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Marine natural products††

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

Covering: 2015. Previous review: *Nat. Prod. Rep.*, 2016, **33**, 382–431

This review covers the literature published in 2015 for marine natural products (MNPs), with 1220 citations (792 for the period January to December 2015) 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 (1340 in 429 papers for 2015), 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 2015 and describes 1340 new compounds from 429 papers, a small reduction from the 1378 new compounds in 456 papers reported for 2014.¹ 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. The new format for this review introduced for the previous review¹ has been retained, with only a selection of highlighted structures (197) now shown in the review. Compound numbers for structures not highlighted in the review are *italicised*, and all structures are available for viewing, along with their names, taxonomic origins, locations for collections, and biological activities, in a ESI†† document associated with this review. The Reviews section (2) contains selected highlighted reviews, with all other reviews referenced in a section of the ESI.†† It is with great regret that we note the passing of Professor Tatsuo Higa, University of the Ryukyus and the Open University of Japan, on May 24 2016. Since 1965 Professor Higa has made many publications of his work, principally on MNPs. Most notable was his discovery of the manzamines. He was a regular participant at MNP conferences, and his quiet and friendly manner will be remembered and missed.

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

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

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

^dChemistry, School of Science, University of Waikato, Hamilton, New Zealand

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2 Reviews

For 2015 there has been an increase (23% from 2014) in the number of reviews of various aspects of MNP studies. Some of the comprehensive reviews (23) are given here while a listing of the remainder (84) is given in the ESI†† section. A full review of MNPs reported in 2013 has appeared.² A statistical analysis of bioactive MNPs discovered from 1985 to 2012 has been made.³ The potential for MNPs as antiviral agents has been extensively reviewed.⁴ Marine fungi as the source of anticancer agents,⁵ antimicrobial compounds⁶ and antiviral agents⁷ have been described. There have been surveys of anticancer compounds from marine sponges⁸ and microalgae,⁹ while the bioactivities of specific classes of MNPs such as peptides,^{10,11} polyacetylenes,¹² indole alkaloids,¹³ and halogenated compounds¹⁴ have been reviewed. More specific types of bioactivity have been examined in reviews of MNPs for management of diabetes from seaweeds,¹⁵ and compounds with neuroprotective activity¹⁶ and antifouling properties.¹⁷ MNPs from marine cyanobacteria¹⁸ and actinomycetes of the genus *Salinispora*¹⁹ have been discussed. The role of

metagenomics in biodiscovery continues to develop as described in two new reviews.^{20,21} Other emerging concepts for enhancing the biodiscovery effort,²² and recent advances in other experimental technologies,²³ have been described. The online database MarinLit²⁴ continues to be updated and has been the principal source of information for this review.

3 Marine microorganisms and phytoplankton

3.1 Marine-sourced bacteria

Although the first paper in this section adds no new compounds to the list of MNPs it touches on a vital thread running right through the chemistry of MNPs. That is the discovery, characterisation, synthesis, development and commercial production of chemotherapeutic compounds. Endosymbiotic origins of ET-743 (Yondelis[®], trabectedin), isolated from the mangrove tunicate *Ecteinascidia turbinata*, have long been postulated. From analysis of the metagenomic DNA isolated from the tunicate the



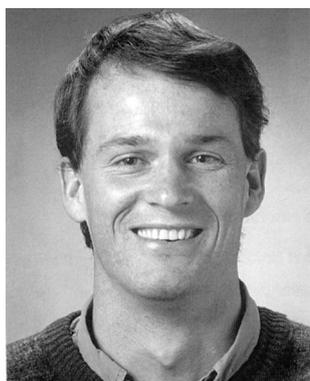
John Blunt obtained his BSc (Hons) and PhD degrees from the University of Canterbury, followed by postdoctoral appointments in Biochemistry at the University of Wisconsin–Madison, and with Sir Ewart Jones at Oxford University. He took up a lectureship at the University of Canterbury in 1970, from where 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.



