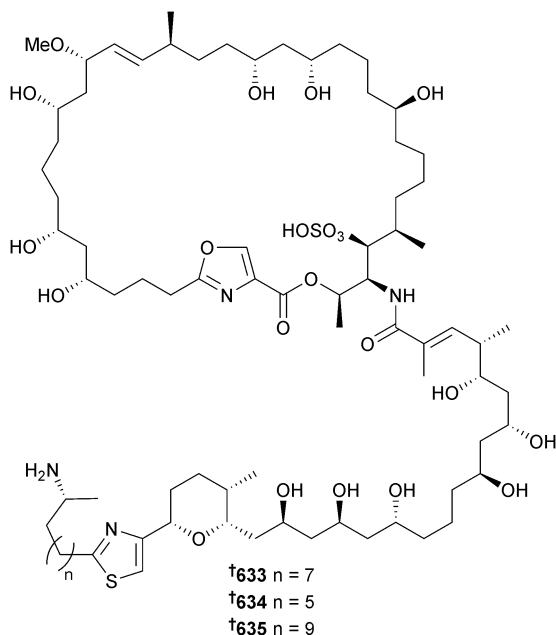
The total syntheses of 18-*epi*-latrunculol A (*Negombata magnifica*)⁶⁵⁰ and haliclamide (*Haliclona* sp.)⁶⁵¹ have been achieved, with the latter study determining the absolute configuration **631** of the NP.^{652,653} Two separate collections of *Pachastrissa nux* (Koh Tao, Surat Thani Province, and Chumphon Is. National Park, Thailand) yielded the antimalarial trioxazole macrolide kabiramide L **632**.⁶⁵⁴



A comprehensive study using *J*-based conformational analysis, the universal NMR database and chemical derivatisations, established the absolute configurations of theonezolid A–C **633–635**, originally isolated from a *Theonella* sponge.^{655–657}

Theonella swinhoei (Bunaken Marine Park, Manado, Indonesia) provided isoswinholide B **636** and swinholide K **637**.

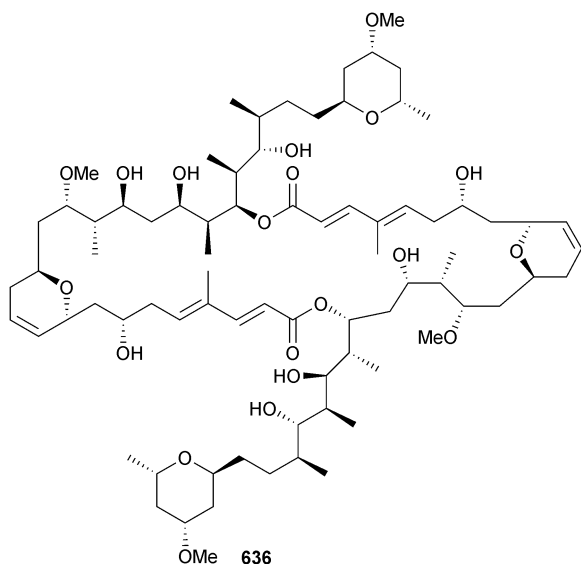
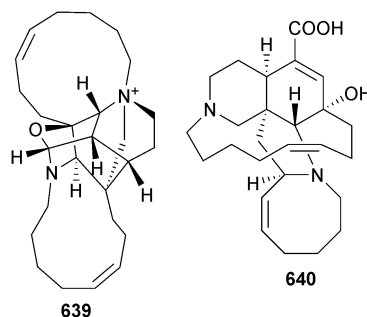
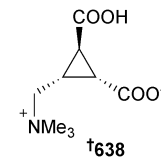




Interestingly **636** was completely inactive while **637** showed significant potency against HepG2 cells consistent with other swinholid congeners.⁶⁵⁸

The absolute configuration of (–)-dysibetaine CPa **638** (*Dysidea herbacea*)⁶⁵⁹ was established by total synthesis, although the current study incorrectly mentions *Lendenfeldia chondrodes* as the original source.⁶⁶⁰

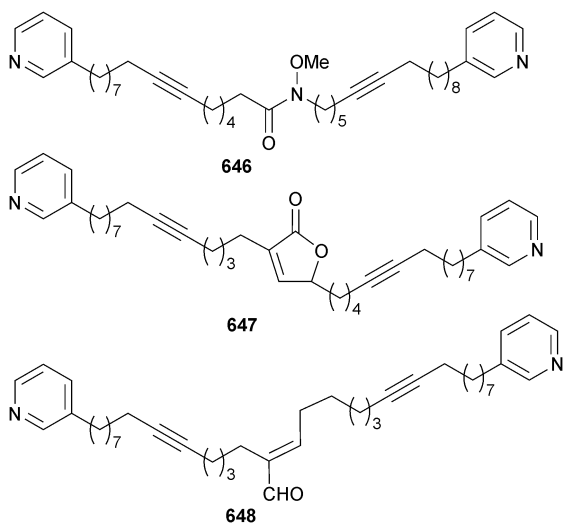
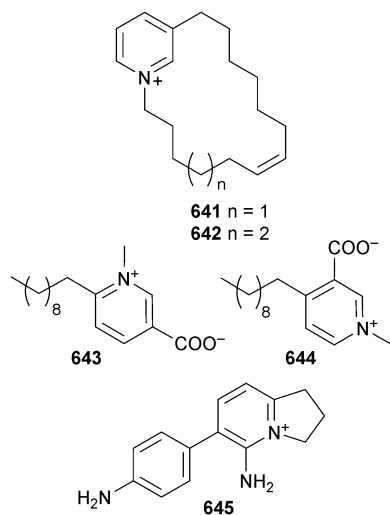
The synthesis of nakinadine C (*Amphimedon* sp.)⁶⁶¹ confirmed the absolute structure.⁶⁶² Synthesis also confirmed the structures of batzellasides A and C (*Batzella* sp.).^{663,664} Manzamine A (*Haliclona* sp.)⁶⁶⁵ inhibited autophagy, and hence could prevent pancreatic cancer, by uncoupling vacuolar ATPases,⁶⁶⁶ as well as suppressing hyperlipidaemia and hence atherosclerosis in apoE-deficient mice.⁶⁶⁷ Zamamiphidin A **639** is a moderately antibacterial (*S. aureus*) manzamine-type alkaloid isolated along with ircinic acid 2 **640** from *Amphimedon* sp. (Zamami, Okinawa).⁶⁶⁸



The synthesis of two unstable stereoisomers of 'upenamide (*Echinochalina* sp.)⁶⁶⁹ has shown that the putative structure was incorrect, although the constitution of the NP could not be established and given the paucity of remaining compound, structural revision will be difficult.⁶⁷⁰ The sponge *Haliclona* sp. (d'Urville Is., New Zealand) yielded dehydrohaliclocyclins C **641** and F **642** but lack of material prevented bioactivity profiling.⁶⁷¹ *Plakortis simplex* (Keomun Is., West Sea, S. Korea) provided two regioisomeric alkylpyridinium carboxylates **643** and **644**.⁶²⁰ The pyridinium diamine callyimine A **645** was obtained from *Callispongia* sp. (Hainan Is., China).⁶³⁰

Synthesis confirmed the structures of amphimedosides A–C (*Amphimedon* sp.).^{672,673} Pyrindemins G–I **646–648** are bis-3-alkylpyridinium alkaloids from *Amphimedon* sp. (Okinawa), although the exact positioning of the alkyne functionalities is uncertain and hence the compounds are likely a mixture of related congeners.⁶⁷⁴

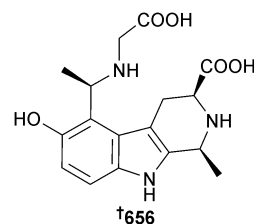
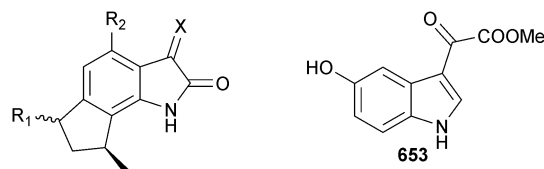




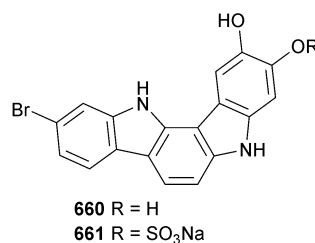
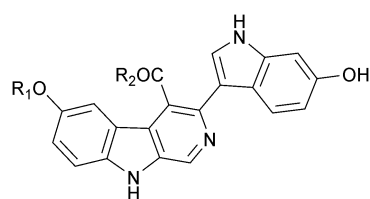
High-level DFT calculations helped confirm the unusually deshielded ^{13}C chemical shifts found in trikentramides A–D **649–652**, isolated using an NMR-guided approach from *Tri-kentrion flabelliforme* (East Point Bommies, Northern Territory, Australia).⁶⁷⁵ The synthesis of igzamide (*Plocamissa igzo*)⁶⁷⁶ was achieved.⁶⁷⁷ Three 5-hydroxyindole compounds **653–655** were reported from *Scalarispongia* sp. (Dokdo, S. Korea).⁶⁷⁸

Hyrtioreticulin F **656** was obtained from *Hyrtios reticulatus* (N. Sulawesi, Indonesia) and is the likely product of a Pictet–Spengler reaction between tryptophan, alanine and glycine.⁶⁷⁹ The bis-indole 6'-de bromohamacanthin A (*Spongosorites* sp.)⁶⁸⁰ inhibited angiogenesis by suppressing vascular endothelial growth factor VEGFR2-mediated PI3K/ALT/mTOR signalling in human umbilical vascular endothelial cells and mouse embryonic stem cells.⁶⁸¹

Hyrtiorectines D–F **657–659** are indolo- β -carboline alkaloids from a Red Sea *Hyrtios* species, with all three showing antimicrobial and radical scavenging activity.⁶⁸² Two brominated indolo-carbazoles **660** and **661** were isolated from a

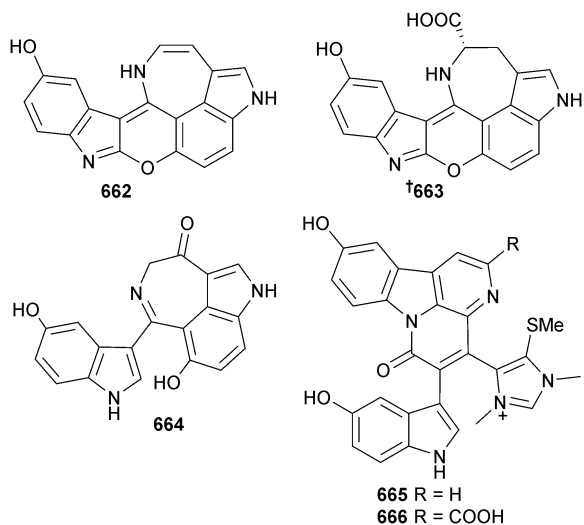


deep water *Asteropus* sp. (offshore from Bimini, Ocean Cay, Bahamas). While catechol **660** showed antimicrobial activity (*C. albicans* and MRSA), sulfonate **661** was completely inactive.⁶⁸³

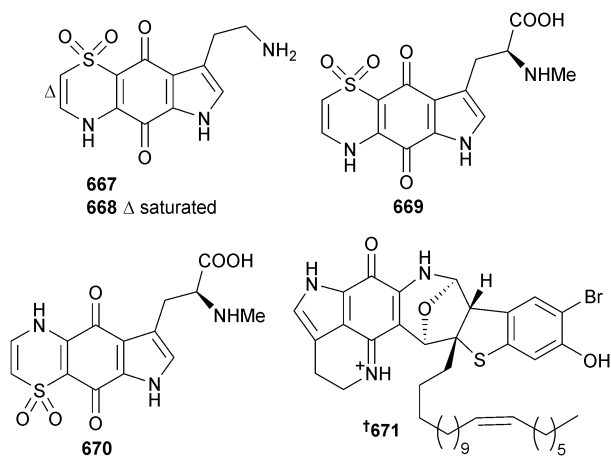


Hyrtimomines A–C **662–664** are 5-hydroxyindole alkaloids from *Hyrtios* sp. (Kerama Is., Okinawa), although only **662** showed activity against tumour cells.⁶⁸⁴ Hyrtimomines D **665** and E **666** from the same collection are bisindole dimers with some activity against *C. albicans*, *C. neoformans*, *S. aureus* and *Trichophyton mentagrophytes*.⁶⁸⁵



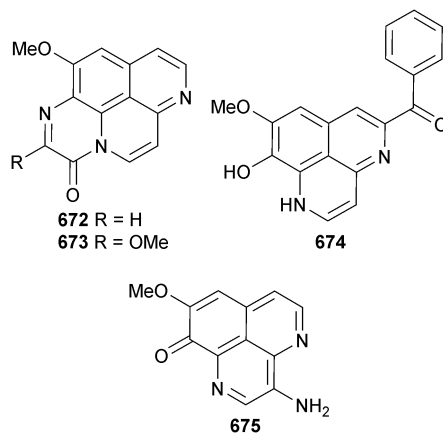


The Australian sponge *Plakortis lita* (Tydeman Reef, Queensland) yielded thiaplakortones A–D **667–670** following HTS of a library of 202 983 fractions from 18 453 extracts. All were potent inhibitors of *P. falciparum* with **667** showing greater than 60-fold selectivity for *Plasmodium* over human embryonic kidney cells.⁶⁸⁶ The total syntheses of zyzzyanones A–D (*Zyzya fuliginosa*)^{687,688} have been achieved.⁶⁸⁹ Atkamine A **671** is a new pyrroloiminoquinone isolated from a deep water *Latrunculia* sp. (Aleutian Is., Alaska). Olefin metathesis was used to identify the location of the side-chain alkene of this surprisingly inactive metabolite.⁶⁹⁰

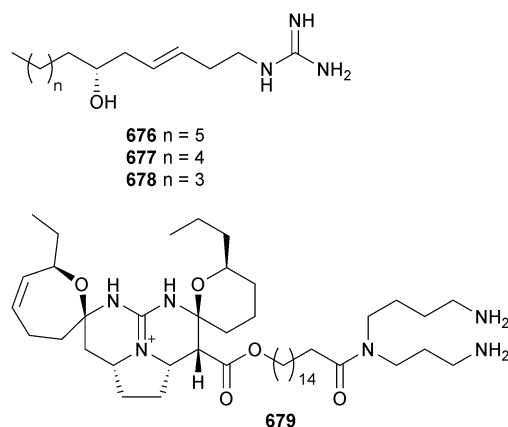


Of four new aaptamine-derivatives **672–675** (*Aaptos suberitoides*, Ambon, Indonesia) only **674** showed any activity against murine lymphoma.⁶⁹¹ The total synthesis of 2-deoxy-2-aminoketone (*Leucetta chagosensis*)⁶⁹² confirmed the structure of the NP.⁶⁹³

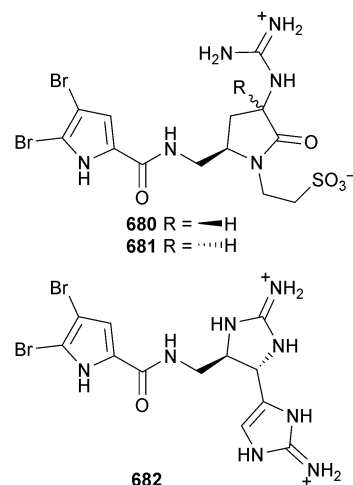
Pulchransins A–C **676–678**, isolated from two dredged *Monachora pulchra* samples (Kuril Is. Chain, Russia), were moderately active inhibitors of the transient receptor potential cationic channel subfamily V (capsaicin receptor), and hence are pain and thermal reception modulators.^{694,695} The same sponge that yielded pulchransins B and C also yielded

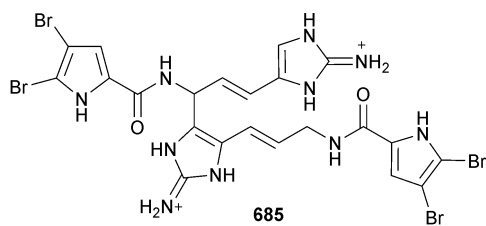
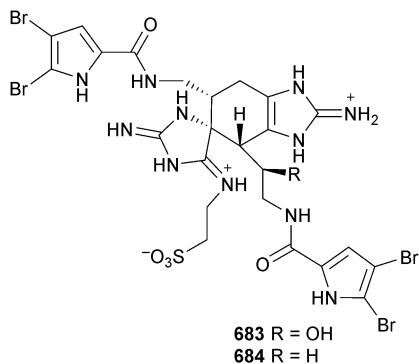


monanchomycalin C **679**, a modest inhibitor of MDA-MB-231 breast cancer cells.⁶⁹⁶

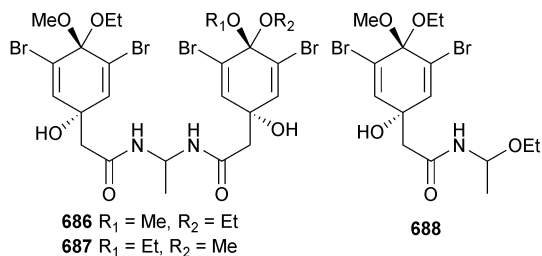


Spongiacidin C (*Stylissa massa*, Indonesia)⁶⁹⁷ is the first selective inhibitor of USP-7 over other ubiquitin-specific-processing proteases to be isolated from a natural source, and hence is a new lead as an oncological therapeutic.⁶⁹⁸ Nagelamides U–Z **680–685** are bromopyrrole alkaloids from *Agelas* sp. (Kerama Is., Okinawa) with a variety of biological activities, especially the inhibition of the growth of *C. albicans*. Congeners **683** and **684** were isolated as racemates.^{699,700}

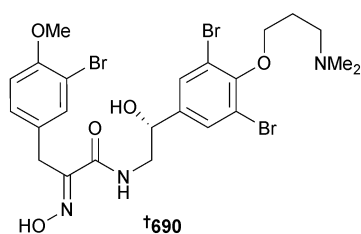
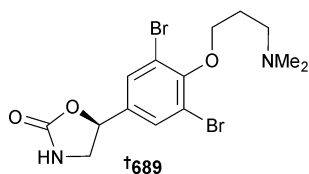




Three new bromotyrosine compounds **686–688** were isolated from *Aplysina* sp. (Ladda Reef, S. China Sea),⁷⁰¹ while the structures of ma'edamines A and B (*Suberea* sp.)⁷⁰² have been confirmed by synthesis.⁷⁰³

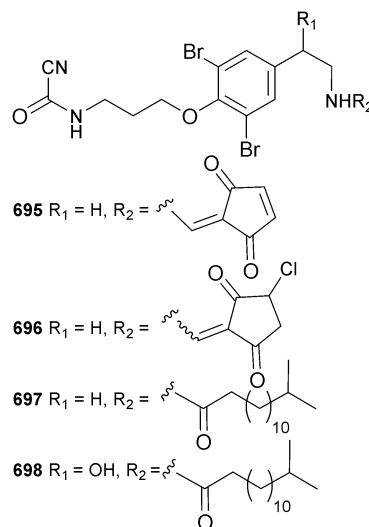
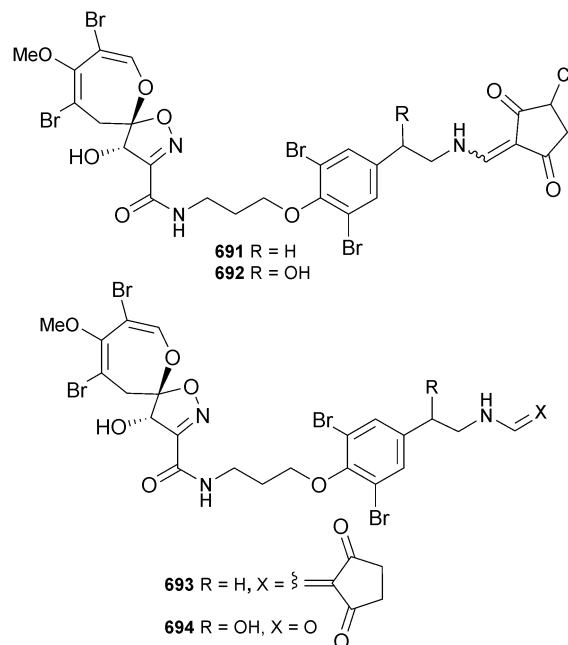


Pseudoceratina verrucosa (Hook Reef Lagoon, Queensland, Australia) yielded pseudoceralidinone A **689** and aplysamine 7 **690**, with the absolute configurations established by Mosher's method and by total synthesis, respectively. The latter compound inhibited the growth of PC3 prostate adenocarcinoma cells while the former was inactive.⁷⁰⁴



Eight new bromotyrosine derivatives of the psammaplysin **691–693**, ceratinamide **694** and subereamide **695–698** classes

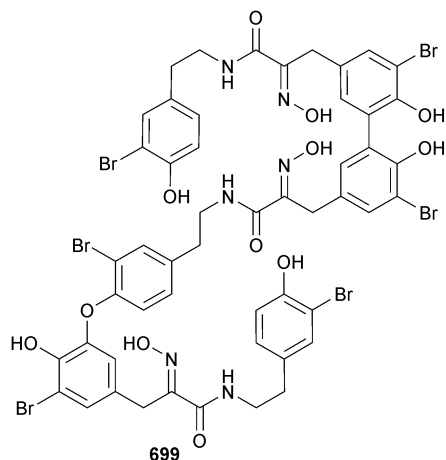
were isolated from *Suberea* sp. (Chuuk, Federated States of Micronesia). Only psammaplysin X **691** and the 19-hydroxy derivative **692** showed activity against six HTCLs.⁷⁰⁵



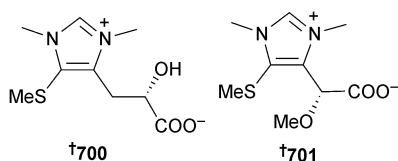
Sesquibastadin **699** (*Ianthella basta*, Ambon, Indonesia) is a trimer of hemibastadin that inhibited a variety of protein kinases from a panel of 24 enzymes, but had no effect on the proliferation of murine lymphoma cells (L5178Y).⁷⁰⁶