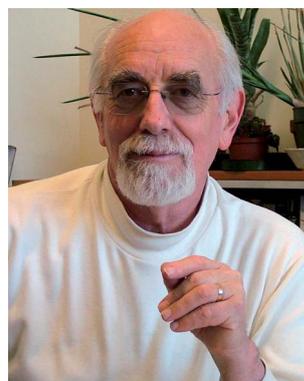
Rob Keyzers carried out his BSc (Hons) and PhD studies at Victoria University of Wellington. His thesis research, carried out under the guidance of Assoc. Prof. Peter Northcote, a former contributor to this review, focused on spectroscopy-guided isolation of sponge metabolites. He then carried out post-doctoral 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.



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 post-doctoral 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.

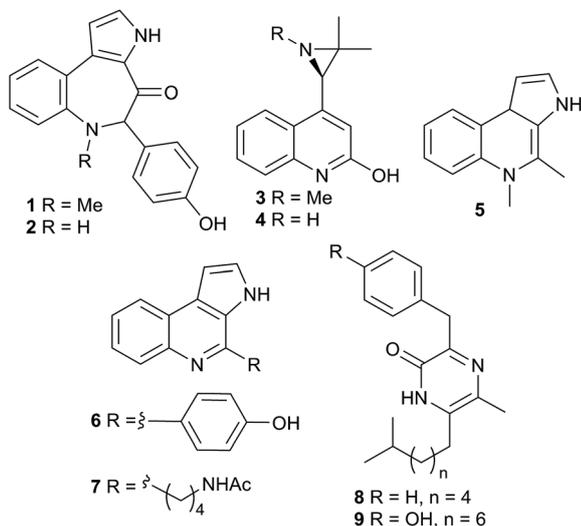


Murray Munro, Emeritus Professor in Chemistry at the University of Canterbury, has worked on natural products right through his career. This started with diterpenoids (PhD; Peter Grant, University of Otago), followed by alkaloids during a post-doctoral spell with Alan Battersby at Liverpool. A sabbatical with Ken Rinehart at the University of Illinois in 1973 led to an interest in marine natural products with

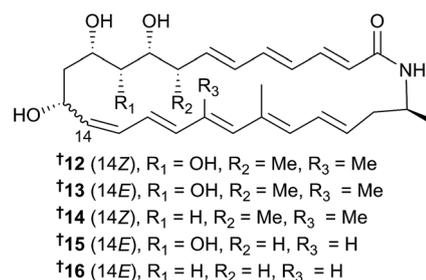
a particular focus on bioactive compounds which has continued to this day. In recent years his research interests have widened to include terrestrial/marine fungi and actinomycetes.



complete genome of *Candidatus Endoecteinascidia frumentensis*, the ET-743 producer, has now been assembled. Analysis of the phylogenetic markers and protein coding genes suggest that *Ca. E. frumentensis* belongs to a novel family of the γ -proteobacteria. This better understanding of the biosynthesis of ET-743 will promote efforts to produce the drug directly by *in vitro* methods or heterologous expression rather than the current semi-synthetic process starting from cyanosafracin.²⁵ By utilising low-nutrient conditions and long incubation times 20 previously uncultured species of Gram-negative bacteria were isolated from a variety of marine sources. These species represent new families in the phyla Bacteroidetes and Proteobacteria and include clades that had only been observed before under culture-independent conditions. In the subsequent chemical studies on two species from the new families, *Mooreiaceae* and *Catalimonadaceae*, nine new structures were characterised, some with antibiotic properties. From the type strain CNX-216^T (*Mooreiaceae*) the marinazepinones A **1** and B **2**, the marinoaziridines A **3** and B **4**, and the marinoquinolines G-I **5-7** were isolated, while CNU-194^T (*Catalimonadaceae*) and CNX-216^T both produced the marinopyrazinones A **8** and B **9**.²⁶



This is the first occurrence of azepin-3-one alkaloids in nature and also the first occurrence of aziridine- and pyrazinone-based alkaloids in Gram-negative bacteria. Two new peptaibols **10** and **11** were isolated from *Microbacterium sediminis* and is the first reported isolation of peptaibols from an actinomycete, not a fungal source.²⁷ Following the discovery of an antitrypanosomal series of macrolactams the genome of the producing *Micromonospora* sp. was sequenced and the responsible biosynthetic gene cluster (BGC) identified. By a combination of spectroscopy and sequence data the structures and absolute configurations of the lobosamides A-C **12-14** were established.²⁸ In a neat twist the BGC was assembled as a query sequence and used to identify similar BGCs in other organisms that have been sequenced, but not chemically annotated. By this process the grass-derived Actinomycete, *Actinosynnema mirum* ATCC 29888,²⁹ was shown to contain a highly similar BGC. Consequent work led to the isolation and characterisation of the non-MNP mirilactams A **15** and B **16**, confirming the validity and usefulness of this approach to genome-mining.²⁸



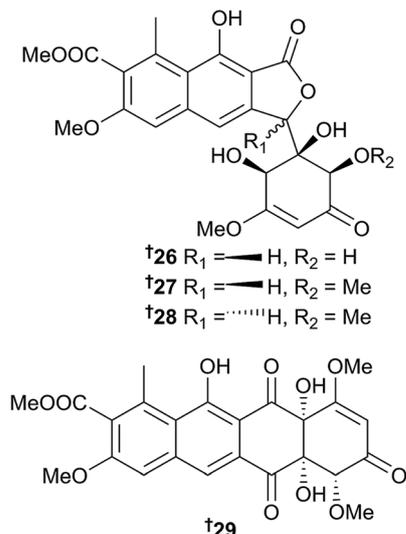
The putative BGC for the fluostatins from *Micromonospora rosaria*³⁰ was expressed heterologously in *Streptomyces coelicolor* and led to the isolation of fluostatin **L 17** and a fluostatin heterodimer **18**,³¹ while investigation of another *Micromonospora* sp. resulted in isolation of a pimarane derivative **19**.³² Based on *Micromonosporaceae* spp. the parameters for induced biosynthesis by interspecies interaction in co-culture were explored using a micro-scale approach and LC/MS-PCA methods to assess secondary metabolite production.³³ Aminoimidazoles **20** and **21**,³⁴ diketopiperazines **22** (ref. 35) and **23** (ref. 36) (new to marine)³⁷ and dimeric indoles **24** and **25** (ref. 38) were reported from *Norcardiopsis* and *Rubrobacter* spp. Work on the actinomycete *Saccharothrix* sp. led to the isolation of further aromatic polyketides saccharothrixones A-D **26-29**, new members of the tetracenomyacin (Tcm) family. Saccharothrixone D is unusual in that it has the opposite chirality to Tcm C at each stereocentre.³⁹

Another innovative genome-mining approach is pattern-based and employs molecular networking. This approach was applied to 35 *Salinospora* samples across the three defined species. 30 Draft genome sequences were known. Cultures were grown under standard conditions to the commencement of stationary phase growth. Analysis of the extracts by HRMS/MS generated over 200 000 spectra, which in turn generated 1137 parent ion nodes. Seeding this *Salinospora* molecular network with previously identified *Salinospora* sp. compounds allowed identification of known compounds, possible media

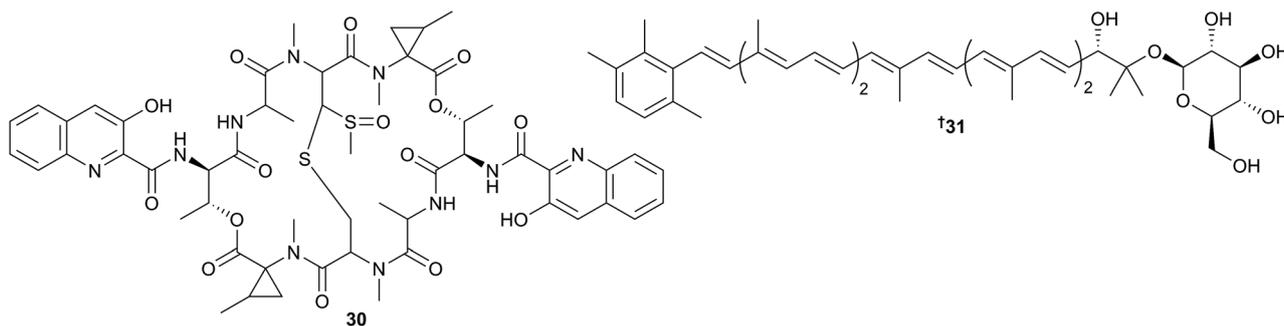


Michèle Prinsep received her BSc (Hons) and PhD degrees from the University of Canterbury, where she studied the isolation and structural elucidation of biologically active secondary metabolites from sponges and bryozoans under the supervision of Professors Blunt and Munro. She undertook postdoctoral 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 an Associate Professor.