The Verongid sponges *Ianthella basta* and *Aplysina cavernicola* were examined for the presence of brominated skeletal components within their organic and siliceous matrices. The conclusions drawn from this work were that the bastadin and aethionin compounds found are likely of microbial origin and that the known secondary metabolites are not associated with the sponge skeletons. However, a considerable quantity of brominated mass was found within the skeleton and it is possible that this represents tightly bound sponge-derived

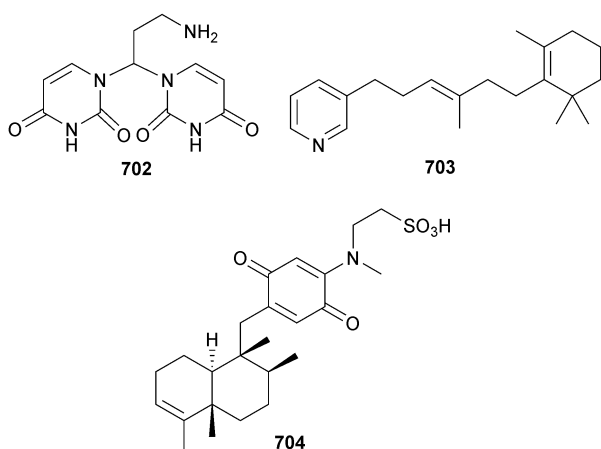




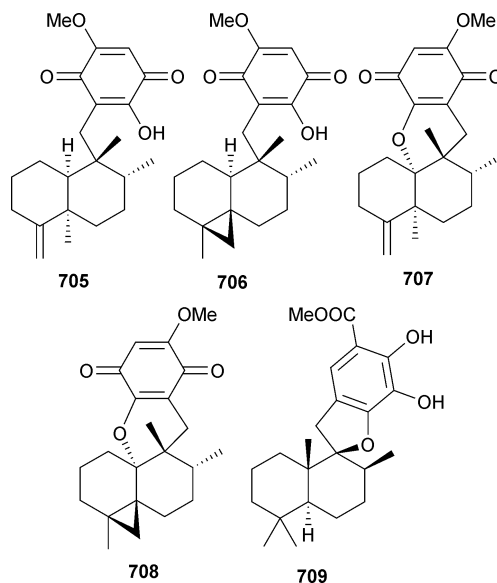
secondary metabolites with a defensive role.⁷⁰⁷ Reticulatin A **700** and B **701** are dimethylimidazolium cations isolated from *Hyrrios reticulatus* (N. Sulawesi, Indonesia). Surprisingly, they differ in absolute configuration of the side chain carbinol.⁶⁷⁹



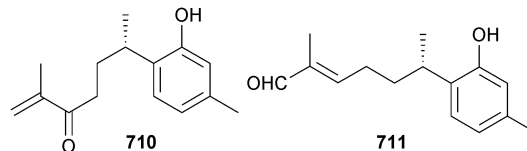
Bis-uracil **702** was isolated from *Agelas clathrodes* (Yongxing Is., S. China Sea).⁷⁰⁸ A *Fasciospongia* sp. (Weizhou Is., Guangxi, China) gave the sesquiterpene alkaloid fasciospyrinadine **703**,⁷⁰⁹ while *Dysidea avara* (Fethiye, Turkey) yielded the merosquiterpenoid *N*-methylmelemeleone-A **704**.⁷¹⁰



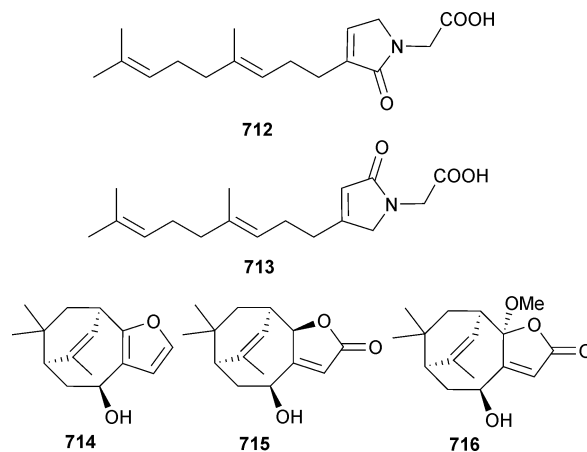
Samples of *Dactylospongia elegans* collected in both Malaysia and Palau contained the related 5,8-di-*epi*-ilimaquinone **705**, 4,5-di-*epi*-dactylospongiaquinone **706**, 8-*epi*-dactyloquinone **707**, 10,17-*O*-cyano,4,5-di-*epi*-dactylospongiaquinone **708** and cyclospongiacatechol **709**. All five compounds showed anti-proliferative effects at high concentrations while **706** and **707** also activated Hypoxia Inducible Factor-1 (HIF-1), with the 1,4-benzoquinone moiety demonstrated as essential for activity.⁷¹¹



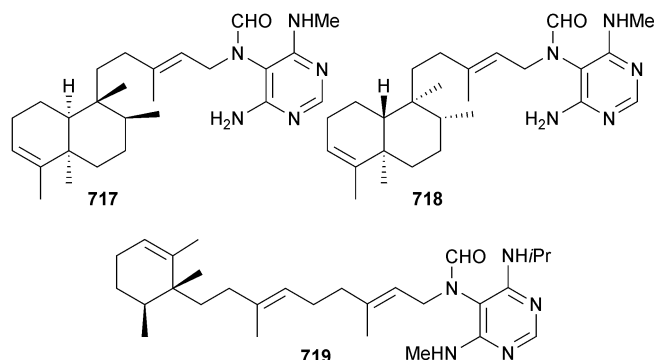
The asymmetric total synthesis of stronglylin A (*Strongylophora hartmani*)⁷¹² confirmed the absolute configuration,⁷¹³ while synthesis of dysideaavaron A (*Dysidea avara*)⁷¹⁴ confirmed the structure and also provided material to demonstrate the compound's potent antimicrobial activity, especially against Gram-positive bacteria, in particular various *Staphylococci* spp.⁷¹⁵ The bisabolane sesquiterpenoids 3-oxobolene **710** and 1-oxocurcphenol **711** were isolated from *Myrmekioderma* sp. (Phi-Phi Is., Thailand) and were potent inhibitors of HT-29 cancer cells.⁷¹⁶



Ianthellalactams A **712** and B **713** (*Ianthella flabelliformis*, Port Philip Heads, Victoria, Australia) did not inhibit Glycine-gated chloride channel receptors (GlyR) like other related glycinal lactams.⁷¹⁷ Euryspongins A–C **714**–**716** (*Euryspongia* sp., Iriomote Is., Okinawa) have rare six- or eight-membered skeletons with either fused furan or γ -lactone rings. The presence of the C-4 hydroxyl group in all three compounds was thought to totally abrogate activity compared with other active analogues.⁷¹⁸

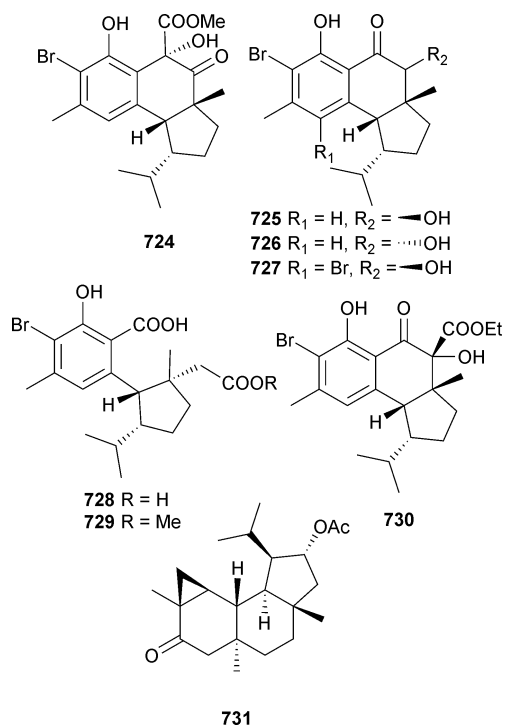


Phorbacin H, originally isolated from *Phorbas gukulensis*⁷¹⁹ but differing from another structure with the same name from *Phorbas* sp.,⁷²⁰ inhibits the hypha-specific HWP1 and ALS3 mRNAs of *C. albicans*, preventing the yeast-to-hyphae transition and therefore inhibits virulence of the pathogen.⁷²¹ Axistatins 1–3 717–719 are pyrimidine diterpenoids from *Agelas axifera* (Koror, Republic of Palau). All three were low μM inhibitors of various human and murine cancer cell lines, as well as being potent broad-spectrum antibiotics against several Gram-positive and negative bacteria.⁷²²

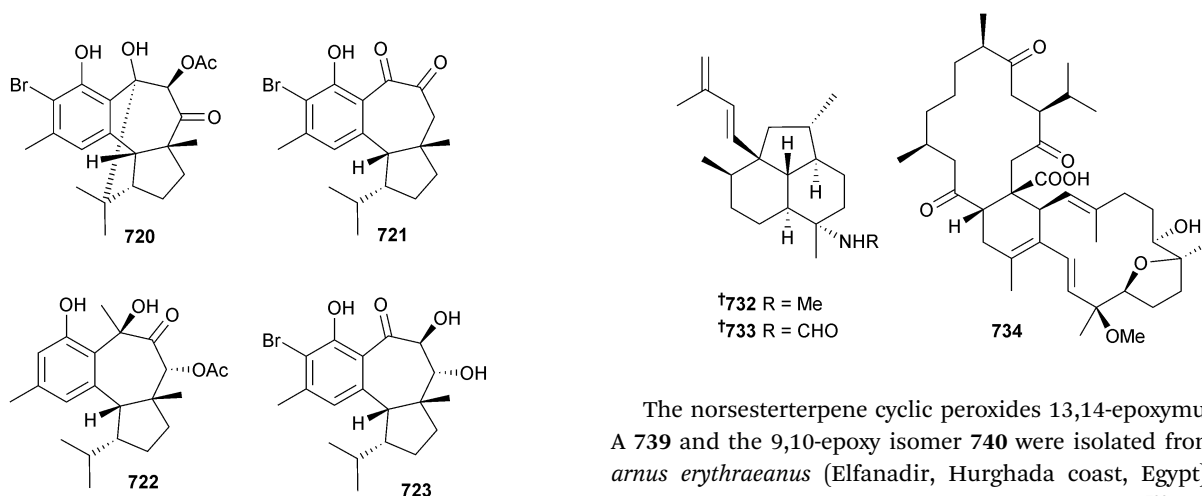


Phenotypic screening using zebra fish as a genome-wide eukaryote assay identified kalihinol F (*Acanthella* sp.)⁷²³ as a copper chelator, resulting in abnormal development as indicated by an undulating notochord, and both pigmentation and neural defects. This study exemplifies the use of zebra fish as a viable chemical genetic tool for assessing bioactives in a complex eukaryotic organism.⁷²⁴ The total syntheses of cyanthiwiggins A, C (*Epipolasis reiswigi*)⁷²⁵ and H (*Myrmekiodermastyx*)⁷²⁶ have been achieved, confirming the absolute structures.⁷²⁷ *Hamigera tarangaensis* (Cape Karikari, North Is., New Zealand) provided hamigerans F–K 720–725, 10-*epi*-hamigeran K 726, 4-bromohamigeran K 727, hamigeran L 728 and the methyl ester 729, hamigeran A ethyl ester 730 and an unrelated congener of *epi*-verrucosane 731. All but the latter compound inhibited the growth of HL-60 cells while chemical genetic screening using yeast as a model organism showed that the

mode of action of the antifungal hamigeran G 721 was *via* influence of Golgi function and Golgi vesicle formation.⁷²⁸

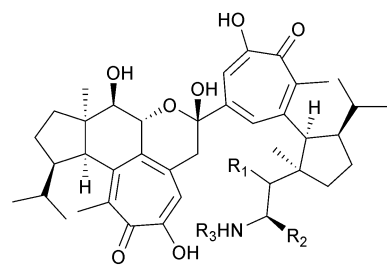


Two new isoneoamphilectane diterpenes 732 and 733 were isolated from *Svenzea flava* (previously described as *Pseudoaxinella flava*) (Great Inagua Is., Bahamas). The absolute configurations of these compounds were secured by comparison of experimental and calculated VCD data. Both compounds inhibited the growth of *Mycobacterium*, but had no effect on mammalian cell lines.⁷²⁹ Petronigrone 734 is a cembranoid dimer from *Petrosia nigricans* (Haivan, Danang, Vietnam) with moderate activity against HTCLs,⁷³⁰ while *Phorbas gukulensis* (Gagu-Do Is., S. Korea) yielded the diterpene pseudo-dimers gukulenin C–F 735–738. All four were cytotoxic against K562 and A549 cancer cell lines but none showed any activity against various microbes.⁷³¹

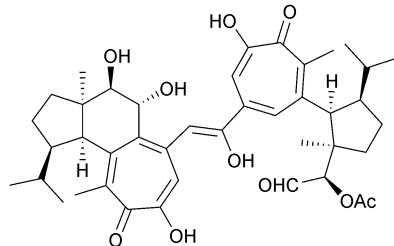


The norsesterterpene cyclic peroxides 13,14-epoxymuquiblin A 739 and the 9,10-epoxy isomer 740 were isolated from *Diacarnus erythraeanus* (Elfanadir, Hurghada coast, Egypt). Both were low micromolar inhibitors of various HTCLs.⁷³²

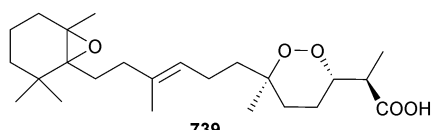




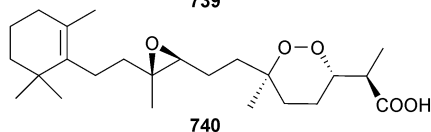
735 $R_1 = \text{OH}, R_2 = \text{OMe}, R_3 = \text{Ac}$
736 $R_1 = \text{OH}, R_2 = \text{OH}, R_3 = \text{Ac}$
737 $R_1 = \text{O}, R_2 = \text{H}, R_3 = \text{CH}_2\text{CH}_2\text{SO}_3\text{H}$



738

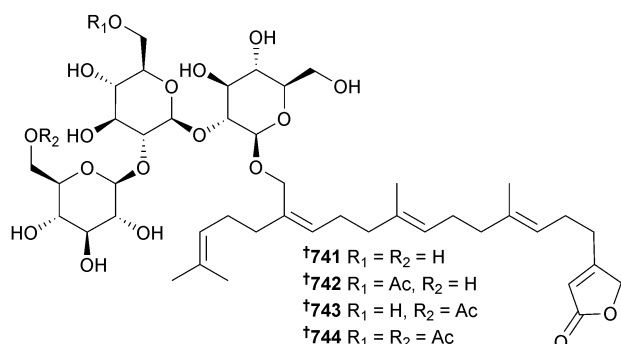


739



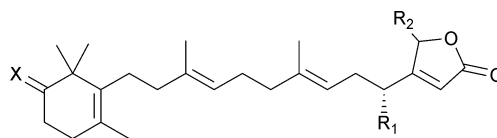
740

Collections of the Homoscleromorpha sponge *Oscarella balibalo* at two sites near Marseilles (Mediterranean Sea) yielded the glucosidated sesterterpenes balibaloside **741**, 6''-O-acetylbalibaloside **742**, 6'''-O-acetylbalibaloside **743** and 6'',6'''-O-diacetylbalibaloside **744**. These metabolites are the first glycosidated sesterterpenes reported and although tested in a wide variety of assays, proved to be inactive.⁷³³

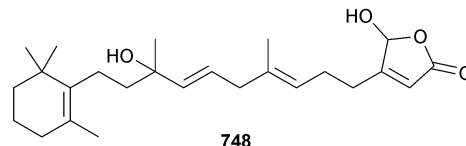


741 $R_1 = R_2 = \text{H}$
742 $R_1 = \text{Ac}, R_2 = \text{H}$
743 $R_1 = \text{H}, R_2 = \text{Ac}$
744 $R_1 = R_2 = \text{Ac}$

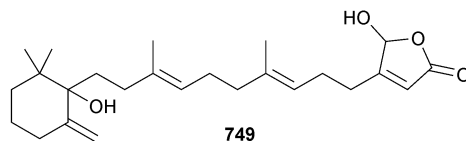
Hyrtios communis (Northern Reef region, Palau) yielded thorectidaelide A **745**, the 4-acetoxy congener **746**, and thorectidaelides B–E **747–750**. Compounds **745–747** inhibited HIF-1 yet did not show any antiproliferative effects against the parent T47D or NDA-MB-231 breast cancer cell lines.⁷³⁴



745 $R_1 = \text{OH}, R_2 = \text{H}, X = \text{O}$
746 $R_1 = \text{OAc}, R_2 = \text{H}, X = \text{O}$
747 $R_1 = \text{H}, R_2 = \text{OH}, X = \text{O}$
750 $R_1 = \text{OH}, R_2 = \text{H}, X = \text{H,H}$

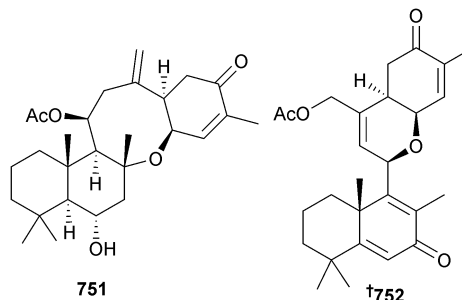


748

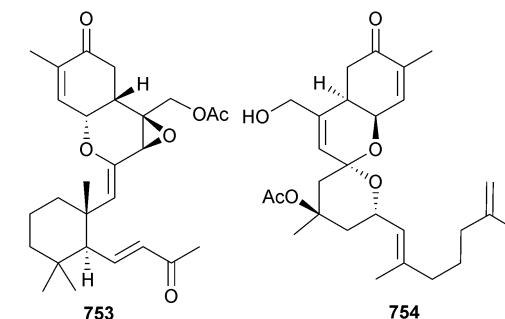


749

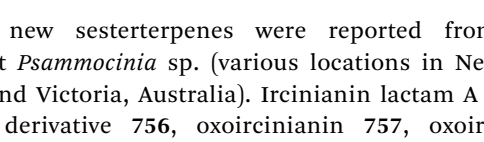
A Canadian *Phorbasp* sp. (Ansell Point, Howe Sound, British Columbia), provided four distinct sesterterpenes ansellone B **751**, phorbadione **752**, secoepoxyansellone A **753** and alota-ketal C **754**. The latter compound showed similar levels of activation of cAMP signalling to the standard probe, forskolin.⁷³⁵



751



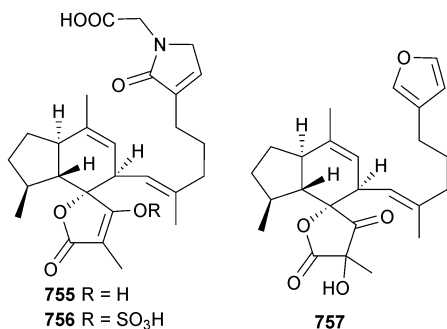
752



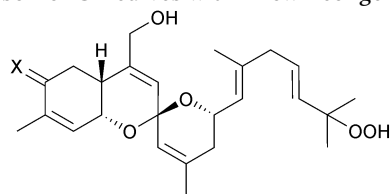
753

Five new sesterterpenes were reported from three different *Psammocinia* sp. (various locations in New South Wales and Victoria, Australia). Ircinianin lactam A **755**, the sulfate derivative **756**, oxoircinianin **757**, oxoircinianin lactam A **758** and ircinianin lactone A **759** were all assessed for GlyR modulating activity with **755** and **758** being selective and potent potentiators of $\alpha 3$ -GlyR and $\alpha 1$ -GlyR, respectively, having potential as leads for treatment of inflammatory pain, epilepsy and both breathing or movement disorders.⁷³⁶

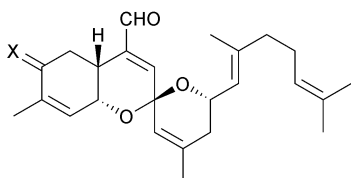
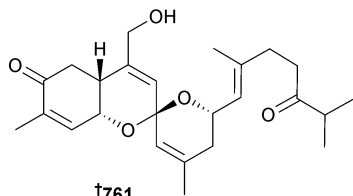




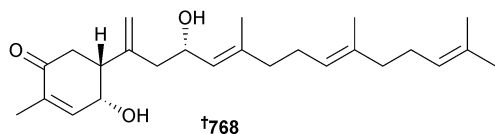
Phorbaketals D–K **760–767** and phorbins A **768** were reported from *Monachora* sp. (Gageo Is., Korea), with **764** and **765** weakly active against A498 cancer cells. The absolute configurations of all the new compounds were established by Mosher's method and comparison of CD-curves with known congeners.⁷³⁷



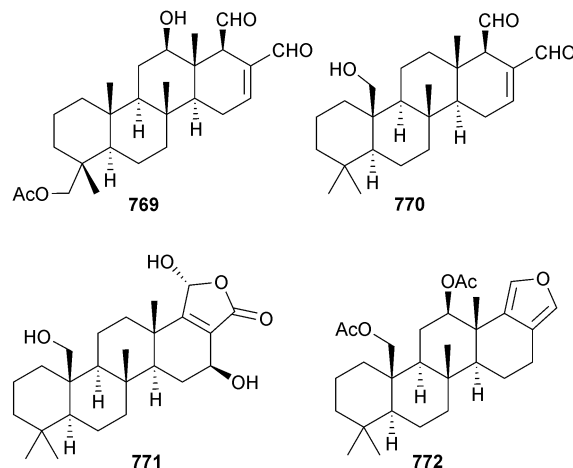
†760 X = O
†762 X =OAc, H
†763 X =OAc, H



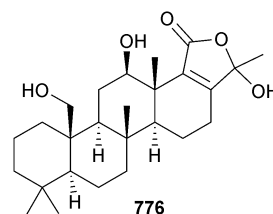
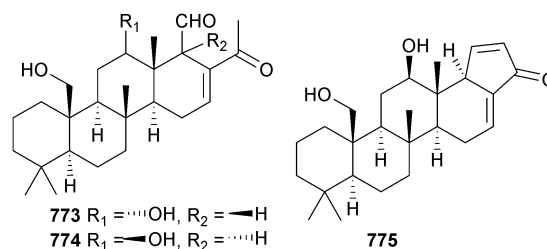
†764 X =OH, H
†765 X = O
†766 X =OAc, H
†767 X =OAc, H