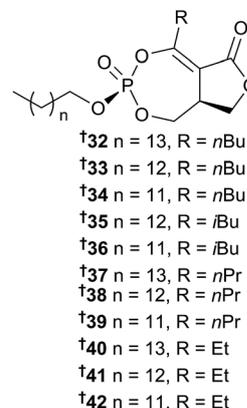


components and new derivatives of known compounds (methylation, hydroxylation, etc.). Molecular networking coupled with genome sequence data allowed for the rapid correlation between a BGC and the resultant secondary metabolite (pattern-generation). In this example it was found that the cluster NPRS40 was unique to one strain. Peptidogenomics was used to correlate this BGC with the 1171.42 Da parent ion node which in turn led to the characterisation of retimycin A **30**, a new quinomycin-like depsipeptide.⁴⁰ Sixoxanthin **31**, an unusual carotenoid in that it is glycosylated at one end with an aryl group at the other end, is the pigment responsible for the distinctive orange coloration of *Salinospora* spp. during vegetative growth. The biosynthesis of sixoxanthin is also unusual as the carotenoid biosynthesis genes are non-clustered in the *Salinospora* genomes.⁴¹



The first successful heterologous expression of a gene cluster from the *Salinospora* genome has been made. An 18kb type II PKS gene cluster from *S. pacifica* with high homology to the enterocin locus in *Streptomyces maritimus* was transferred to *S. coelicolor* M1146 and *S. lividans* TK23. Both clones produced enterocin. This opens the way to further explore the

cryptic pathways of the *Salinospora*'s secondary metabolome.⁴² From the screening of a pre-fractionated library of marine bacterial-derived extracts against *Plasmodium falciparum* (*P. falciparum*) a new class of antimalarials was discovered from a *Salinospora* sp. The salinipostins A–K **32–42** are long-chain bicyclic phosphotriesters, a rarely observed natural product scaffold. VCD (Vibrational CD spectroscopy) was used to establish configuration in the series as (*S_p*, *S_C*). The potency against *P. falciparum* ranged over three orders of magnitude (0.05 μM to 46 μM) varying with the length of R_1 and R_2 : salinipostin A **32** was the most potent. In contrast, the salinipostins were relatively non-toxic to mammalian cells (>50 μM). Encouragingly, initial attempts to select for resistance in *P. falciparum* were not successful.⁴³

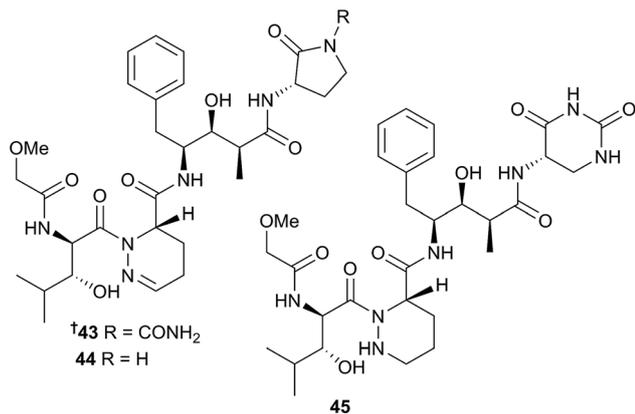


Also in the antimalarial area was the quantitative high throughput screening of another large natural products library (16 503 extracts) across four orders of magnitude in concentration against six geographically different strains of *P. falciparum* which identified two *Streptomyces* spp. for further

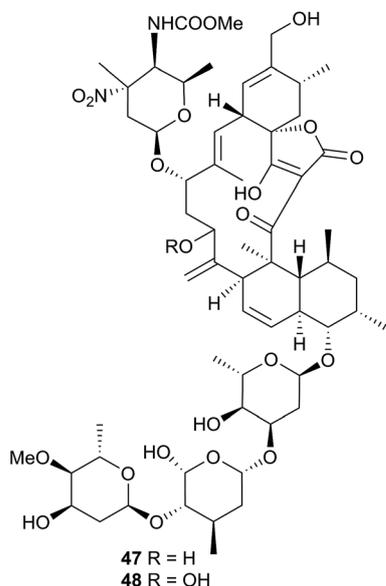
investigation. Each contained a similar suite of compounds so only *S. banglaensis* was explored further. The recently identified actinoramide A/pandanamide A^{44,45} was the major metabolite along with three new analogues actinoramide D–F **43–45**.⁴⁶

Another major screening effort was against >33 000 extracts from 5036 cultivatable Costa Rican marine



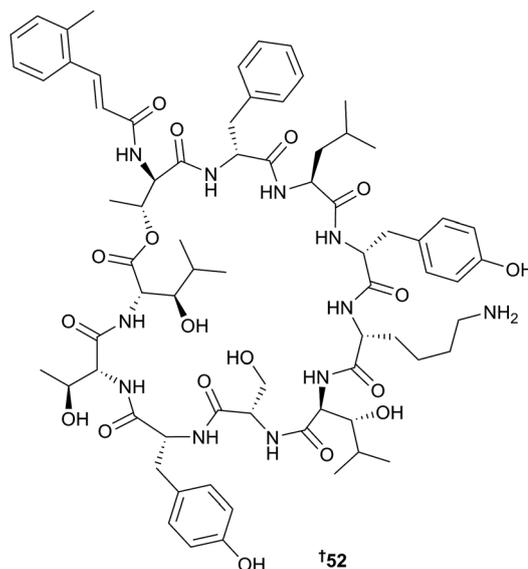


microorganisms to discover activators of the apoptotic arm of unfolded protein response (UPR). High levels of UPR signaling characterize many human cancers. The screening led to the discovery of three further lobophorin^{47–50} congeners **46**, **47** and **48** from a *Streptomyces* sp. and, subject to supply, further studies will examine the mechanism by which active lobophorins activate UPR.⁵¹

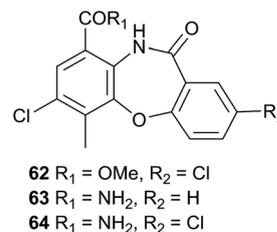


The gene cluster for the anti-infective desotamides from *S. scopuliridis* has been identified and after heterologous expression in *S. lividans* and *S. coelicolor* the desotamide congener **G 49** was characterized.⁵² A further depsipeptide in the salinamide series, **F 50**, was isolated from re-cultivation of *Streptomyces* sp. CNB-091.⁵³ To address the bottleneck that often impedes progress in research, 3D-NMR techniques have been applied to the structure determination of peptidic natural products of interest. To balance costs, yield and relative ¹³C/¹⁵N abundance the growth media used peptone and yeast extract and ¹⁵NH₄Cl and [U-¹³C]-glucose. The *Streptomyces* sp., isolated from *Eudistoma olivaceum* was fermented in this media and the two peptides under study,

eudistamides **A 51** and **B 52**, were isolated. Seven of the typical protein triple resonance experiments were evaluated. Of these HNC(O), CBCANH and CBCA(CO)NH were used to establish the peptide backbone and HCCH-TOCSY was most useful for side-chain assignments. The absolute configurations were assigned by traditional methods. It was concluded that this approach is cost effective and greatly improves the confidence in a proposed structure.⁵⁴



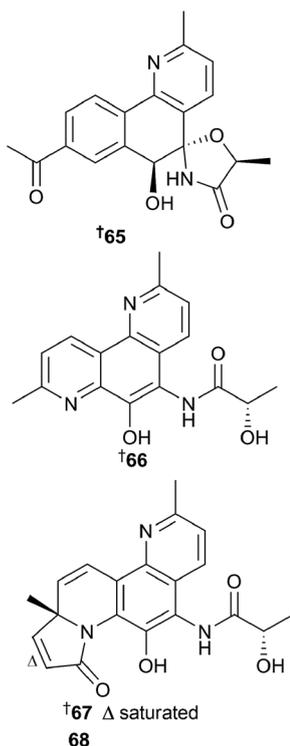
New ansamycin analogues **53–55** were obtained from a mutant strain of *S. seoulensis*,⁵⁵ and further ikarugamycin⁵⁶ derivatives (tetramic acid macrolactams) **56–58** were isolated from a *S. zhaozhouensis*.⁵⁷ A combination of gene inactivation and complementation, synthetic substrates and extensive phylogenetic tree analyses revealed that tetramic acid and pyridone biosynthesis proceeds *via* a series of Dieckmann cyclases.⁵⁸ A new analogue of the dilactone echinomycin **59** was characterized from a *Streptomyces* sp. along with a new diketopiperazine **60**.⁵⁹ Another macrolide in the bafilomycin family **61**, was produced by a *Streptomyces* sp. isolated from litter at a river mouth.⁶⁰ Following genetic manipulation of a marine *Streptomyces olivaceus* by disruption of *orf-1741*, a putative transcriptional gene, three halogenated dibenzoxazapinone derivatives, the mycemycins C–E **62–64**, were isolated from the mutant strain and are the first dibenzoxazapinones produced from a microbial source.⁶¹