The scalarane sesterterpenoid hippospongide C **769** (*Hippospongia* sp., Tai-Tung, Taiwan) had moderate activity against four HTCLs,⁷³⁸ while 12-deacetoxy-23-hydroxyscalardial **770**, 12-deacetoxy-23-hydroxyhyrtiolide **771** and 12-O-acetyl-16-deacetoxy-23-acetoxyscalarafuran **772** from *Psammocinia* sp. (S. Korea) were inactive in all assays used.⁷³⁹

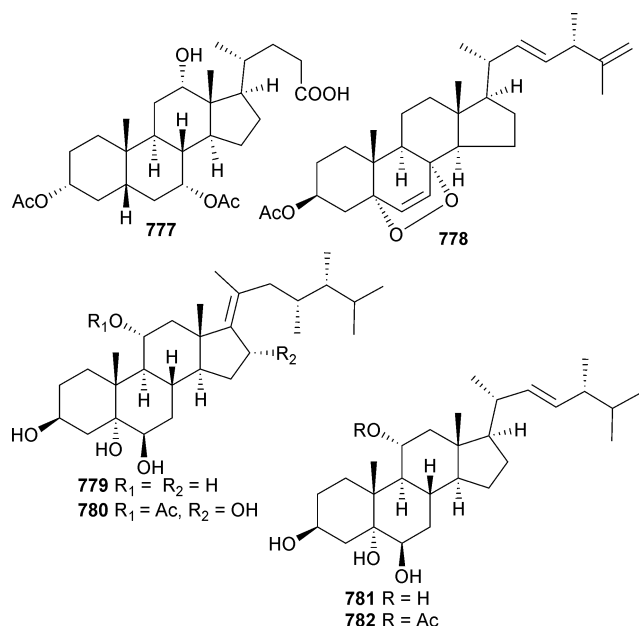


Four new scalaranes **773–776** were reported from *Carteriospongia* sp. (Nosy Be, Madagascar) with **773** and **774** being significantly more active than the other two congeners, indicating the importance of the aldehyde pharmacophore.⁷⁴⁰

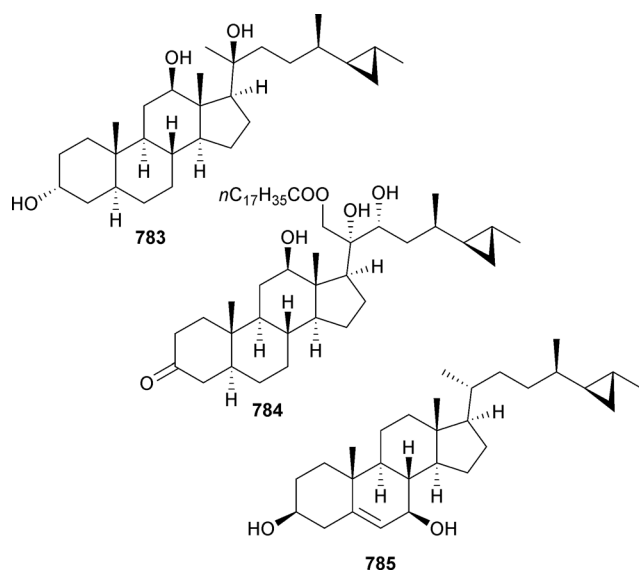


Cholic acid-3,7-diacetate **777** was isolated as an MNP for the first time from *Siphonochalina fortis* (Bahia Bustamante, Chubut, Argentina),⁷⁴¹ while the 5 α ,8 α -epidioxy sterol 3-acetylaxinysterol **778** was isolated from *Axinyssa* sp. (Pingtung, Taiwan).⁷⁴² *Haliclona crassiloba* (Dongshan Is., Guangdong, China) yielded halicrasterols A–D **779–782** with moderate activity against various microbial pathogens.⁷⁴³

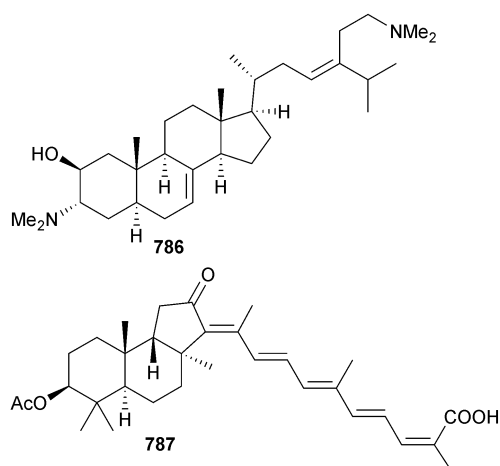




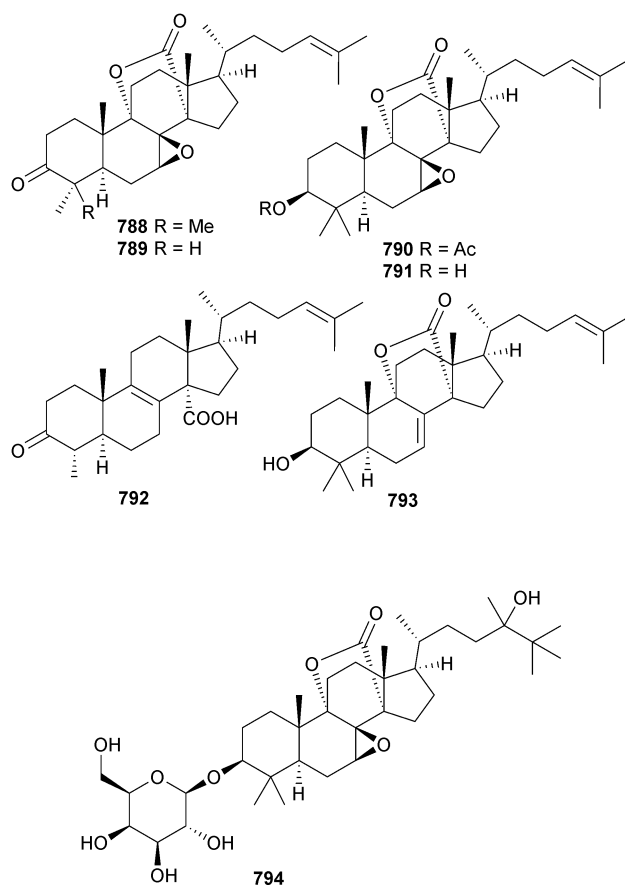
Cyclopropanated sterols aragusterol I **783**, 21-O-octadecanoyl-xestokerol A **784** and 7 β -hydroxypetrosterol **785** were isolated from *Xestospongia testudinaria* (Truong Sa Archipelago, Khanh Hoa, Vietnam). Both **783** and **784** had antifouling potential (growth inhibition of *Pseudoalteromonas* and *Polaribacter* bacterial species) at similar levels of activity to the now-banned antifoulant marine pollutant tributyltin oxide.⁷⁴⁴



The structure of the unusual autophagy-modulating amino-sterol clionamine B (*Cliona celata*)⁷⁴⁵ was confirmed by synthesis, which also confirmed the assumed absolute configuration.⁷⁴⁶ A *Corticium* sp. (New Britain, Papua New Guinea) yielded the steroidal alkaloid plakinamine M **786**, which displayed antitubercular activity.⁷⁴⁷ Stelletin N **787** is an isomalabaricane triterpene acid from *Stelletta* sp. (Lingshui Bay, Hainan, China), which along with the other isolated congeners presented a chemotaxonomic link between three genera within the sponge order Astrophorida.⁷⁴⁸

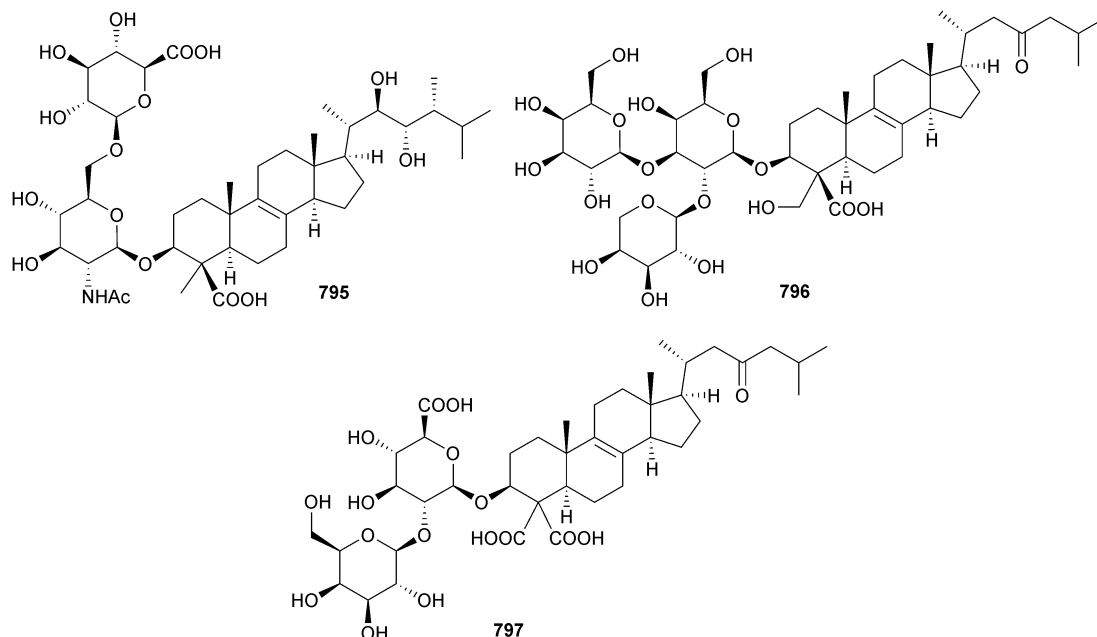


A dredged *Penares* sp. (Vietnam) provided six new lanosterol congeners **788–793**. Only **793** showed any significant activity against HL-60 cells. A combination of CD and X-ray data allowed the assignment of absolute configuration for **789** and also permitted reassignment of the aglycone of eryloside U **794** from 7 α ,8 α to 7 β ,8 β .^{749,750}



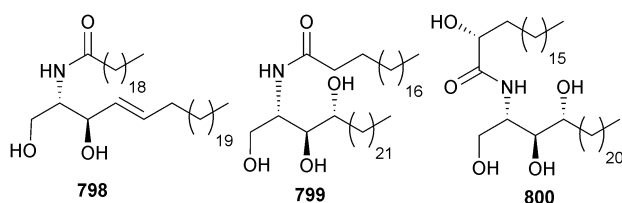
Finally, ulososide F **795**, urabosides A **796** and B **797** are triterpene saponins from *Ectyoplasia ferox* (Caribbean Sea, Colombia), with **797** being the first reported compound with both C-4 methyls elevated to the carboxylic acid oxidation state.⁷⁵¹



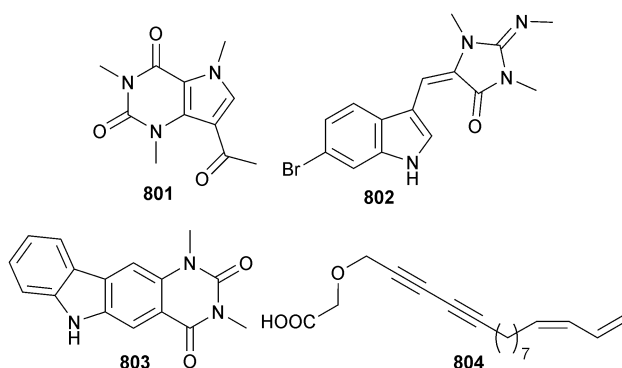


8 Cnidarians

The number of new compounds reported from cnidarians in 2013 (281) has increased by 38% over the average for each of the previous 10 years. In addition to an epidioxysterol (see later), three ceramides **798–800** were isolated from *Simularia candidula* (Safaga, Egyptian Red Sea).⁷⁵² Of the three ceramides, **798** was the most potent anti-H5N1 virus agent.

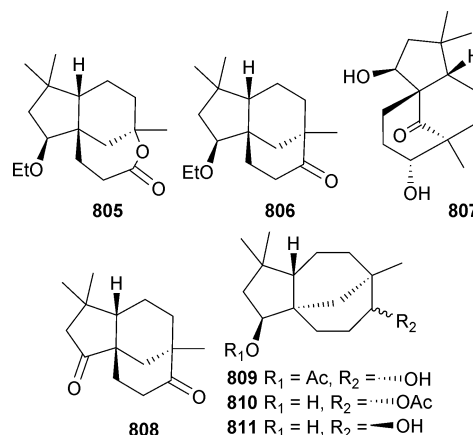


Pyrimidinedione **801** was reported from *Verrucella umbraculum* (Hainan Is., S. China Sea),⁷⁵³ while Mediterranean specimens of the scleractinian coral *Astroides calycularis* afforded the new aplysinopsin analogue **802**.⁷⁵⁴ The highly strained *cyclo*-1,3-carbazole structure originally proposed for



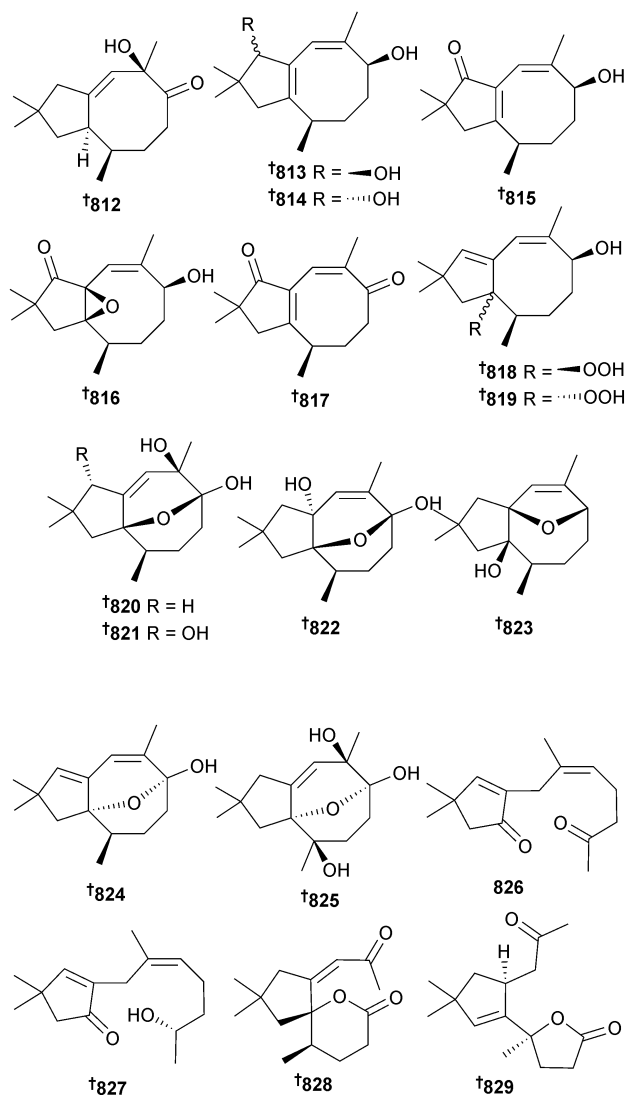
antipathine A (*Antipathes dichotoma*)^{755,756} has been corrected to the 2,3-carbazole **803** by total synthesis.⁷⁵⁷ Polyacetylenic montiporic acid D **804** (*Montipora digitata*, Sesoko Is., Okinawa, Japan) exhibited only mild antibacterial and antioxidant properties.⁷⁵⁸

New clovane-type sesquiterpenes rumphellclovane C–E **805–807** and four unnamed variants **808–811** were reported from the same collection of *Rumphella antipathies* (Southern Taiwan).^{759,760} The latter four compounds are reported as NPs for the first time. Clovane **808** inhibited superoxide generation and elastase release by stimulated human neutrophils.

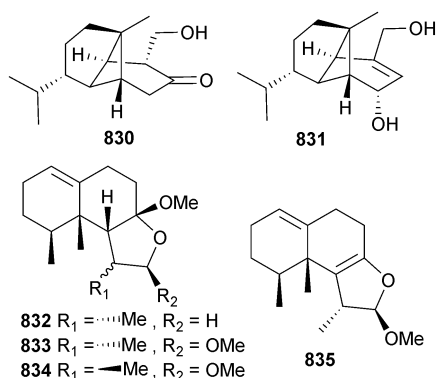


Sesquiterpenes capillosanane A–N **812–825** and *seco*-variants capillosanane O–R **826–829** were isolated from *Simularia capillosa* (Sanya Bay, Hainan Province, China).⁷⁶¹ Absolute configurations were established by combinations of chemical conversions, Mosher's method, CD analysis and biogenetic reasoning. Capillosanane A exhibited antifouling activity against *B. amphitrite*.



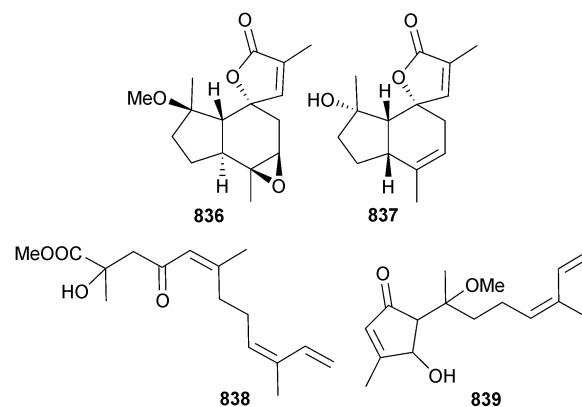


Further examples of tricyclic sesquiterpenes were reported from *Lemnalia philippinensis* (philippinins A 830 and B 831) collected at Lanyu, Taiwan⁷⁶² and *Paralemnalia thyrsoidea* (parathyrsoidins A–D 832–835) collected at Sansiantai, Taitong County also in Taiwan.⁷⁶³

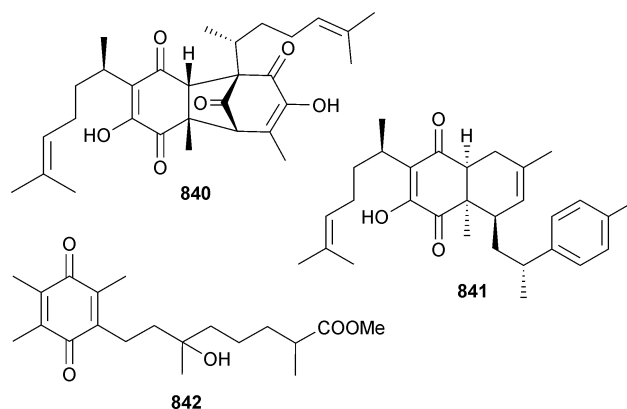


Spiro-butenolides sinularianins C 836 and D 837 and potential biosynthetically-related precursors sinularianins E 838 and F 839 were isolated as mild inhibitors of NF- κ B

activation from *Sinularia* sp. (Dongluo Is., Hainan Province, China).⁷⁶⁴



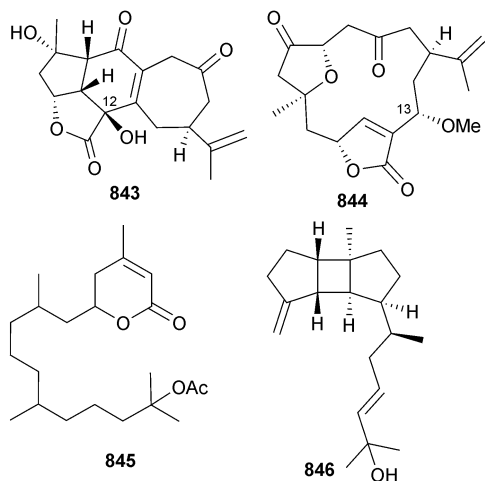
Perezoperezzone 840 and curcuperezzone 841 (*Pseudopterogorgia rigida*, Caribbean Sea) are envisaged to arise, in the case of 840, from non-symmetrical dimerisation of known co-metabolite perezzone⁷⁶⁵ and in the case of 841, through coupling of perezzone and α -curcumene.⁷⁶⁶ Flexibilisquinone 842 (cultured specimen of *Sinularia flexibilis*)⁷⁶⁷ was claimed to be the enantiomer of sarcophytonone (*Sarcophyton crassocaule*)⁷⁶⁸ based upon optical rotation data (842 $[\alpha]_D -19.6$, sarcophytonone $[\alpha]_D +5.8$).



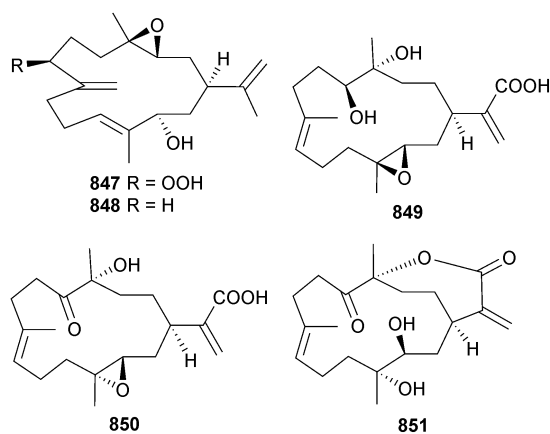
Of two new C₁₉-norditerpenes 12-hydroxy-scabrolide A 843 and 13-*epi*-scabrolide C 844 (*Sinularia maxima*, Nha Trang Bay, Vietnam) the latter was identified as an inhibitor of the production of IL-6 and IL-12 by LPS-stimulated bone marrow-derived dendritic cells.⁷⁶⁹ In addition to five sterols (see later), δ -lactone 845 was isolated from *Scleronephthya gracillimum* (Green Is., Taiwan) as a modest inhibitor of expression of iNOS and COX-2 in stimulated macrophages.⁷⁷⁰ The weakly cytotoxic spatane diterpene leptoclalin A 846 was reported from cultured specimens of *Sinularia leptoclados*.⁷⁷¹

As with most years, a diverse array of cembranoid diterpenes were reported from soft corals in 2013. Arbolides A 847 and B 848, epoxy-alcohols with the former also containing a hydroperoxide functional group, were obtained from *Sinularia arborea* (southern Taiwan).⁷⁷² Similarly functionalised cembranes flexibilins A 849 and B 850 in addition to ϵ -lactone-

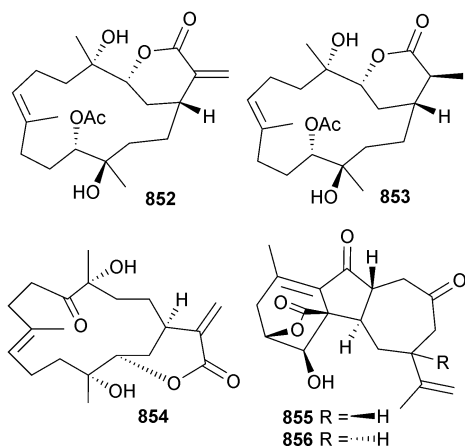




containing flexibilin C **851** were reported from *S. flexibilis* also collected from southern Taiwan.⁷⁷³

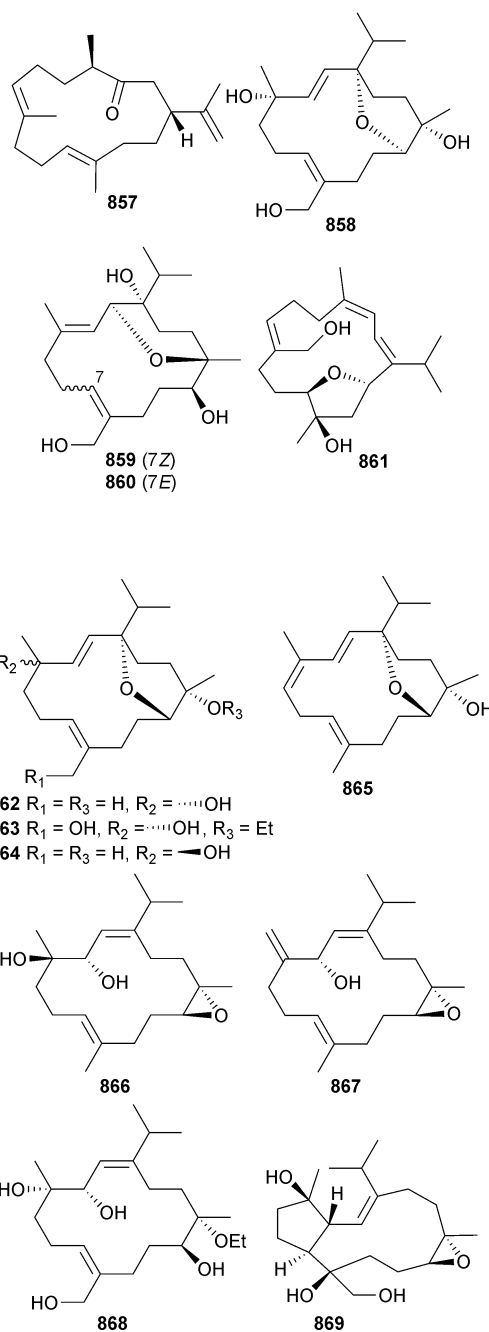


The absolute configuration of co-metabolite (–)-sandenso-
lides (*Dendronephthya* sp.)⁷⁷⁴ was confirmed by X-ray crystal
analysis. Of the δ -lactones 11-acetylsinuflexolide **852** and dihydro
analogue **853** (*S. flexibilis*, Pingtung county, Taiwan), only
the former exhibited cytotoxicity as anticipated for an exo-
methylene-conjugated lactone.⁷⁷⁵ *Sinularia flexibilis* (southern
Taiwan) was also the source of flexibilin D **854** and of known



congener 5-dehydrosinulariolide⁷⁷⁶ the absolute configuration
of which was determined by X-ray crystal analysis.⁷⁷⁷ The same
publication and a second one⁷⁷⁸ also described sinulanorcem-
branolid A **855** and the 1-*epi*-diastereomer **856** from the same
collection of *S. gaweli* (Sansiantai, Taitung county, Taiwan).

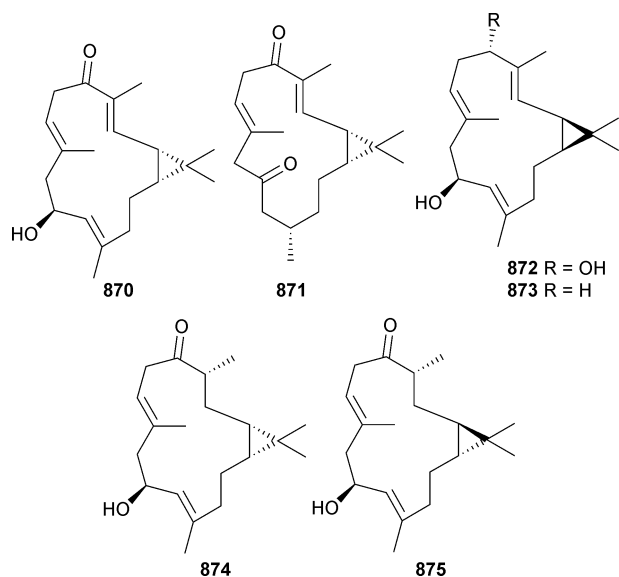
While cembranoid cugibberosene A **857** (*S. gibberosa*, Ping-
tung, Taiwan)⁷⁷⁹ was found to be devoid of cytotoxic or anti-
bacterial properties, one of sinulariols T-Z₅ **858–869** (*S. rigida*,
Sanya Bay, Hainan Is., S. China Sea), specifically **864**, exhibited
effects against the model fouling organisms *B. amphitrite* and *B.*
neritina.⁷⁸⁰



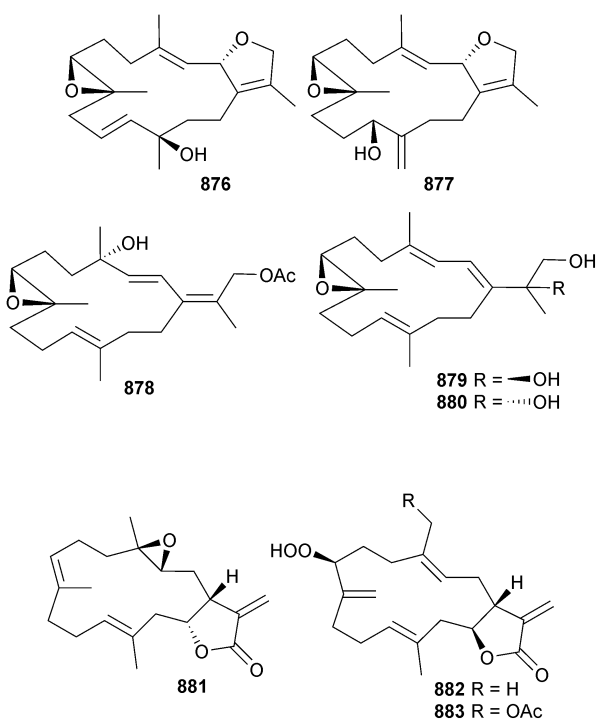
The casbane family of cembranoid diterpenes is charac-
terised by the presence of a fused dimethyl-cyclopropyl ring. Of



new examples sinularcasbanes A-F **870–875** (*Sinularia* sp., Ximao Is., Hainan, S. China Sea), **871** and **874** exhibited modest ability to inhibit NO production by stimulated macrophages.⁷⁸¹

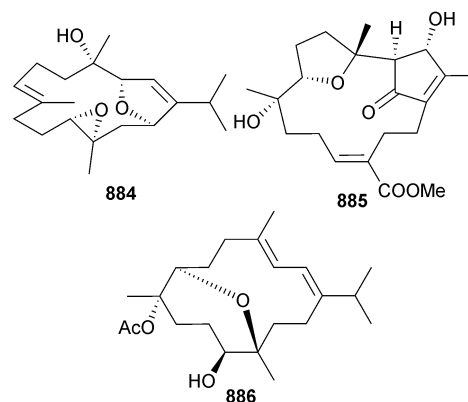


Two separate collections of *Lobophytum* sp. yielded epoxycembranes **876–880** (Ximao Is., Sanya Bay, Hainan, China)⁷⁸² and α -methylene- γ -lactones **881–883** (Sanya Bay, Hainan, China).⁷⁸³ This is the first report **880** as an NP. Epoxycembrane **878** was a modest inhibitor of NO production by stimulated macrophages, while **881–883** were each found to be moderately cytotoxic towards a range of human and murine tumour cell lines.

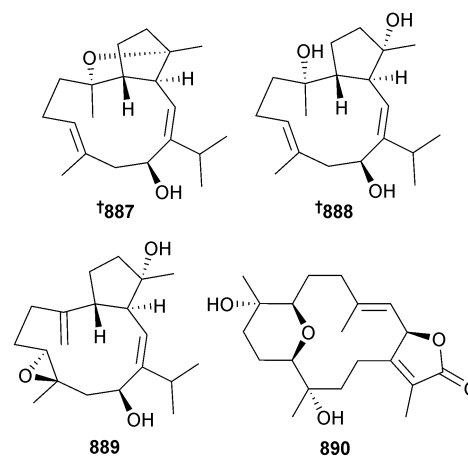


Hydroxycembrane sarcophytol W **884** was isolated from *Sarcophyton* sp. (Xuwen coral reef area, Guangdong Province,

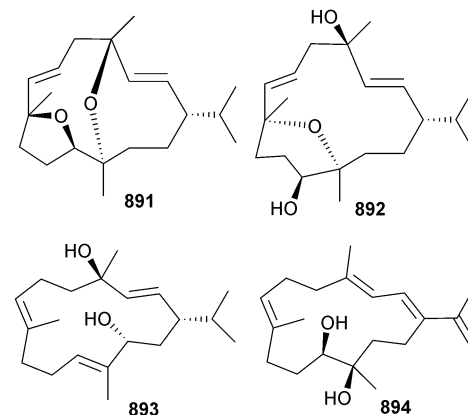
China) – absolute configuration was assigned based upon that determined for a previously reported (*Sinularia ovispiculata*)⁷⁸⁴ co-metabolite.⁷⁸⁵ *Sarcophyton ehrenbergi* (San-hsian-tai, Taitong county, Taiwan) was the source of diterpenes ehrenbergol C **885** and acetylehrenberoxide B **886** which both exhibited mild cytotoxicity (P388) but **886** was more potent as an anti-human cytomegalovirus agent.⁷⁸⁶



Of the sarcophyllides B–E **887–890** isolated from *S. elegans* (Xidao Is., Hainan, China), the structures and absolute configurations of **887** and **888** were established by X-ray crystal studies.⁷⁸⁷

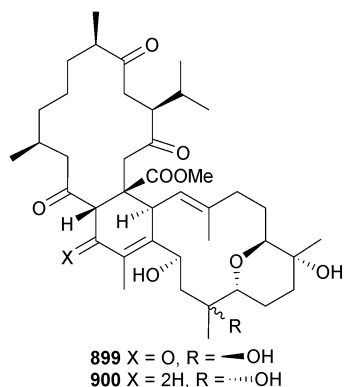
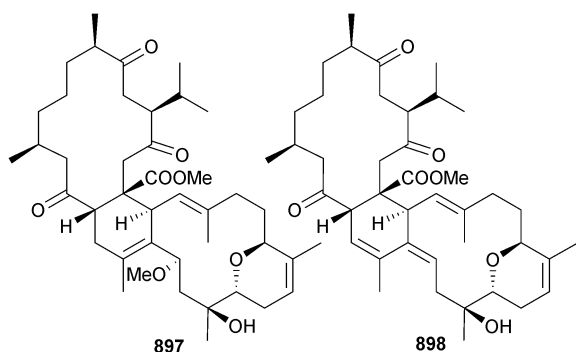
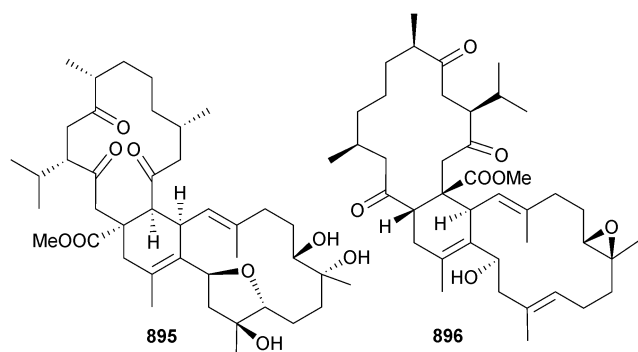


Sarcophyllide B exhibited modest cytotoxicity. Red Sea collections of *S. glaucum* afforded **891–893** with **893** being reported as an NP for the first time.⁷⁸⁸ While **891** and **892** were

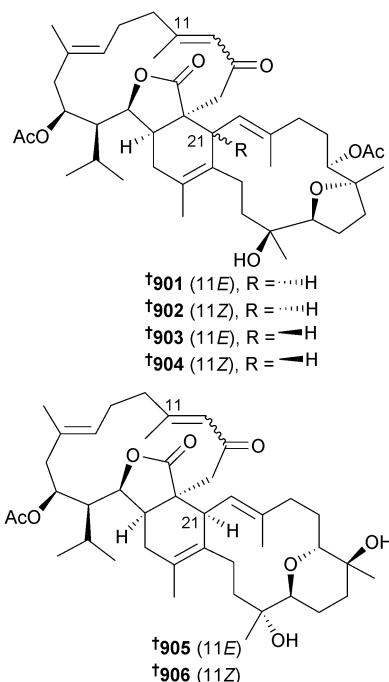


equally cytotoxic towards a melanoma and a mouse kidney cell line, **892** exhibited selectivity towards the tumour cell line. Due to the presence of the conjugated triene functionality in sarglaucol **894** (*S. glaucum*, Sanya Bay, Hainan, China), it can be considered a diene-precursor to biscebranoids typically isolated from soft corals of the genus *Sarcophyton*.⁷⁸⁹

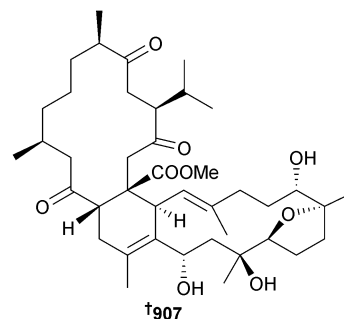
The same collection of *S. elegans* that afforded sarcophylides B–E (see earlier) also yielded new examples of an isobiscebranoid and biscebranoids, the sarcophytolides G–L **895–900**.⁷⁹⁰ These structures represent minor modifications to previously reported biscebranoids, being a dihydroxylated analogue of lobophytone F,⁷⁹¹ a positional isomer of lobophytone S,⁷⁹² a methoxylated analogue of lobophytone H,⁷⁹³ a dehydrated analogue of methyl tortuoate A,⁷⁹⁴ an oxidised analogue of lobophytone U⁷⁹⁵ and a 31-epimer also of lobophytone U, respectively.



Further investigation of *S. latum* (Sanya, Hainan Province), that had previously afforded, amongst other metabolites, biscebranoids bislatumlides A and B,⁷⁹⁶ has now yielded four more congeners bislatumlides C–F **901–904**.⁷⁹⁷ Detailed examination of the absolute configuration of **901** and **903** by time dependent DFT (TDDFT) calculations of ECD data necessitated reassignment of the C-21 configuration of bislatumlides A **905** and B **906**.

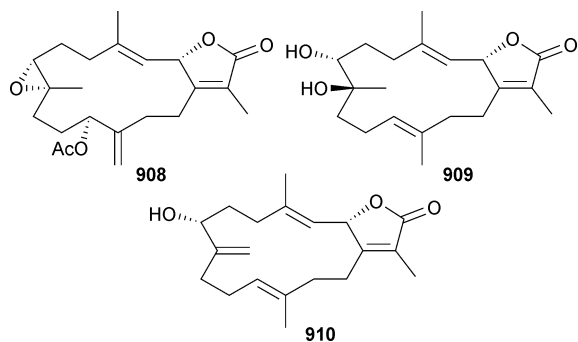


Re-isolation of methyl tortuoate D⁷⁹⁸ (*Sarcophyton tortuosum*, Yalong Bay, Hainan, China) has led to its structural revision to **907**, with absolute configuration assigned by comparison of ECD data with that of co-metabolite ximaolide A.⁷⁹⁹ The study also concluded that the structure previously attributed to lobophytone K (*Lobophytum pauciflorum*)⁸⁰⁰ should also be corrected to **907**.

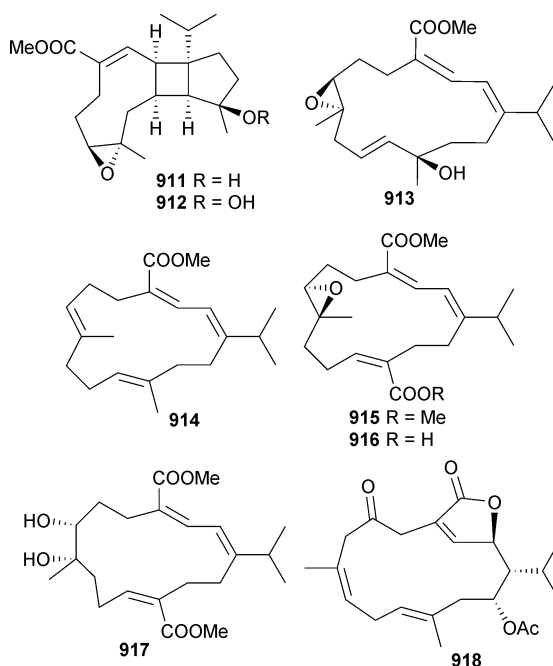


A Red Sea (Hurgada) collection of *S. trocheliophorum* provided trochelioids A **908** and B **909** and 16-oxosarcophytonin E **910**, the latter reported for the first time as an NP.⁸⁰¹

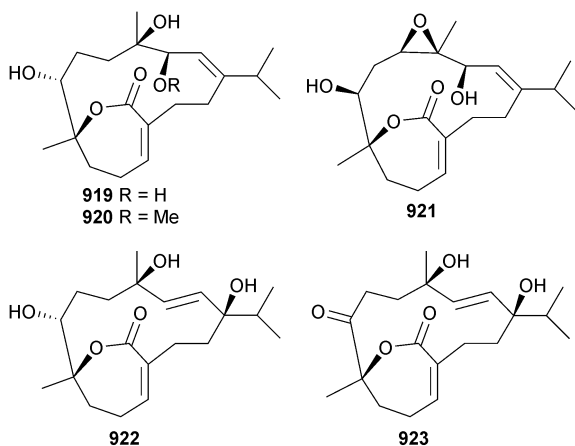




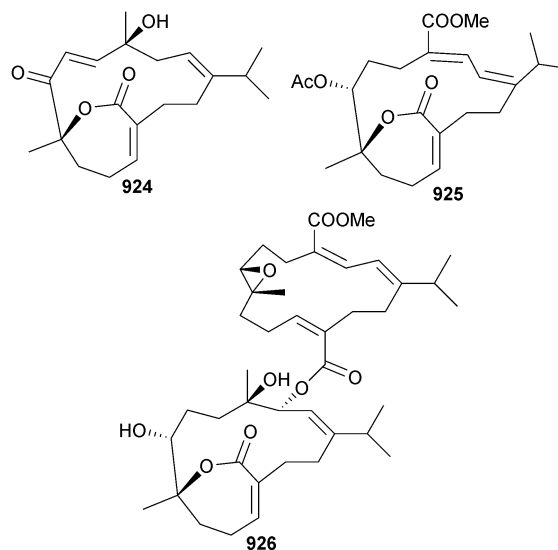
In three separate accounts, sixteen new cembranoids were reported from *S. trocheliophorum* (Yalong Bay, Hainan, China). Of methyl sarcotroates A **911** and B **912**, and sarcophytonolides M–R **913–918**, only hydroperoxide-containing **912** and sarcophytonolide N **914** were found to inhibit human PTP1B.^{802,803}



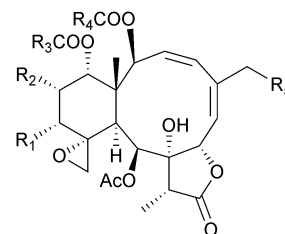
Also isolated were ϵ -lactone-containing cembranolides sartrolide A–G **919–925** and dimer bissartrolide **926**.⁸⁰⁴ The unusual (1*E*,3*Z*)-diene configuration of **925** was supported by



X-ray crystal analysis of isomeric co-metabolites sarcassin D⁸⁰⁵ and emblide.⁸⁰⁶ Bissartrolide represents a dimer of sartrolide A and a free carboxylic acid analogue of sarcophytonolide B.⁸⁰⁷

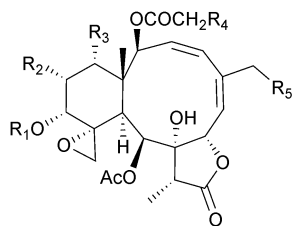


A total of 34 new briarane diterpenes were reported from two collections of *Dichotella gemmacea*: gemmacolides AA–AR **927–944** (S. China Sea)⁸⁰⁸ and dichotellides F–U **945–960** (Meishan Is., Hainan, China).⁸⁰⁹ The absolute configurations of **927–944** were assigned by comparison of ECD data with those of dichotellide T **941**, the absolute configuration of which was established by X-ray crystal analysis. Modest to moderate levels of cytotoxicity were observed for the gemmacolides while the dichotellides were all poorly cytotoxic with some examples exhibiting strong antifouling activity.