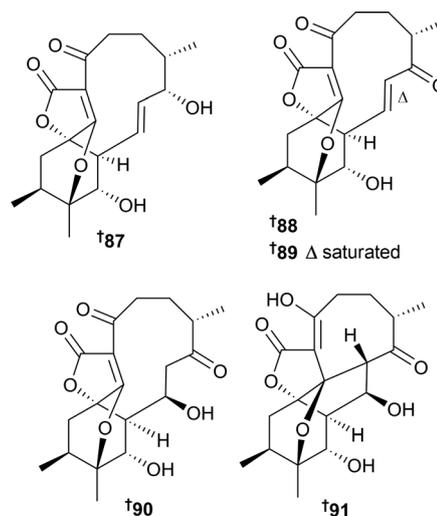
Marine Actinobacteria continue to surprise with the versatility of their biosynthetic machinery. Phylogenetic studies have



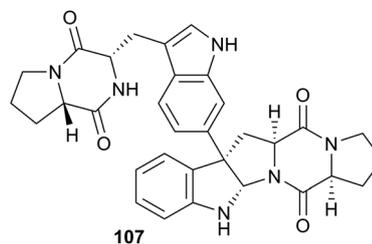
led to the identification of 13 distinct marine actinomycete groups. The chemical investigation from one of these groups, a member of the family Streptomycetaceae, led to the isolation of two new classes of marine alkaloid, represented by actinobenzoquinoline **65**, and the actinophenanthrolines A–C **66–68**. Both these new classes are unprecedented in the alkaloid literature. Structural proof relied heavily on long-range gHMBC and was supported by X-ray diffraction analysis.⁶²



Further boheminine derivatives **69** and **70**,⁶³ two epimeric benzofurans **71** and **72**,⁶⁴ ten angucyclinone derivatives **73** and **74**,⁶⁵ **75–82**,⁶⁶ anthracyclines **83** and **84** (ref. 67) a naphthacene glycoside **85** (ref. 68) (new to marine) and a further aureolic acid **86** (ref. 69) were isolated from sedimentary or endophytic *Streptomyces* spp. A strategy for containing HIV is reactivation of the latent virus in combination with HAART. In the search for reactivators a 5000 strong microbially-derived pre-fractionated natural product library was screened against a model of *in vitro* HIV latency in human CD4⁺ T cells. Selected pre-fractions were subjected to LC/MS fractionation and re-assayed. This identified a series of abyssomicin⁷⁰ congeners 1–5 **87–91** as the optimal leads. Of these, abyssomicin 2 **88**, was prioritised based on its robust reactivating activity. Abyssomicin 2 appeared to be identical with a synthetic derivative of abyssomicin I,⁷¹ but further examination revealed that abyssomicin 2 **88** was enantiomeric with the synthetic derivative as the absolute configuration of abyssomicin I had been incorrectly assigned. In this process the structure of abyssomicin I was also reassigned as abyssomicin 1 **87**. The mechanism of reactivation by the abyssomicins remains to be elucidated.⁷²