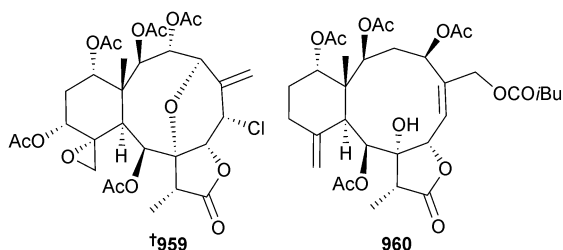


- [†]**927** R₁ = R₂ = OAc, R₃ = Me, R₄ = CH₂OH, R₅ = OMe
[†]**928** R₁ = OCO*i*Bu, R₂ = OAc, R₃ = Me, R₄ = CH₂OH, R₅ = OMe
[†]**929** R₁ = OCO*i*Bu, R₂ = OAc, R₃ = R₄ = Me, R₅ = OMe
[†]**930** R₁ = OCO*i*Bu, R₂ = OAc, R₃ = *i*Bu, R₄ = Me, R₅ = OMe
[†]**931** R₁ = R₂ = H, R₃ = Me, R₄ = CH₂OCO*i*Bu, R₅ = OMe
[†]**932** R₁ = R₅ = OCO*i*Bu, R₂ = OAc, R₃ = R₄ = Me
[†]**933** R₁ = R₂ = OAc, R₃ = R₄ = Me, R₅ = OCO*i*Bu
[†]**934** R₁ = R₅ = OCO*i*Bu, R₂ = OAc, R₃ = Me, R₄ = CH₂OCO*i*Bu
[†]**935** R₁ = OH, R₂ = OAc, R₃ = Me, R₄ = CH₂OCO*i*Bu, R₅ = OCO*i*Bu
[†]**936** R₁ = OCO*i*Bu, R₂ = OAc, R₃ = Me, R₄ = CH₂OCO*i*Bu, R₅ = Cl
[†]**937** R₁ = OAc, R₂ = OCO*i*Bu, R₃ = Me, R₄ = CH₂OH, R₅ = OMe
[†]**938** R₁ = OAc, R₂ = OCO*i*Bu, R₃ = Me, R₄ = CH₂OCO*i*Bu, R₅ = OMe
[†]**939** R₁ = OAc, R₂ = OCO*i*Bu, R₃ = Me, R₄ = CH₂OCO*i*Bu, R₅ = Cl
[†]**940** R₁ = OAc, R₂ = OCO*i*Bu, R₃ = Me, R₄ = CH₂OH, R₅ = Cl
[†]**941** R₁ = R₂ = R₅ = OCO*i*Bu, R₃ = Me, R₄ = CH₂OH
[†]**942** R₁ = R₂ = OAc, R₃ = *i*Bu, R₄ = CH₂OH, R₅ = Cl
[†]**943** R₁ = R₂ = OAc, R₃ = *i*Bu, R₄ = Me, R₅ = OH
[†]**944** R₁ = R₂ = R₅ = OAc, R₃ = *i*Bu, R₄ = Me

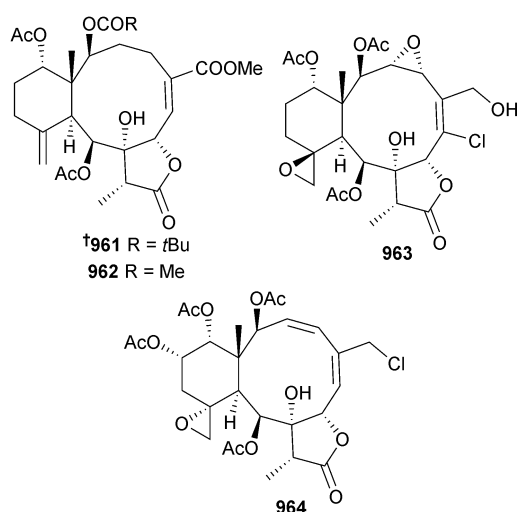




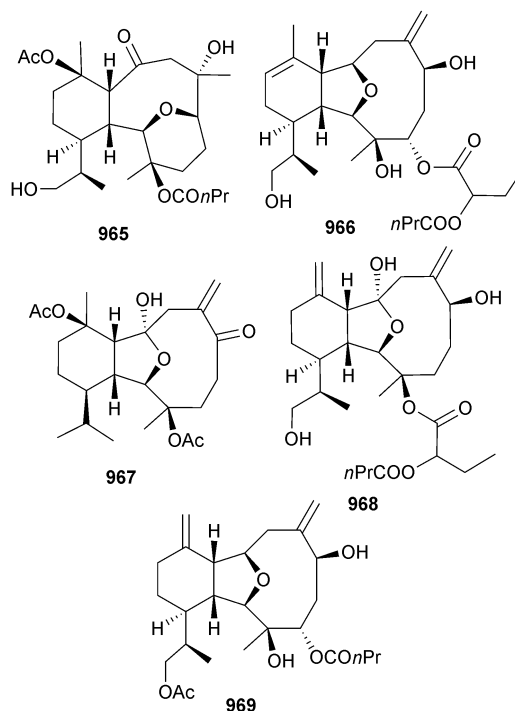
- 945** $R_1 = \text{Ac}$, $R_2 = R_3 = \text{OAc}$, $R_4 = \text{OCO/Bu}$, $R_5 = \text{OMe}$
946 $R_1 = \text{Ac}$, $R_2 = R_4 = \text{OCO/Bu}$, $R_3 = \text{OAc}$, $R_5 = \text{OMe}$
947 $R_1 = \text{CO/Bu}$, $R_2 = R_3 = \text{OAc}$, $R_4 = \text{OCO/Bu}$, $R_5 = \text{Cl}$
948 $R_1 = \text{Ac}$, $R_2 = R_3 = \text{OAc}$, $R_4 = R_5 = \text{OCO/Bu}$
949 $R_1 = \text{Ac}$, $R_2 = R_3 = R_5 = \text{OAc}$, $R_4 = \text{H}$
950 $R_1 = \text{Ac}$, $R_2 = R_5 = \text{OCO/Bu}$, $R_3 = \text{OAc}$, $R_4 = \text{H}$
951 $R_1 = \text{Ac}$, $R_2 = \text{OAc}$, $R_3 = R_5 = \text{OCO/Bu}$, $R_4 = \text{H}$
952 $R_1 = \text{CO/Bu}$, $R_2 = \text{OCO/Bu}$, $R_3 = \text{OAc}$, $R_4 = \text{H}$, $R_5 = \text{OMe}$
953 $R_1 = \text{Ac}$, $R_2 = R_4 = \text{H}$, $R_3 = \text{OCO/Bu}$, $R_5 = \text{OMe}$
954 $R_1 = \text{CO/Bu}$, $R_2 = R_4 = \text{H}$, $R_3 = \text{OAc}$, $R_5 = \text{OMe}$
955 $R_1 = \text{Ac}$, $R_2 = R_4 = \text{H}$, $R_3 = R_5 = \text{OCO/Bu}$
956 $R_1 = R_4 = \text{H}$, $R_2 = \text{OCO/Bu}$, $R_3 = \text{OH}$, $R_5 = \text{Cl}$
957 $R_1 = R_4 = \text{H}$, $R_2 = R_5 = \text{OCO/Bu}$, $R_3 = \text{OH}$
958 $R_1 = R_4 = \text{H}$, $R_2 = \text{OAc}$, $R_3 = \text{OH}$, $R_5 = \text{OCO/Bu}$



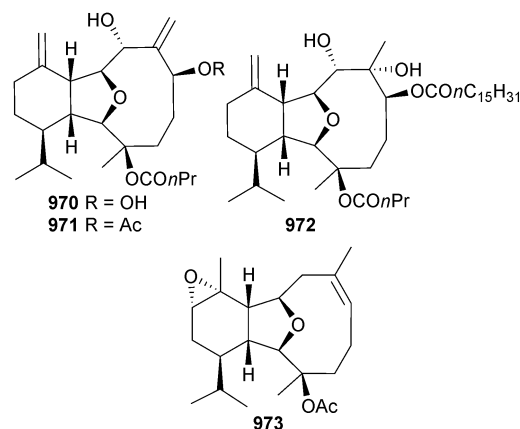
Junceella fragilis (Tai-Tong county, Taiwan) was the source of four more briaranes, frajunolide P–S **961**–**964**.⁸¹⁰ Hirsutalins I–M **965**–**969** are eunicellin diterpenes isolated from *Cladiella hirsuta* (Sianglu Islet, Penghu Is., Taiwan).⁸¹¹ Moderate inhibition of NO production by stimulated macrophages for **967** was shown.



In addition to a number of related metabolites, *C. krempfi* (Weizhou Is., S. China Sea) yielded oxylitophynol **970**, litophynol A acetate **971**, litophynol C **972** and krempfenin **973**.⁸¹²



Reduction of **970** gave a product identical to known co-metabolite litophynol A,⁸¹³ subsequent acetylation of which afforded a product identical to **971**.

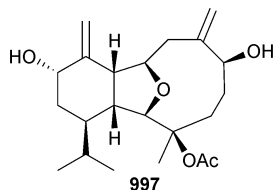
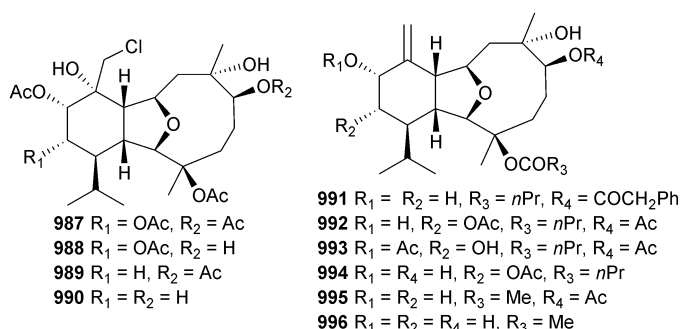
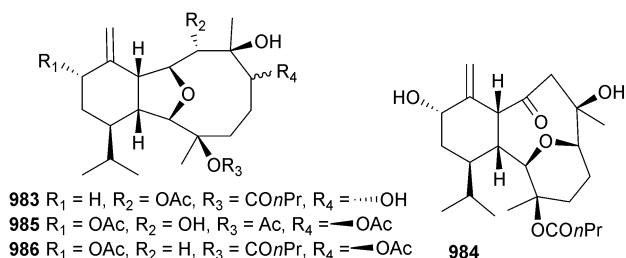
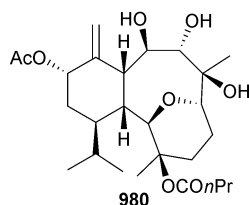
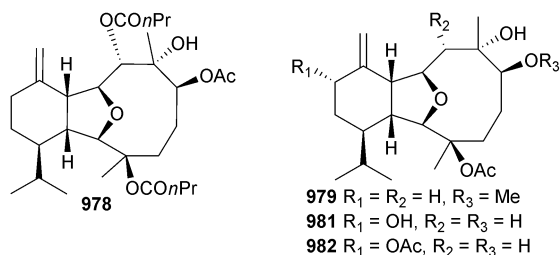
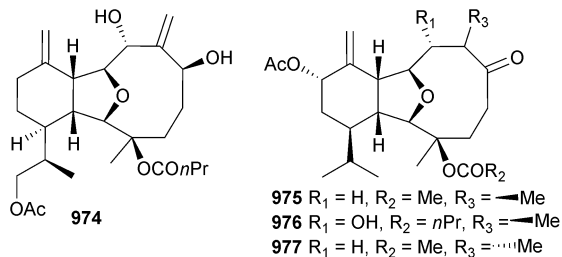


Also isolated from *C. krempfi* (Penghu Is., Taiwan) were krempfielins E–M **974**–**982**.^{814,815} Although **974**–**977** were inactive in antitumour and anti-inflammatory assays, structurally related co-metabolites did exhibit activity.

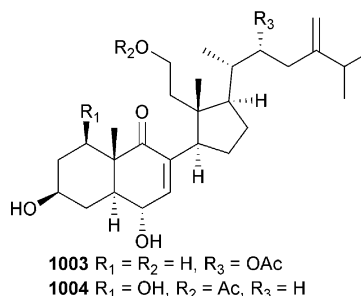
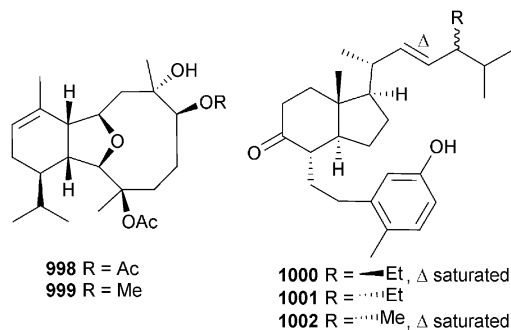
Of four new eunicellins reported from *Cladiella* sp. (Penghu Is., Taiwan), cladieunicellins I **983**, K **984**, and L **985** and litophynin I diacetate **986**, the latter has been previously reported⁸¹⁶ as a semi-synthetic derivative.^{817,818} Cladieunicellins I and L exhibited moderate activity towards an HTCL.

An unusual member of the klymollins I–S **987**–**997** (*Klyxum molle*, Penghu Is., Taiwan) is the phenylacetate-bearing klymollin M **991**.⁸¹⁹ This same metabolite was the most potent of the set, exhibiting cytotoxicity and the ability to inhibit superoxide generation and elastase release from stimulated human neutrophils.





In addition to two eunicellin diterpenes sibogin A **998** and B **999**, investigation of the NPs from *Muricella sibogae* (Weizhou Is., China) also afforded three new *seco*-sterols sibogol A–C **1000–1002**.⁸²⁰ A further two *seco*-sterols **1003** and **1004** were reported from *Sinularia nanolobata* (Xiao-Liuqiu Is., Pingtung county, Taiwan)⁸²¹ and eleven, subergorgol A–J **1005–1014** and **1015**, from *Subergorgia suberosa* (Meishan coast, S. China Sea).⁸²² The latter unnamed *seco*-sterol is reported as an NP for the first time. Subergorgols C **1007** and D **1008**, and F **1010** and G **1011** were isolated as their respective epimeric pairs but with unassigned configuration. The latter two were considered artefacts of isolation. While **1013** was found to be the most cytotoxic (moderate), **1015** was devoid of activity.

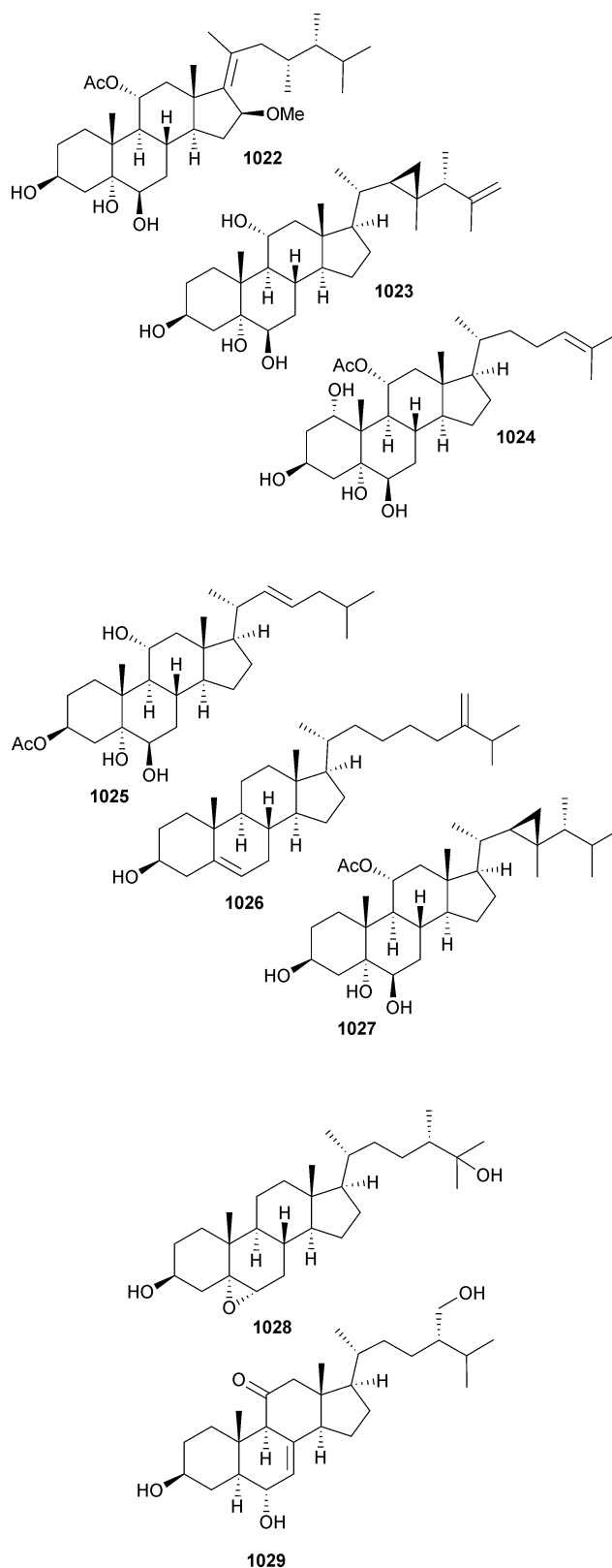
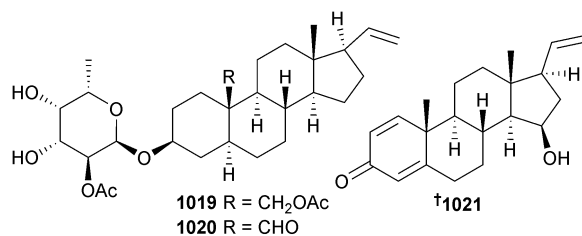
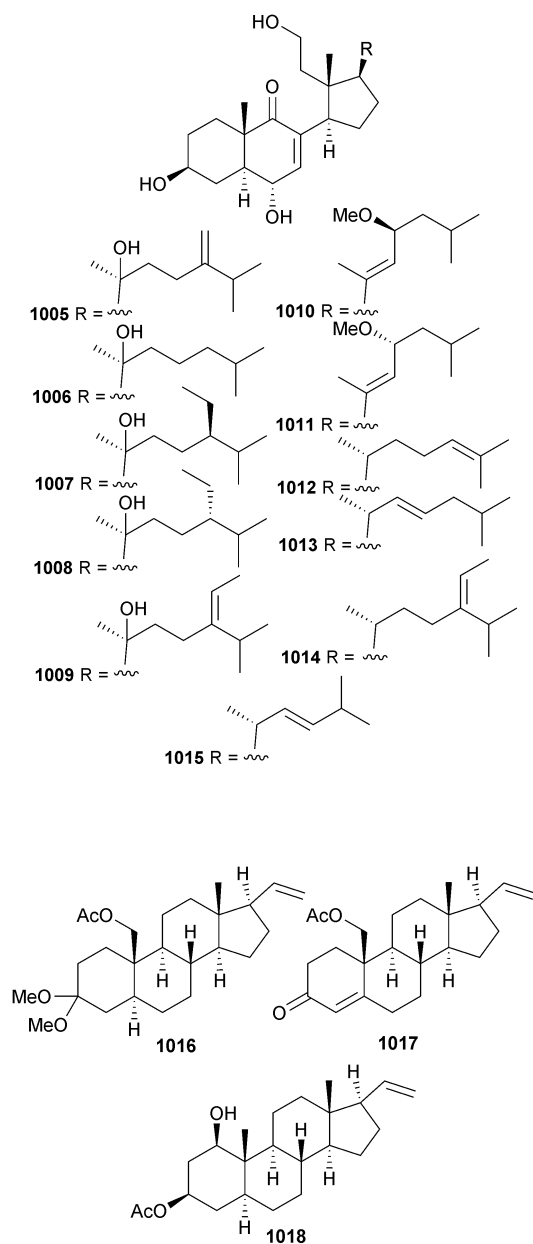


As well as a modestly bioactive δ -lactone noted earlier, an extract of *Scleronephthya gracillimum* (Green Is., Taiwan) also afforded pregnanes sclerosteroid J–N **1016–1020**.⁷⁷⁰ Sclerosteroids K and M were more active than the other metabolites at inhibiting expression of iNOS and COX-2 in stimulated macrophages. Pregnane **1021** (*Carijoa* sp., Weizhou Is., S. China Sea) exhibited potent antimicrobial properties.⁸²³

In addition to a number of known congeners, three new mildly cytotoxic polyhydroxylated steroids **1022–1024** were isolated from *Sarcophyton* sp. (Weizhou Is., S. China Sea).⁸²⁴ The possible artefactual origin of methylether **1022** was noted.

A collection of *Anthogorgia caerulea* from the same general location afforded caerulsteroid A **1025**.⁸²⁵ Three studies of Red Sea (Hurghada) cnidarians afforded steroids – hurgadacin **1026** was isolated from *Sinularia polydactyla*,⁸²⁶ gorgostane **1027** (= 11-acetyl-sarcoalldosterol A⁸²⁷) from *Heteroxenia ghardagensis*⁸²⁸ and zahramycins A **1028** and B **1029** from *Sarcophyton*



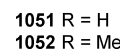
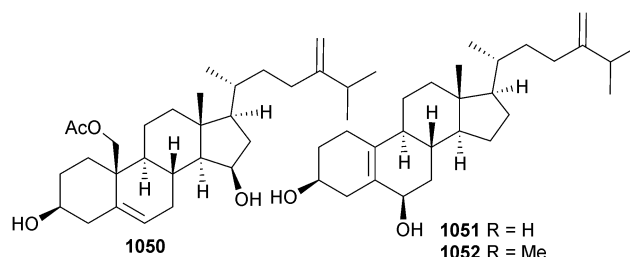
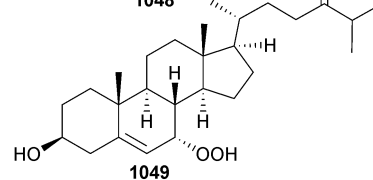
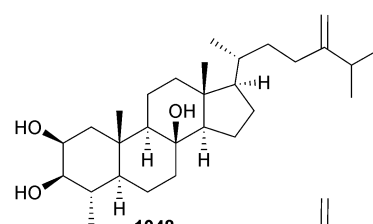
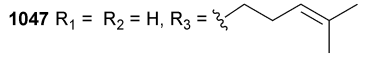
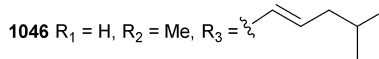
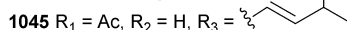
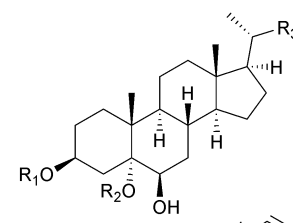
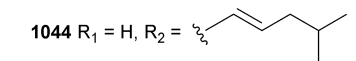
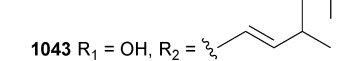
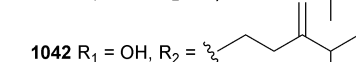
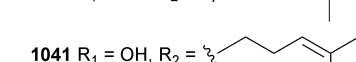
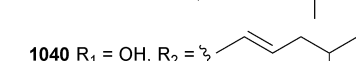
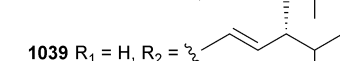
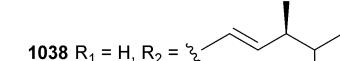
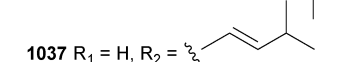
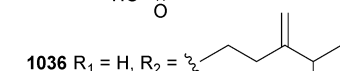
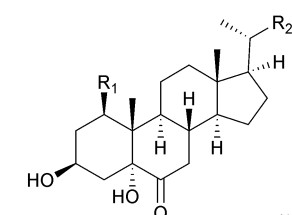
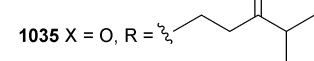
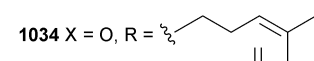
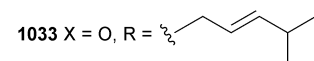
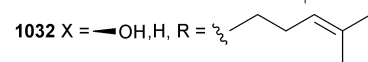
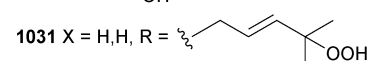
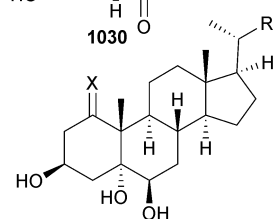
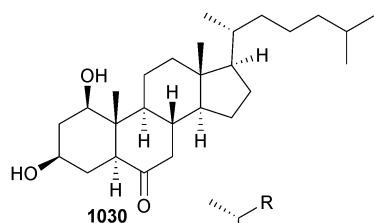


trocheliophorum.⁸²⁹ Zahramycin B exhibited modest antibacterial activity.

Fourteen new sterols **1030–1043**, plus one **1044** reported as an NP for the first time, were isolated as mildly cytotoxic constituents of *Menella kanisa* (coast of Beihai, Guangxi province, China).⁸³⁰

In addition to a number of co-metabolites, muriflasteroids A–C **1045–1047** were identified as weak to moderate cytotoxins (*Muriceopsis flavida*, Beihai, Guangxi province, China).⁸³¹ Sterols containing 24(28)-unsaturation were reported from *Sinularia depressa* (**1048** and **1049**, Lingshui Bay, Hainan, S. China Sea)⁸³²





and *Nephtea chabrolui* (nebrosteroids Q–S, **1050–1052**, San-Hsian-Tai coast, Taitung county, Taiwan).⁸³³ The latter three sterols exhibited mild cytotoxicity.

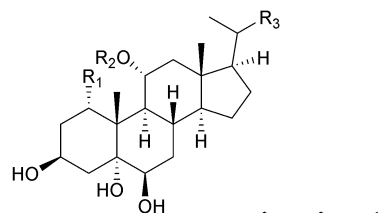
While sterols **1053–1059** (*Sarcophyton* sp., Weizhou Is., S. China Sea)⁸³⁴ exhibited variable levels of antimicrobial activity, disesterol **1060** (*Sinularia dissecta*, Hai Van-Son Cha, Hue,

Vietnam) was a strong inhibitor of IL-12 p40 cytokine production by stimulated bone marrow-derived dendritic cells.⁸³⁵ One new 18-acetoxy sterol **1061** was isolated from a South China Sea (Xuwen coral reef area) collection of *Sarcophyton* sp.⁸³⁶

Two 5 α ,8 α -epidioxysterols were reported: mildly cytotoxic **1062** from *Sinularia gaweli* (Sansiantai, Taitung county, Taiwan)⁸³⁷ and antiviral (H5N1) **1063** from *S. candidula* (Safaga, Egyptian Red Sea).⁷⁵²

A range of ring-A cross-conjugated steroids, including lactone side-chained withanolides, were reported from cnidarians. All five cholestadienones **1064–1068** (*Nephtea* sp., Naozhou Is., S. China Sea)⁸³⁸ exhibited cytotoxicity towards a panel of HTCLs, while of three carboxylic acid-containing examples, paraminabic acid A–C **1069–1071** (*Paraminabea acronocephala*, Pingtung county, Taiwan), **1071** exhibited the most potent cytotoxicity.⁸³⁹



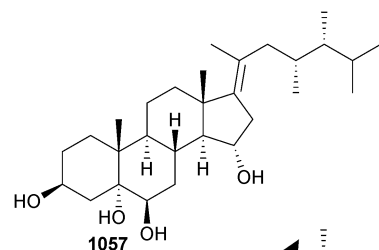


1053 $R_1 = H$, $R_2 = Ac$, $R_3 = \text{isopentenyl}$

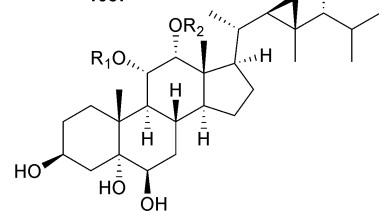
1054 $R_1 = H$, $R_2 = Ac$, $R_3 = \text{farnesyl}$

1055 $R_1 = OH$, $R_2 = H$, $R_3 = \text{isopentenyl}$

1056 $R_1 = R_2 = H$, $R_3 = \text{farnesyl}$

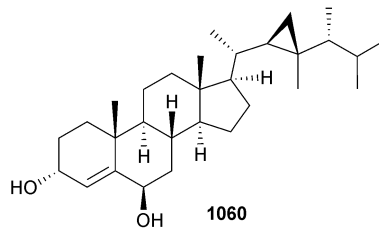


1057

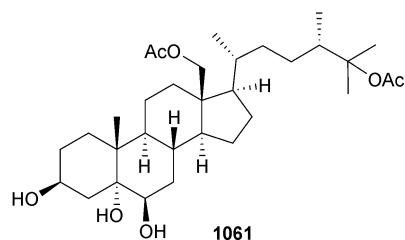


1058 $R_1 = Ac$, $R_2 = H$

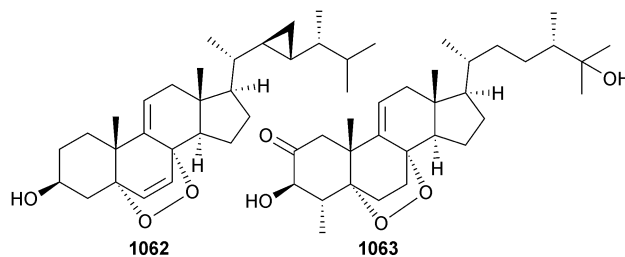
1059 $R_1 = H$, $R_2 = Ac$



1060

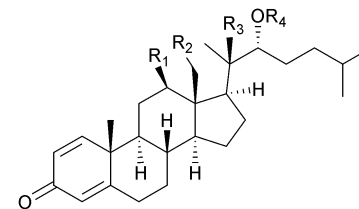


1061



1062

1063



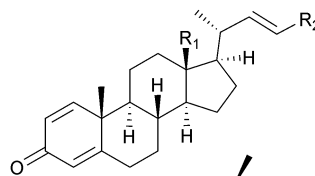
1064 $R_1 = OAc$, $R_2 = R_3 = R_4 = H$

1065 $R_1 = OH$, $R_2 = R_3 = H$, $R_4 = Ac$

1066 $R_1 = OAc$, $R_2 = R_3 = H$, $R_4 = Ac$

1067 $R_1 = R_3 = H$, $R_2 = OAc$, $R_4 = Ac$

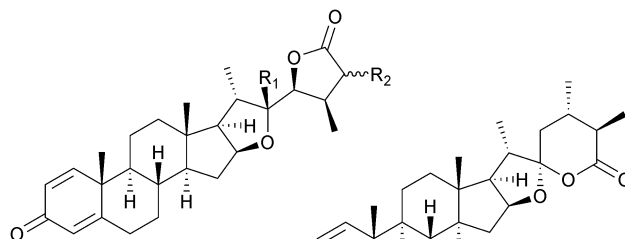
1068 $R_1 = R_2 = H$, $R_3 = OH$, $R_4 = Ac$



1069 $R_1 = Me$, $R_2 = \text{isopentenyl}$, $R_3 = COOH$

1070 $R_1 = Me$, $R_2 = \text{farnesyl}$, $R_3 = COOH$

1071 $R_1 = COOH$, $R_2 = \text{isopentenyl}$, $R_3 = OH$

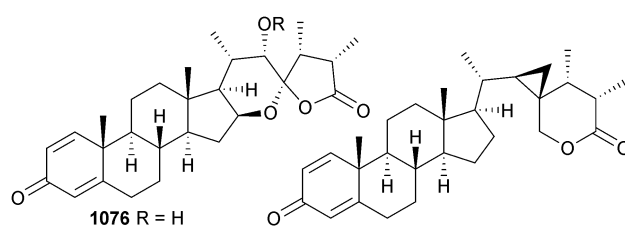


†1072 $R_1 = H$, $R_2 = \text{isopentenyl}$, $R_3 = Me$

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

1074 $R_1 = OH$, $R_2 = \text{isopentenyl}$, $R_3 = Me$

1075



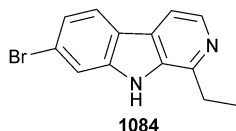
1076 $R = H$
1077 $R = Ac$

1078



9 Bryozoans

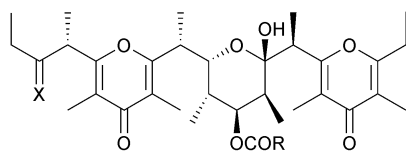
Only one new metabolite was reported from bryozoans in the last year, continuing the trend of minimal NP research efforts on this phylum. A new alkaloid, 7-bromo-1-ethyl- β -carboline **1084** was isolated from *Pterocella vesiculosa* (Aldermen Islands, New Zealand).⁸⁶⁸



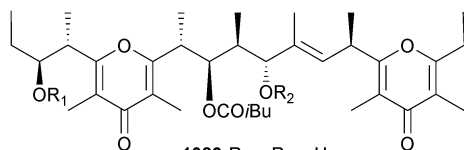
Wilsoniamines A and B, tribrominated alkaloids originally obtained from an Australian collection of *Amathia wilsoni*,⁸⁶⁹ have been synthesised in two steps featuring a condensation reaction between (2,4,6-tribromo-3-methoxyphenyl)acetaldehyde and (*S*)-*N*-methylpyrrolidine-2-carboxamide as a key step.⁸⁷⁰ Convolutamydine A, a dibrominated oxindole originally obtained from *Amathia convoluta*,⁸⁷¹ (along with two synthetic analogues) has/have been shown to possess antinociceptive effects comparable to those of morphine.⁸⁷²

10 Molluscs

The number of new metabolites reported from molluscs (15) is just over half the yearly average number reported over the past decade. The previously noted ability of molluscs to acylate dinoflagellate-produced toxin okadaic acid has been confirmed with acylating activity located in the digestive gland of various molluscs.⁸⁷³ A range of unusual Δ^8 unsaturated 4-methyl and 4,4-dimethyl sterols was identified in extracts of the gonads of the Japanese limpet *Cellana grata* and *C. toreuma*.⁸⁷⁴ Matrix solid-phase dispersion combined with GC-MS was demonstrated as a useful technique to detect the presence of brominated diphenyl ethers and newer halogenated flame retardants in mussel, cockle and clam extracts.⁸⁷⁵ New onchidione



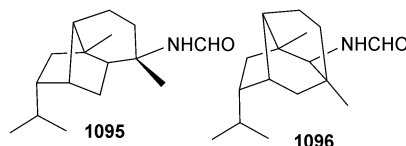
- 1085** R = Et, X = O
1086 R = *i*Bu, X = OH, H
1087 R = *i*Bu, X = OAc, H
1088 R = *i*Bu, X = OCOEt, H



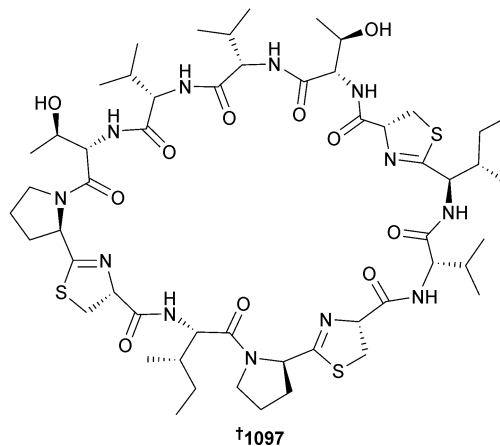
- 1089** R₁ = R₂ = H
1090 R₁ = H, R₂ = Ac
1091 R₁ = R₂ = Ac
1092 R₁ = H, R₂ = COEt
1093 R₁ = Ac, R₂ = COEt
1094 R₁ = R₂ = COEt

analogues **1085–1088** and ilikonapyrone esters **1089–1094** were reported from different *Onchidium* sp. molluscs.⁸⁷⁶ Acylation of **1086** gave **1087** and **1088**, while reduction of co-metabolite onchidione afforded two diastereomers, one of which was identical to onchidionol **1086**. The configurational relationships between **1089–1094** were identified by methanolysis of each, affording a product identical to co-metabolite ilikonapyrone.⁸⁷⁷ Mild cytotoxicity was observed for some of the compounds.

Two formamide-containing pupukeanane sesquiterpenoid congeners **1095** and **1096**, the latter previously known as a synthetic derivative, were reported from the tubercle nudibranch *Phyllidia coelestis* (Koh-Ha Islet, Krabi province, Thailand).⁸⁷⁸ Moderate to strong cytotoxicity towards tumour cell lines was observed.

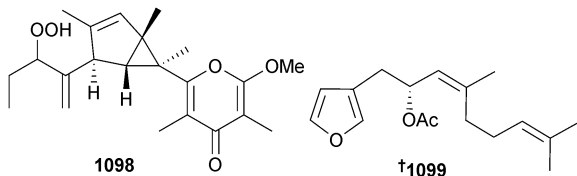


The absolute configuration of the mildly cytotoxic cyclic dodecapeptide cycloforskamide **1097** (*Pleurobranchus forskalii*, Ishigaki Is., Okinawa) was established by combinations of ozonolysis and acid hydrolysis.⁸⁷⁹ In addition to this peptide, the ergot alkaloid ergosinine⁸⁸⁰ was also isolated, an unusual finding as ergot alkaloids are usually only isolated from terrestrial higher plants and fungi.⁸⁸¹



A potentially artefactual hydroperoxide, photo-tridachiapyrone **1098** was isolated from the sacoglossan mollusc *Elysia patagonica* (San Jorge Gulf, Patagonia, Argentina).⁸⁸² The search for new leads for the treatment of leishmaniasis has identified the known 5 α ,8 α -epidioxycholest-6-en-3 β -ol (*Dolabrifera dolabrifera*) as mildly active against the amastigote form with nearly sixty-fold selectivity versus Vero cells.⁸⁸³ The structure of furan **1099** (*Hypselodoris jacksoni*, S. E. Queensland) was confirmed and absolute configuration established by a thorough study using combinations of synthesis, chiral HPLC and MPA derivatisation.⁸⁸⁴



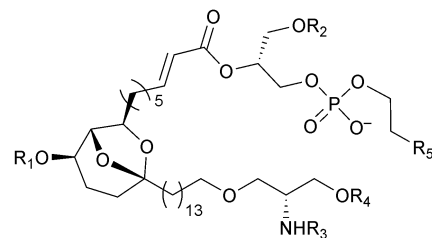


A new enantioselective route to oxazinin alkaloids (*Mytilus galloprovincialis*)^{885,886} has helped confirm the absolute configuration of amongst others, oxazinin-1 and -2.⁸⁸⁷ Synthesis of a library of analogues of cytotoxic depsipeptide kulokekahlide-2 (*Philinopsis speciosa*)^{888,889} has revealed requirements of conformation, ring formation and ring size for biological potency.⁸⁹⁰ Aplysiatoxin (*Stylocheilus longicauda*)⁸⁹¹ is a potent PKC binding tumour promoter – synthesis and evaluation of simplified debromo analogues suggest that activation of PKC δ might play a role in the observed antiproliferative activity.⁸⁹² Following the synthesis of sanguinamide B (*Hexabanchus sanguineus*),⁸⁹³ the same group has reported that the use of biotinylated analogues of two cytotoxic D-Phe analogues in combination with pull-down assays have identified cellular targets that include eukaryotic ribosomal subunits.⁸⁹⁴ Close investigation of the mechanisms of cell death induced by the compounds indicates that the exact mechanism depends on the position of the D-Phe group. The results of a dose-escalating phase I study of kahalalide F (originally mollusc *Elysia rufescens* and green alga *Bryopsis pennata*)⁸⁹⁵ have been reported,⁸⁹⁶ while evaluation of a kahalalide F analogue, elisidepsin, against a panel of tumour cell lines suggests that cell lines that exhibit high E-cadherin, ErbB3 and Muc1 gene expression can be regarded as being sensitive to the clinical candidate.⁸⁹⁷ Drug resistance was associated with the presence of KRAS activating mutations. Using constrained NOESY NMR data, a conformational search has helped assign the configuration (3*S*) in the 9-methyl-3-decanol subunit of kahalalide Y (*Elysia rufescens*):⁸⁹⁸ unfortunately the study made use of the enantiomer of the NP and so the configuration should in fact be (3*R*).^{899,900} Investigation of the mechanism of cytotoxic action of aplyronine A (*Aplysia kurodai*)⁹⁰¹ using photoaffinity biotinylated derivatives has identified aplyronine A to synergistically bind to tubulin in association with actin in a 1 : 1 : 1 ratio, leading to inhibition of tubulin polymerisation, and ultimately prevention of spindle formation and mitosis.⁹⁰² Similar experiments using aplyronine C⁹⁰² (lacks the trimethylserine sidechain of aplyronine A;⁹⁰³ three orders of magnitude less cytotoxic) showed it to bind to actin, as previously reported, but it did not bind to tubulin in this present study. Model compounds of the *N*-methylformamide sidechain of aplyronine A exhibit cytotoxicity towards tumour cell lines which is strongly correlated with their ability to induce the disruption of actin filaments.⁹⁰⁴

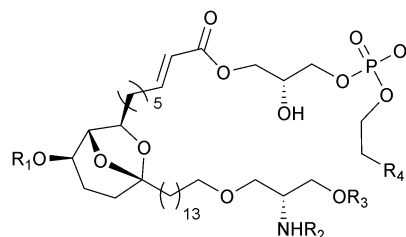
11 Tunicates (ascidians)

The 35 new tunicate-derived NPs presented in this review is average for the number reported per annum over the last

decade. The sulfonated serinol lipids siladenoserinol A–L **1100**–**1111** (Didemnidae, North Sulawesi, Indonesia) inhibited the interaction of tumour suppressor p53 with Hdm2, potentially leading to reactivation of p53 and induction of apoptosis in cancer cells.⁹⁰⁵ The absolute configuration of **1100** was established by a combination of degradation, modified Mosher's analysis and comparison with similar fragments of defined configuration.

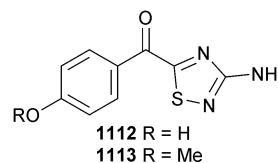


- †**1100** R₁ = R₂ = Ac, R₃ = SO₃H, R₄ = H, R₅ = N⁺Me₃
1101 R₁ = R₂ = Ac, R₃ = SO₃H, R₄ = H, R₅ = N⁺H₃
1102 R₁ = R₃ = H, R₂ = Ac, R₄ = SO₃H, R₅ = N⁺H₃
1103 R₁ = Ac, R₂ = R₄ = H, R₃ = SO₃H, R₅ = N⁺Me₃
1104 R₁ = R₃ = H, R₂ = Ac, R₄ = SO₃H, R₅ = N⁺Me₃
1105 R₁ = R₄ = H, R₂ = Ac, R₃ = SO₃H, R₅ = N⁺Me₃
1106 R₁ = R₂ = Ac, R₃ = H, R₄ = SO₃H, R₅ = N⁺Me₃



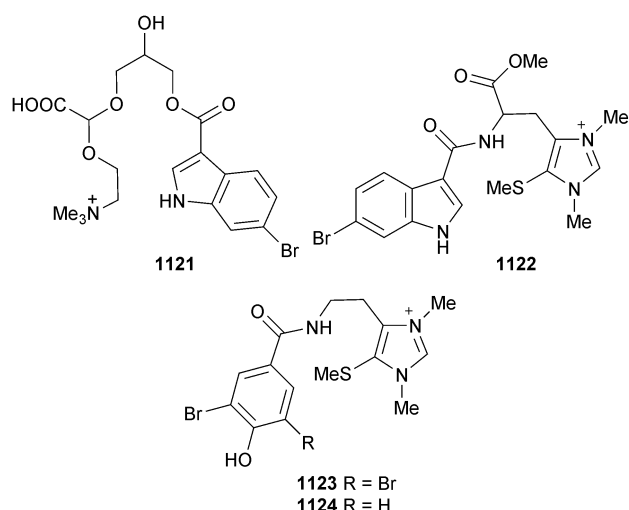
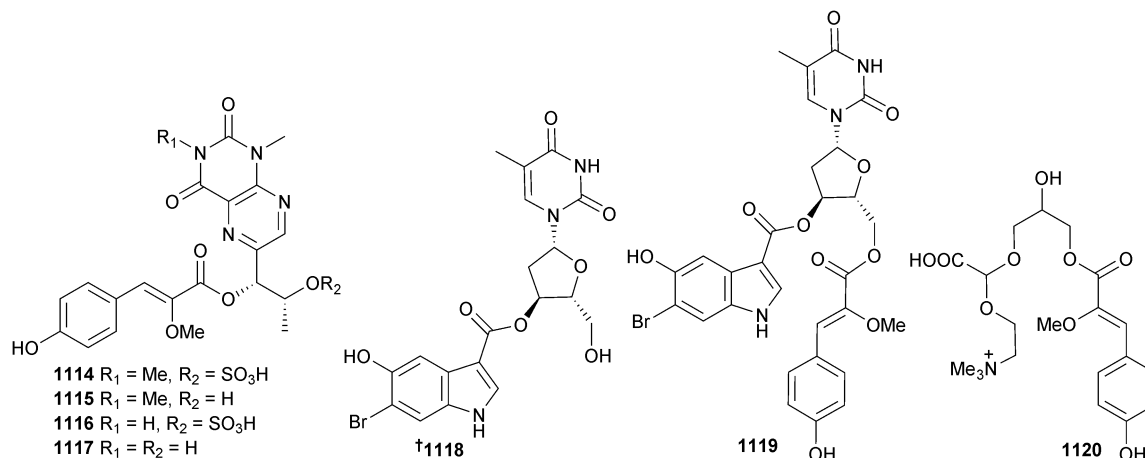
- 1107** R₁ = Ac, R₂ = SO₃H, R₃ = H, R₄ = N⁺Me₃
1108 R₁ = Ac, R₂ = H, R₃ = SO₃H, R₄ = N⁺Me₃
1109 R₁ = R₂ = H, R₃ = SO₃H, R₄ = N⁺H₃
1110 R₁ = R₃ = H, R₂ = SO₃H, R₄ = N⁺Me₃
1111 R₁ = R₂ = H, R₃ = SO₃H, R₄ = N⁺Me₃

Two new examples of the rare 1,2,4-thiadiazole ring system, polycarpathamine A **1112** and B **1113**, were isolated from *Polycarpa aurata* (Ambon, Indonesia). While **1112** exhibited sub-micromolar cytotoxicity (L5178Y), **1113** was inactive.⁹⁰⁶ The regiochemistry of the 1,2,4-thiadiazole ring was established by analysis of ¹H–¹⁵N HMBC data and by synthesis of a model compound.