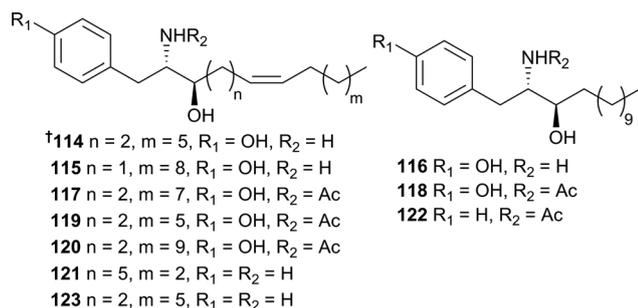
A number of other compounds of lower molecular weight were also isolated from actinomycetes or *Streptomyces* spp. These included two butenolides **92** and **93**,⁷³ four cycloheximide derivatives **94–97**,⁷⁴ a furanone **98**,⁷⁵ an α -pyrone **99**,⁷⁶ four benzothioate glycosides **100–103**,⁷⁷ an alkylamide **104**,⁷⁸ an aniline derivative **105** with algicidal properties⁷⁹ and an incompletely characterized cyclabdan-like compound **106**.⁸⁰ Anti-dormant mycobacterial properties were reported for the known terrestrial antibiotic nybomycin⁸¹ isolated, in this instance, from a marine *Streptomyces*. This is the first report of nybomycin from a marine source.⁸² The biodiversity of the Yellow Sea was explored with sediment samples collected from five locations between 50–100 m. Culturing led to the isolation of 613 actinomycete samples of which 89 species were shown to produce extracts with good antimicrobial properties against an array of microorganisms. Of these 76 were *Streptomyces* spp. while the remaining 12 split across four genera (*Kocaria*, *Micromonospora*, *Nocardiosis*, *Saccharomonospora*). After 16S rRNA gene analysis the *Streptomyces* spp. could be split into 17 clades. This survey indicated that this previously under-explored ocean contains a wealth of microbial potential. One of the *Streptomyces* species further explored produced three diketopiperazine dimers, including the new dimer isonasesezazine B **107**, a stereoisomer of nasesezazine B.^{83,84}



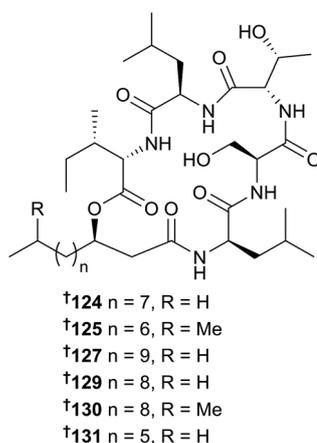
A modified diketopiperazine **108** with antimalarial properties was isolated from a *Streptomyces* sp. isolate from the Florida Keys as part of the outcome of screening a large collection of microorganisms for antiproliferative and antiplasmodial properties.⁸⁵ There were three reports of new compounds from the phylum Firmicutes. These covered the isolation of new glycolipids **109** and



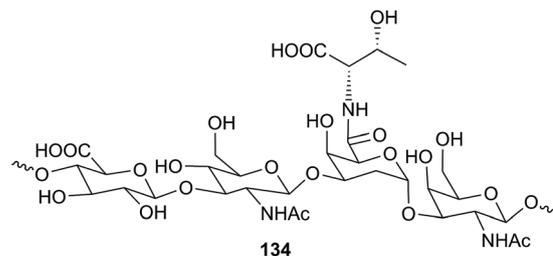
110 from a sediment-derived *Bacillus licheniformis*,⁸⁶ and two lipopeptides **111** and **112** that differ only in the chain-length of the 3-hydroxy fatty acid.⁸⁷ A cyclic tetrapeptide **113** was isolated from the culture broth of a *Staphylococcus* sp.⁸⁸ A number of papers reported new compounds from the phylum Proteobacteria. An imaging mass spectrometry and molecular networking approach led to the discovery of the vitroprocines A–J **114–123**. Selective assaying reduced the 265 marine-derived microorganisms from the Taiwan Strait to a single *Vibrio* sp. active against *Acinetobacter baumannii*. Imaging mass spectrometry on the intact organism was used to determine the mass range of the metabolites and concluded from the spatial distribution that they were secretory in nature and matched the data from LC/MS analysis of the crude EtOAc extract of the *Vibrio* sp. Molecular networking analysis generated three clusters of 43 nodes of which 31 could be differentiated into seven sub-groups. The molecular masses in these sub-groups did not correspond to known microbial products (MarinLit,²⁴ AntiBase⁸⁹). Of the 10 vitroprocines subsequently isolated, vitroprocines A–C **114–116** were most active against *A. baumannii*.⁹⁰