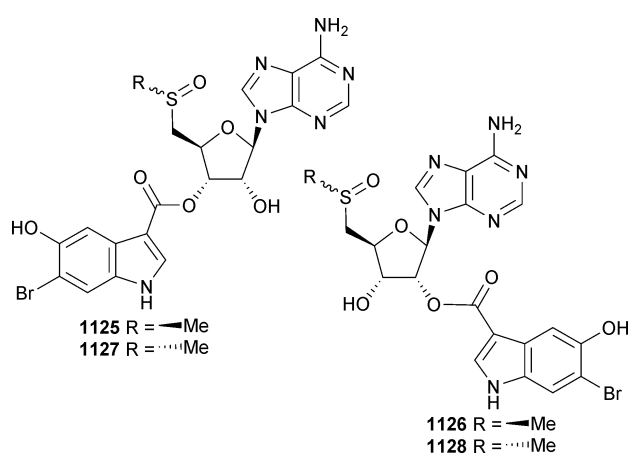


A diverse range of pteridine (duramidines A–D **1114**–**1117**), thymidine (leptoclinidines A **1118** and B **1119**), choline (dura-betaines A **1120** and B **1121**) and imidazole (leptoclinidamines D–F **1122**–**1124**) analogues was isolated from *Leptoclinides durus* (Swains Reef, Great Barrier Reef).⁹⁰⁷

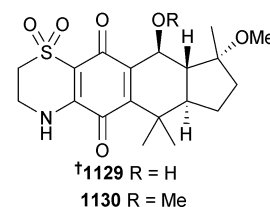




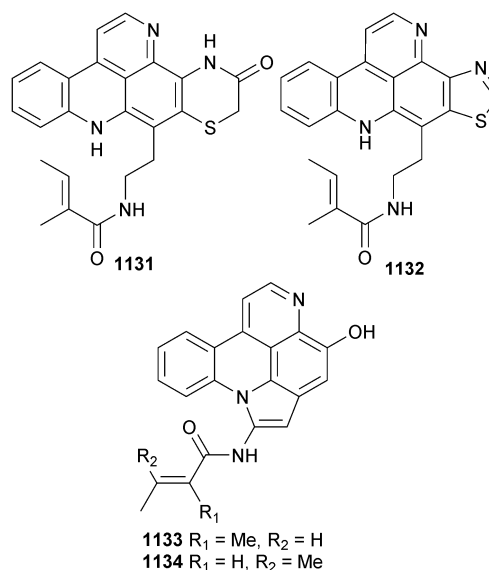
Four methylsulfinyladenosine derivatives, momusine A-D **1125–1128**, isolated as pairs of interconverting isomers, were reported from extracts of *Herdmania momus* (Jeju Is., S. Korea).⁹⁰⁸



The structures of the modestly cytotoxic dioxothiazinomer-terpenes conthiaquinone A **1129** and B **1130** (*Aplidium conicum*, Porto Cesareo, Lecce, Italy) were established by interpretation of NMR data in combination with DP4 calculated chemical shifts.⁹⁰⁹ The absolute configuration of **1129** was proposed from TDDFT calculated ECD data.

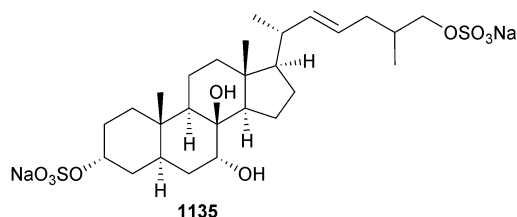


Four new examples of pyridoacridine alkaloids, shermilamine F **1131**, dehydrokuanoniamine F **1132**, arnoamine C **1133** and D **1134** (*Cystodytes violatinctus*, Solomon Is.) exhibited modest cytotoxicity towards a panel of HTCLs.⁹¹⁰ A variant biosynthetic pathway to address the formation of arnoamines C and D was proposed. New analogues of the structurally related



styelsamines⁹¹¹ were prepared and assessed for DNA binding ability and cytotoxicity.⁹¹²

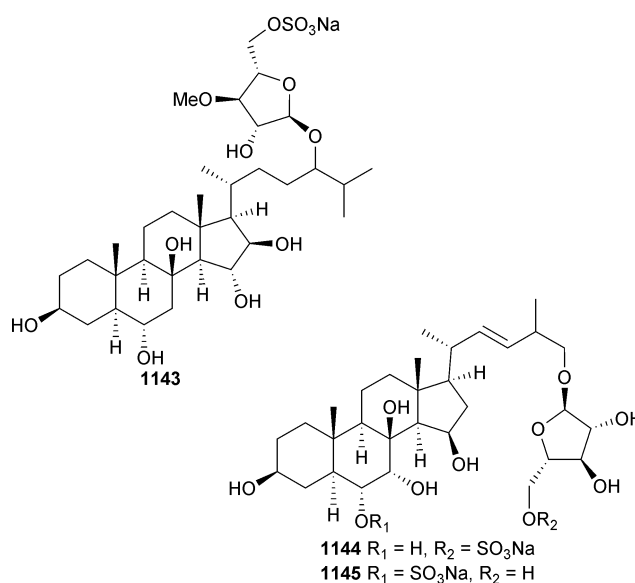
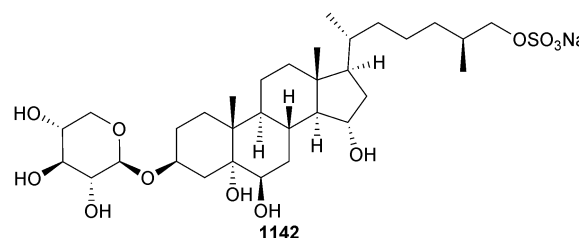
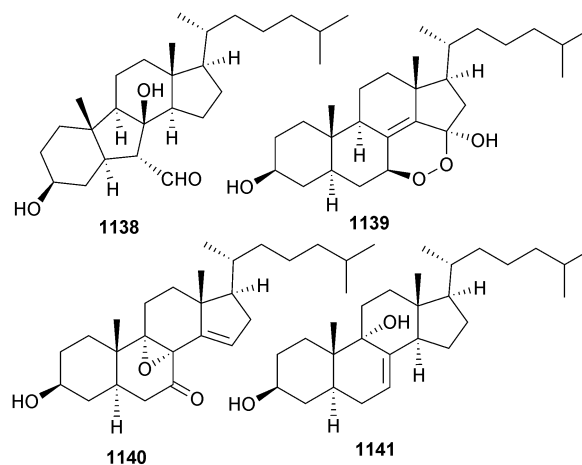
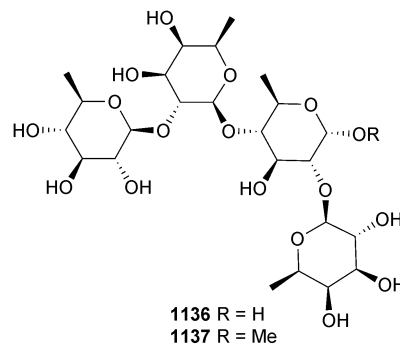
A sperm activation and attractant **1135** was isolated from egg seawater of *Ascidia sydneiensis*; structure elucidation by NMR and MS was performed on 2.6 μg (4 nmol) of material.⁹¹³ The proposed planar and stereo structure of **1135** was supported by the synthesis of model compounds. The structure of this sperm attractant is very similar to that previously reported from *Ciona intestinalis* and *C. savignyi*.⁹¹⁴



Synthesis and cytotoxic evaluation of aminol lipids clavaminol G⁹¹⁵ (*Clavelina phlegrea*)⁹¹⁶ and crucigasterins A, B and D^{917,918} (*Pseudodistoma crucigaster*)⁹¹⁹ have been reported; mild activity was observed. First syntheses of kottamide E⁹²⁰ (*Pycnoclavella kottae*),⁹²¹ lukianol B⁹²² (unidentified tunicate)⁹²³ and eudistomin Y₇^{924–926} (*Eudistoma* sp.)⁹²⁷ have been published. Syntheses of an isomer of didemnaketal A⁹²⁸ and the proposed structure of didemnaketal B⁹²⁹ (*Didemnum* sp.)⁹³⁰ provide further evidence that the NPs require revision of configurational assignments. Synthesis and structure–activity relationship studies on orthidine F⁹³¹ (antimalarial),⁹³² ascidiathiazone⁹³³ (antimalarial),⁹³⁴ meridianin G⁹³⁵ (antimalarial),⁹³⁶ perspicamide A⁹³⁷ (antileishmanial),⁹³⁸ rigidin⁹³⁹ (antitumour),⁹⁴⁰ and ningalin B⁹⁴¹ (P-glycoprotein modulator)⁹⁴² have been reported. Further investigation of recently reported ascidian metabolites of the cadiolide and synoilde families of furanones (*Synoicum* sp.)⁹⁴³ has identified cadiolides E, H and I as being potent inhibitors of *C. albicans* isocitrate lyase, an enzyme associated with microorganism virulence.⁹⁴⁴ Semi-synthetic *N*-acyl derivatives of ecteinascidin 770 (*Ecteinascidia thurstoni*)⁹⁴⁵ has identified quinoline- and fluorocinnamoyl-containing examples that exhibit 50–70 fold increased cytotoxicity towards the HCT-116 cell line *versus* the parent NP.⁹⁴⁶ Minor corrections to manuscripts describing the mandelalides (*Lissoclinum* sp.)⁹⁴⁷ and herdmanine K (*Herdmania momus*)⁹⁴⁸ have been noted.

12 Echinoderms

The 33 new metabolites reported from echinoderms in this review is lower than the average number reported per annum over the last decade. A commercially available specimen of the starfish *Asterias rollestoni* (Xiamen food market, China) afforded the tetraosides **1136** and **1137** (ref. 949) while *Astropecten polyacanthus* (Cat Ba, Haiphong, Vietnam) contained the inactive or mildly cytotoxic sterols astropectenol A–D **1138–1141**.⁹⁵⁰ The latter set of compounds was also reported to inhibit the expression of pro-inflammatory cytokines in bone marrow-derived dendritic cells.⁹⁵¹

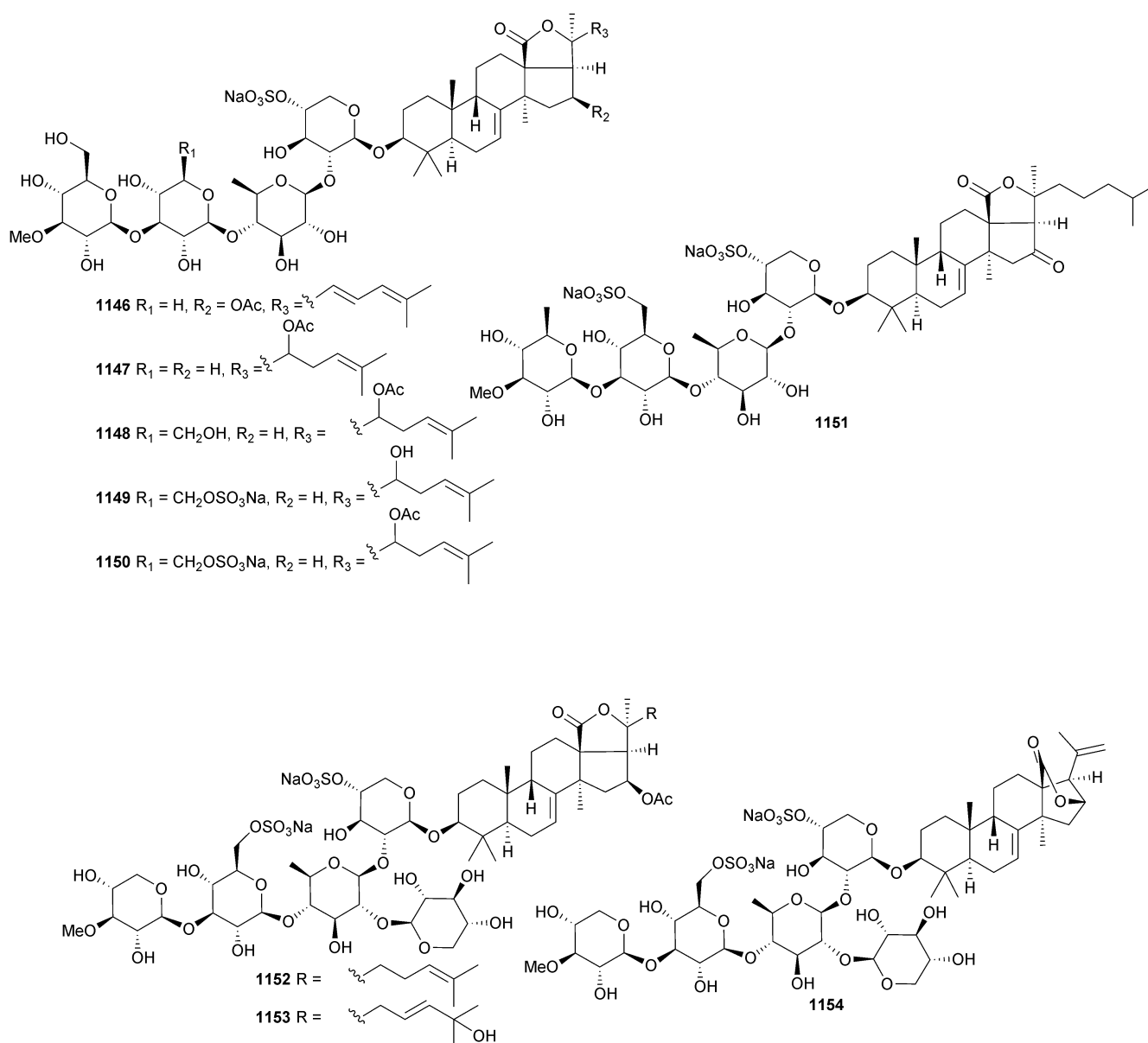


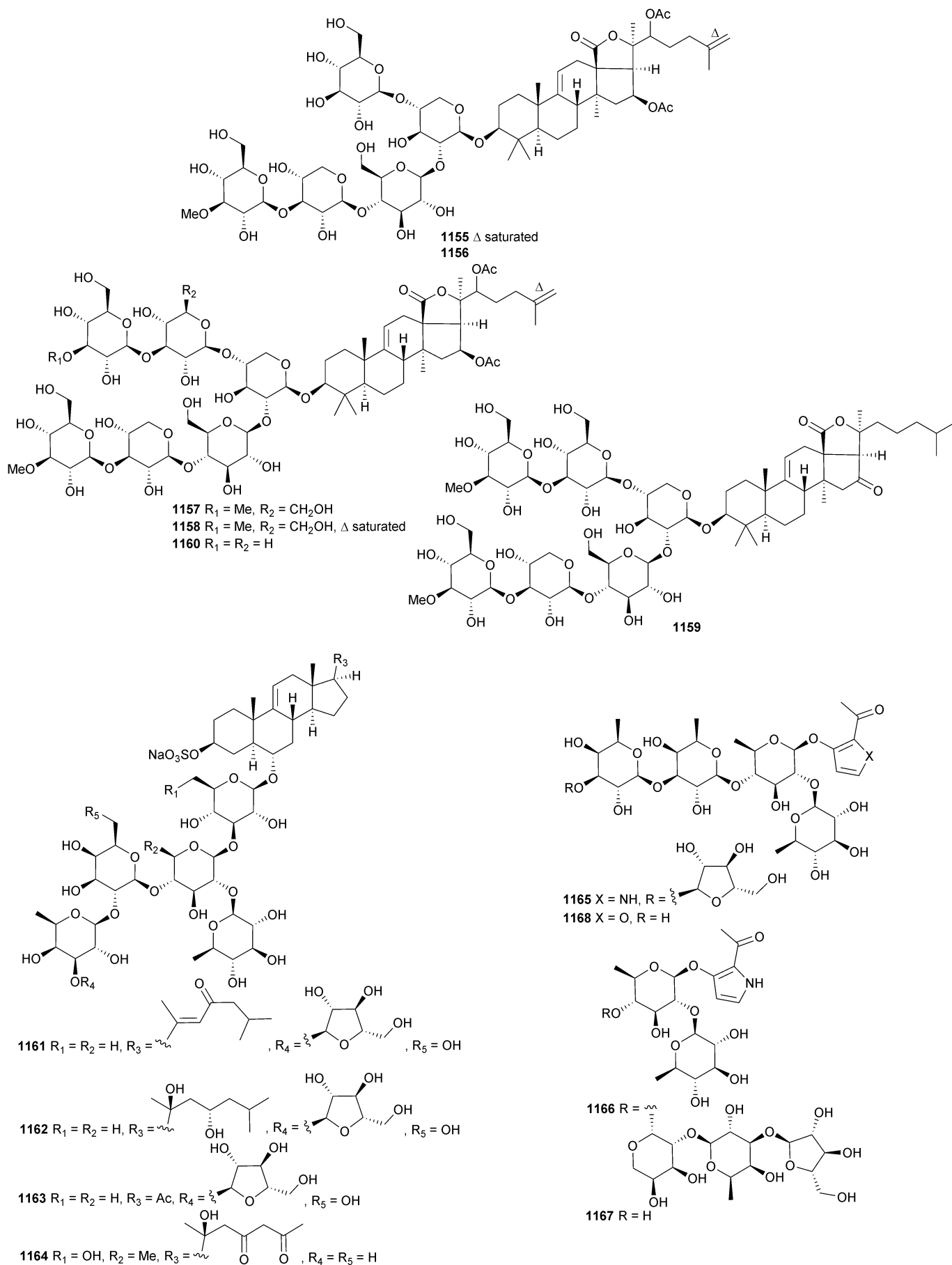
Aphelasteroside E **1142**, which contains the rare sulfation at C-26, was isolated from *Aphelasterias japonica* (Poset Bay, Sea of Japan)⁹⁵² and the C-24-arabinosides pectinioside H–J **1143–1145** were identified in extracts of *Asterina pectinifera* (Dalian coast, Yellow Sea, China).⁹⁵³

Tetraosides typicoside A₁ **1146** (the 24*E* isomer of previously reported intercedenside A (*Mensamaria intercedens*)⁹⁵⁴), A₂, B₁, C₁ and C₂ **1147–1150** are minor metabolites isolated from the sea cucumber *Actinocucumis typica* (Vizhinjam coast, Arabian Sea, India).⁹⁵⁵ Antifungal, haemolytic and cytotoxic evaluations of the five NPs identified widespread activity, with typicoside C₁ being markedly less active in all assays. The presence of disulfated tetraoside turquetoside A **1151**, which contains the rare 3-*O*-methyl-*D*-quinovose sugar unit, in both *Staurocucumis turqueti* and *S. liouvillei* suggests the sugar is a taxonomic character of this particular genus of Antarctic sea cucumber.⁹⁵⁶

Of the disulfated pentaosides cucumarioside I₁, I₃ and I₄ **1152–1154** (*Eupentacta fraudatrix*, Peter the Great Gulf, Sea of Japan), only **1152** exhibited biological activity including cytotoxicity (weak) and haemolytic activity (strong).⁹⁵⁷ Pentaosides cladoloside B₁ **1155** and B₂ **1156** and hexaosides cladoloside C, C₁, C₂ and D **1157–1160** (*Cladolabes schmeltzii*, Nha Trang Gulf, S. China Sea) all exhibited similar levels of strong cytotoxicity and haemolytic activity.⁹⁵⁸

Extracts of the starfish *Astropecten monacanthus* (Cat Ba, Haiphong, Vietnam) afforded the hexaosides astrosteroside A–C **1161–1163** and pentaoside astrosteroside D **1164**.⁹⁵⁹ While **1161** and **1163** exhibited mild inhibition of IL-6 production by stimulated bone marrow-derived dendritic cells, diketo-containing **1164** exhibited potent inhibition of production of IL-6, IL-12 p40 and TNF- α .



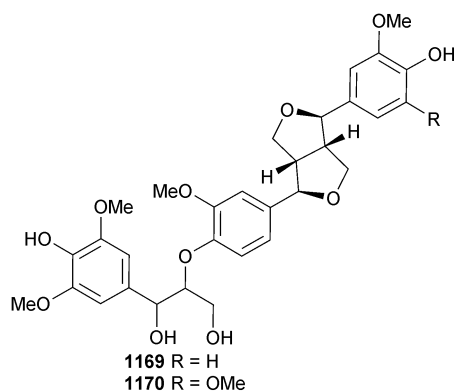


The pyrrole and furan oligoglycosides astebatherioside A–D **1165–1168** were reported from the starfish *Asterina batheri* (Catba, Haiphong, Vietnam).⁹⁶⁰ While **1165** was either inactive or weakly active, **1166–1168** demonstrated inhibition of IL-12 p40 production, and to a lesser extent of IL-6 production, in LPS-stimulated bone marrow-derived dendritic cells.

The synthesis of goniopectenoside B (starfish *Goniopecten demonstrans*)⁹⁶¹ has been reported.⁹⁶² Purified polar steroids previously reported from the starfish *Patiria pectinifera* and *Distolasterias nipon* are potent enhancers of neurite outgrowth and acted as neuroprotectors against damage caused by oxygen-glucose deprivation.⁹⁶³ Crude preparations of cerebroside from the sea cucumber *Acaudina molpadioides* and the starfish *Asterias amurensis* were found to protect PC12 cells from oxidative damage due to exposure to H₂O₂ or *tert*-butyl hydroperoxide.⁹⁶⁴ In both cases the neuroprotection appeared to be conferred by upregulation of superoxide dismutase activity and modulation of components of the mitochondrial apoptotic pathway. High-energy CID tandem mass analysis has been used to determine the structures of ceramides and cerebroside isolated from *Distolasterias nipon*.⁹⁶⁵ Stable isotope biosynthesis feeding experiments have determined that dietary cholesterol and cholesterol 3-sulfate are elaborated into polyhydroxylated sterols in the starfish *Patiria* (= *Asterina*) *pectinifera*.⁹⁶⁶

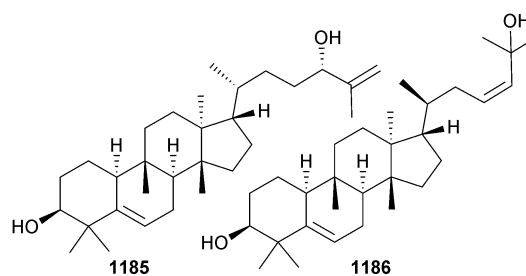
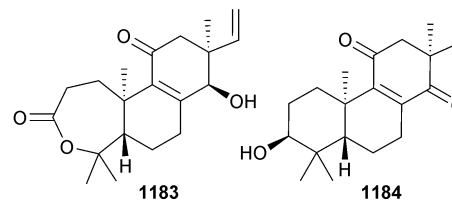
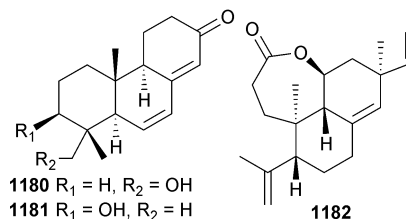
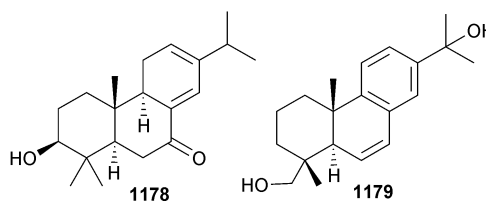
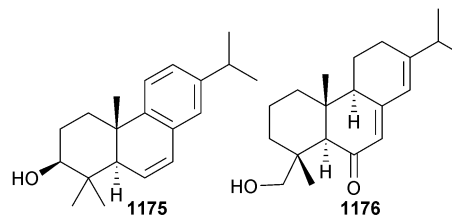
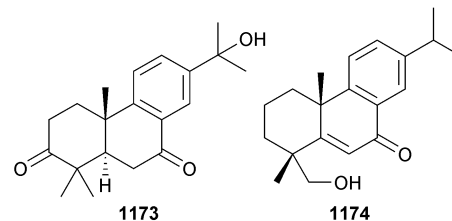
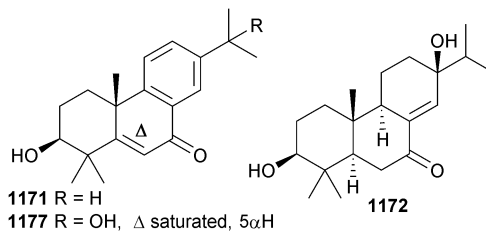
13 Mangroves

Aerial parts of the mangrove plant *Kandelia obovata* (Ximen Is., Zhejiang Province, China) afforded two new furofuran lignans kandelisesquilignan A **1169** and B **1170**.⁹⁶⁷ Similar levels of antioxidant activity (DPPH assay) were observed for **1169** and **1170** versus ascorbic acid.



Ethanollic extracts of the bark of *Ceriops decandra* (Godavari estuary, Andhra Pradesh, India) afforded diterpenes decandrin A–K **1171–1181**, the structures of which encompass abietane and podocarpane skeletons,⁹⁶⁸ while the wood of *Excoecaria agallocha* (Corangi forest, Godavari estuary) afforded *ent*-isopimarane diterpenoids agallochaexcoerin D–F **1182–1184**.⁹⁶⁹

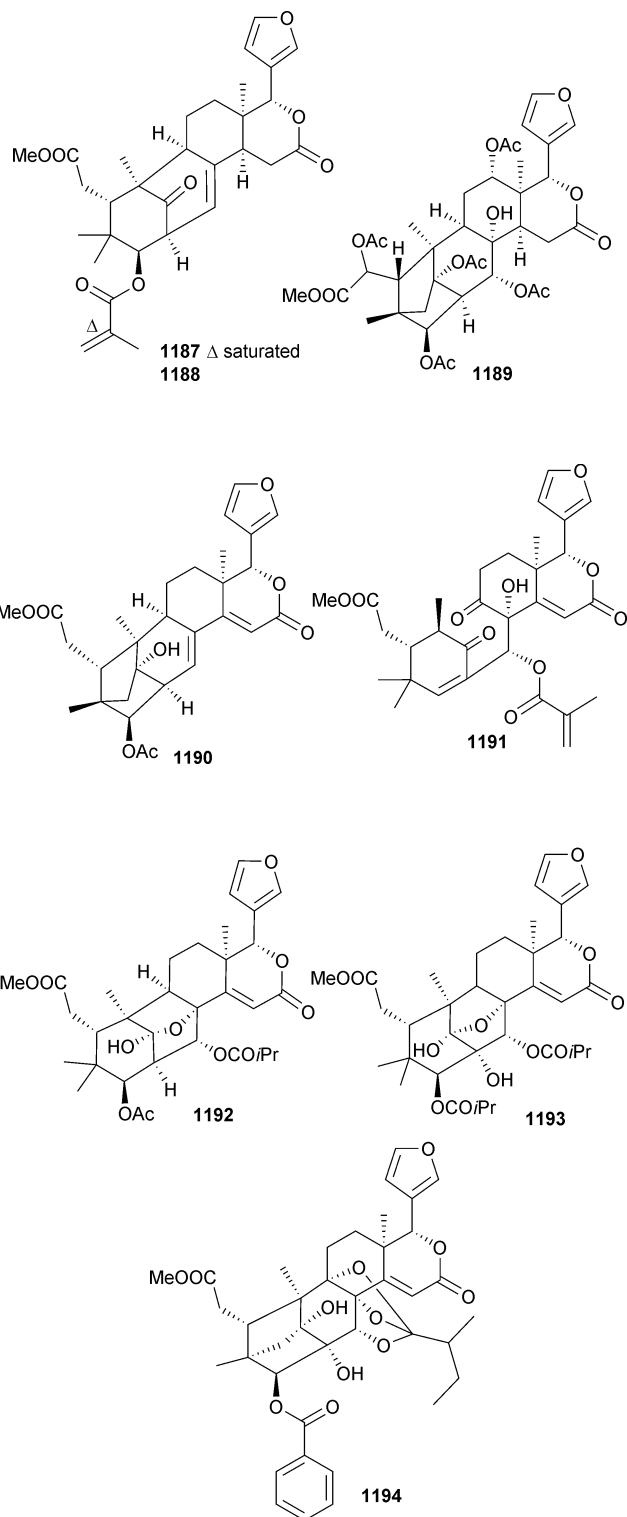
Two triterpenes tiliacol A **1185** and B **1186** were isolated from the semi-mangrove plant *Hibiscus tiliaceus* (Hainan Is., China).⁹⁷⁰



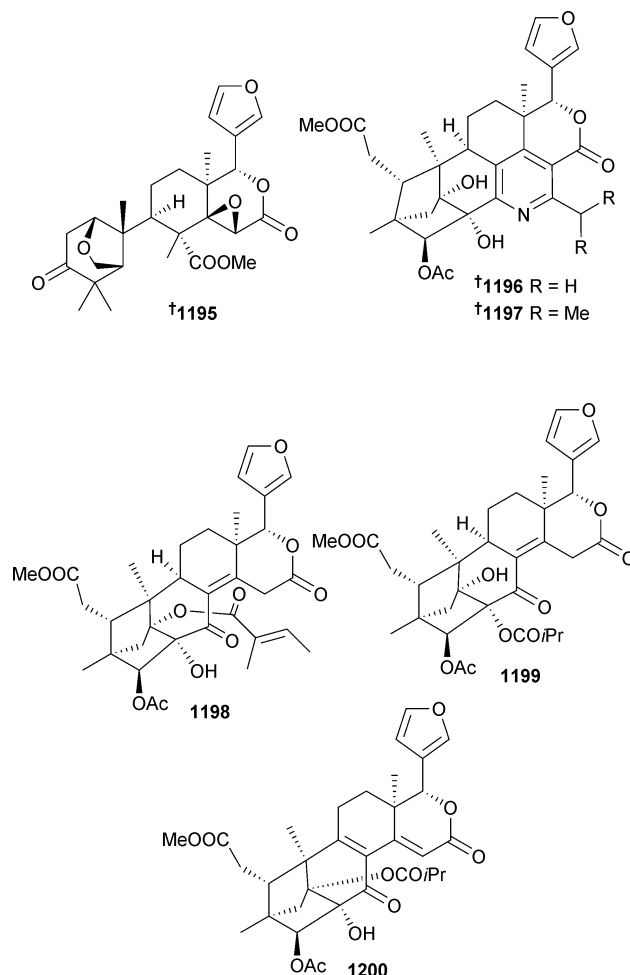
A diverse range of liminoids were reported from extracts of *Xylocarpus granatum*: granatamins H–K **1187–1190** (seeds, Krishna estuary, Andhra Pradesh),⁹⁷¹ xylomexicanins C **1191**



and D **1192** (seeds, Hainan Province, China),⁹⁷² and xylogranins A **1193** and B **1194** (leaves, Sundarbans Mangrove Forest, Bangladesh).⁹⁷³ Xylomexicanin C **1191** exhibited modest cytotoxicity towards a breast tumour cell line, while xylogranin B **1194** and co-metabolite swietephragmin were potent inhibitors of the Wnt signalling pathway and exhibited sub-micromolar cytotoxicity towards two human colorectal tumour cell lines.

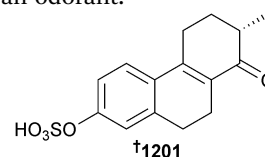


Extracts of the seeds of *X. moluccensis* (Trang province, Thailand) afforded thaixylomolins A–F **1195**–**1200**.^{974,975} The structure of **1195** was secured by X-ray diffraction analysis and TDDFT calculations were used to establish the absolute configurations of **1196** and **1197**, while **1198** was assigned by comparison of ECD data. The 4-hydro-dithiosulfonate, bruguiesulfurol (*Bruguiera gymnorhiza*)⁹⁷⁶ was detected as a modest inhibitor of PTP1B, prompting its synthesis and preparation of a library of analogues, some of which exhibited more potent activity.⁹⁷⁷



14 Miscellaneous

Investigation of water conditioned with sea lamprey (*Petromyzon marinus*) larvae afforded the hexahydrophenanthrene sulfate petromyzonin **1201**.⁹⁷⁸ Absolute configuration was assigned by ECD analysis. Petromyzonin elicited potent (10^{-11} M) response in electro-olfactogram recordings using olfactory epithelia of adult male sea lamprey, indicating a likely ecological role as an odorant.



The detection of 5,11-dideoxytetrodotoxin,⁹⁷⁹ isolated as an NP for the first time, in the pufferfish *Takifugu poecilonotus* and the flatworm *Planocericid* sp. 1 (Guam) prompted speculation on the putative biosynthetic pathways for the biosynthesis and metabolism of tetrodotoxins.⁹⁸⁰ A new method involving sonication, SPE and LC-MS/MS has been reported to allow simultaneous quantification of Pacific ciguatoxins-1, -2 and -3 in the whole blood of fish.⁹⁸¹

15 Conclusion

Fifty years ago in 1963 just four papers were published on MNPs with only one paper containing new compounds. At that time MNPs was becoming established as a field of interest. In this Conclusion the phylum-preferences of the MNP community across the subsequent 50 years period are examined. These preferences are presented (Fig. 1) as the annual number of publications reporting the isolation of new compounds for each phylum that has been sampled over this period. The most aggressively selected phylum has been the Porifera, but the popularity of this target has diminished somewhat since the mid 1990s coinciding with the very rapid rise in popularity of the Ascomycota, Actinobacteria and the Cyanobacteria. The Cnidaria have steadily increased in popularity across the years and while the phyla Rhodophyta, Ochrophyta, Echinodermata and Mollusca were as popular as the Porifera in the early years, interest waned in later years. The popularity of these phyla in

earlier years may have been a reflection of the relative ease of collection by snorkeling and shore-wading as in the 1960s and 1970s SCUBA diving was more of a specialist technique. The numeric totals for the 50 years of collection are given in Table 1 along with the percentage contribution of each phylum to the marine literature. For the 50 years period from 1963 9220 papers have reported the isolation of 24 662 new compounds. These 9220 papers constitute 37% of the total papers in MarinLit.⁷⁷ The other 17 284 papers are associated with topics such as reviews, syntheses, stereochemistry, corrections of structure or stereochemistry, bioactivities, and ecological surveys. Other data shown in Table 1 include the numbers of compounds reported/phylum over the 50 years period as well as the % contributions each phylum has made to the number of papers reporting new compounds or the number of compounds. These relative proportions are comparable as the number of isolated compounds reported/paper is 2–3 across most of the phyla. Also included are the *recognised* totals of species/phylum from the World Register of Marine Species (WORMS),⁹⁸² allowing comparison of the numbers of samples of each phylum collected with the actual number of recognised species. This comparison should be used carefully as multiple collections of the *same* species have been made, or the sample may have only been identified to the genus level. However the comparison does offer insights into the coverage of each phylum. This point is emphasised by considering the various contributions the most studied genus for each phylum has made. For example, for

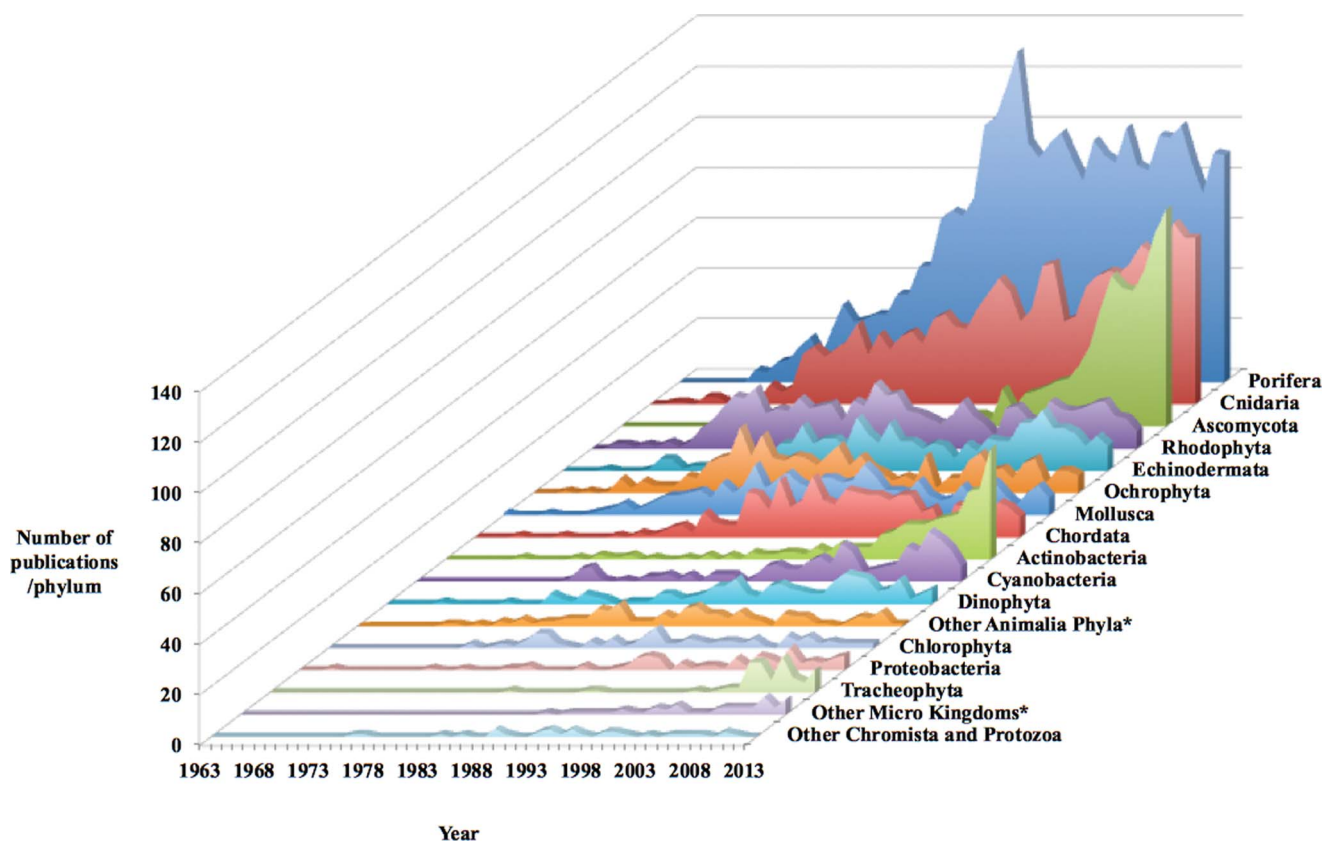


Fig. 1 The phylum-preferences of the marine natural product research community across a 50-year period from 1963.





Table 1 The numeric totals and percentage contribution of each phylum to the marine literature over a 50 years period from 1963. Also included are the numbers of compounds reported/ phylum, the % contributions each phylum has made and the recognised totals of species/phylum from the World Register of Marine Species^a

Kingdom	Number of genera	Most studied genus	Number of papers and compounds		Papers/ phylum	% MLit papers with new compounds		Compounds/ phylum	% of MLit	Compounds	Compounds/ paper	Number of recognised species
			from the most studied genus	from the most studied genus		compounds	compounds					
Animalia	13	<i>Odontosyllis</i>	5	12	24	0.3%	46	0.2%	1.9	2640		
	8	<i>Megabalanus</i>	2	2	9	0.1%	10	0.0%	1.1	6216		
	24	<i>Bugula</i>	19	33	86	0.9%	199	0.8%	2.3	6036		
	66	<i>Didemnum</i>	54	144	434	4.7%	1102	4.5%	2.5	1898		
	161	<i>Sinularia</i>	234	678	1589	17.2%	4949	20.1%	3.1	10 839		
	136	<i>Asterias</i>	35	69	493	5.3%	1335	5.4%	2.7	295		
	3	<i>Cephalodiscus</i>	9	19	11	0.1%	27	0.1%	2.5	30		
	116	<i>Aplysia</i>	87	184	468	5.1%	1095	4.4%	2.3	44 233		
	2	<i>Amphiporus</i>	1	1	2	0.0%	2	0.0%	1.0	6997		
	3	<i>Amphiscolops</i>	2	2	3	0.0%	6	0.0%	2.0	11 836		
Archaea	285	<i>Dysidea</i>	163	418	2991	32.4%	8152	33.1%	2.7	8320		
	1	<i>Thermococcus</i>	2	24	2	0.0%	24	0.1%	12.0	98		
	28	<i>Streptomyces</i>	201	465	322	3.5%	778	3.2%	2.4	72		
	9	<i>Rapidiithrix</i>	3	4	12	0.1%	24	0.1%	2.0	235		
	28	<i>Lyngbya</i>	140	283	234	2.5%	484	2.0%	2.1	436		
	5	<i>Bacillus</i>	43	94	47	0.5%	101	0.4%	2.1	96		
	38	<i>Pseudomonas</i>	16	33	110	1.2%	225	0.9%	2.0	772		
	7	<i>Rhizosolenia</i>	2	7	10	0.1%	24	0.1%	2.4	2675		
	4	<i>Euplotes</i>	8	24	12	0.1%	37	0.2%	3.1	2676		
	1	<i>Chrysophaeum</i>	2	9	2	0.0%	9	0.0%	4.5	91		
Chromista	26	<i>Prorocentrum</i>	20	27	194	2.1%	297	1.2%	1.5	2194		
	6	<i>Coccolithus</i>	2	3	8	0.1%	11	0.0%	1.4	260		
	57	<i>Dictyota</i>	94	249	460	5.0%	1247	5.1%	2.7	5009		
	129	<i>Aspergillus</i>	187	545	783	8.5%	2165	8.8%	2.8	966		
	29	<i>Caulerpa</i>	30	90	116	1.3%	272	1.1%	2.3	1810		
	84	<i>Laurencia</i>	369	824	672	7.3%	1668	6.8%	2.5	6399		
	23	<i>Xylocarpus</i>	27	119	75	0.8%	253	1.0%	3.4	432		
	1	<i>Euglena</i>	1	3	1	0.0%	3	0.0%	3.0	231		
	Totals/Averages	1300	1758	4361	9220	100%	24 662	100%	2.7			

^a In the 28 phyla sampled by MNP chemists WORMS lists 210 892 species. Across all Kingdoms WORMS lists 226 070 marine species.

the Rhodophyta the most studied genus has been *Laurencia*. Even though *Laurencia* is only one of 84 genera studied, this one genus contributed 369 out of the total 672 papers from the Rhodophyta describing new MNPs and was the source of 824 of the 1668 new compounds from this phylum. The important consideration is that even though multiple collections of the same genus/species may have been made, the same genus or species at different locations is giving rise to a different suite of metabolites. Apart from Porifera and Cyanobacteria, the coverage of most phyla is very limited, although the credibility of the numbers of species recognised by WORMS⁹⁸² for the Ascomycota and Actinobacteria is probably suspect as much of the micro-world has yet to be fully recognised. Over the past 50 years MNP chemists have studied samples collected from 1300 genera across 28 phyla. These 28 phyla represent an estimated (WORMS) 210 892 marine species out of an estimated total of 224 070 for all marine phyla.⁹⁸² In other words MNP chemists have collected widely, but perhaps thinly across the Kingdoms. The Kingdom Virus (119 representatives) has not been sampled at all by MNP chemists and so has been excluded from consideration. As chemists we have published 9220 papers over the past 50 years describing new compounds from these 28 phyla. But, in fact, the 9220 papers describe compounds elicited from just 2657 named species with another 2485 occurrences across 484 genera that are only described as sp. So, the number of distinct species studied is a long way short of 9220. This nicely emphasises the point that there is still an enormous MNP resource waiting to be explored; probably in excess of 200 000 species still to be evaluated.

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