A series of known depsipeptides, kailuin B–F **124–128**, and two new analogues kailuin G **129** and H **130** were isolated from *Photobacterium halotolerans*. During this study the double bond configuration of kailuin D **126** was corrected and the previously unreported configuration at C-3 of the β -acyloxy grouping of all of the kailuins **124–126** and **129–131** assigned using a combination of Mosher's chemistry and α, β, γ ¹³C-NMR shifts. It was suggested that as the kailuins had previously been isolated from *Vibrio* spp., which predated the description of the type strain for *Photobacterium halotolerans*, revisiting the taxonomy might be in order.⁹¹



A new siderophore **132** and pre-pseudomonine **133** (new to marine) were isolated from a sponge-associated *Pseudomonas fluorescens*.⁹² The primary structure of a capsular polysaccharide from the Arctic psychrophilic bacterium *Colwellia psychrerythraea* has been defined from extensive NMR studies and chemical analysis and was reported as a repeating tetrasaccharide unit comprising two amino sugars, two uronic acids and a threonine substituent, **134**.⁹³



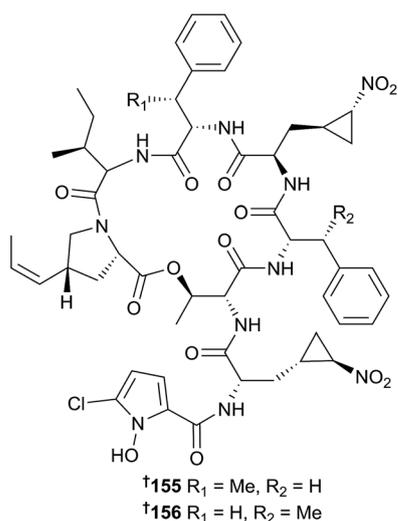
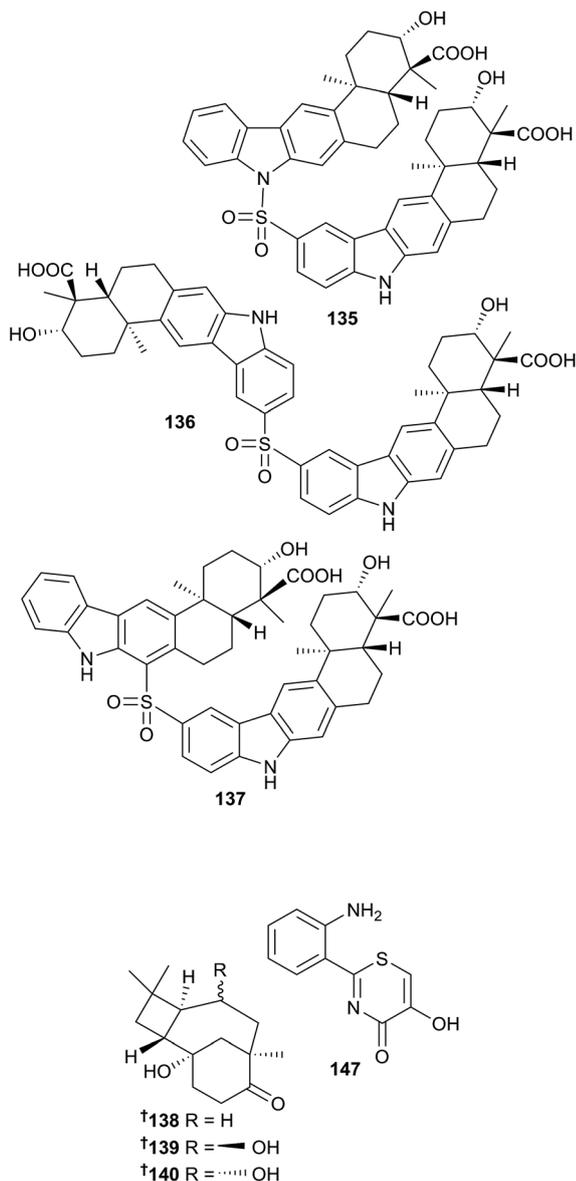
The seashore Actinobacteria derived from mangroves, seagrasses, salterns and mud-flats have been grouped separately on the grounds that as a group they have been exposed to much greater changes in temperature, submersion, salinity and sunlight than their oceanic counterparts. Following isolation of a series of the polycyclic xiamycin⁹⁴ and other indolesesquiterpenes⁹⁵ from mangrove *Streptomyces* sp. endophytes the xiamycin biosynthetic gene cluster was successfully transferred to *S. griseus*. From the recombinant strain three minor, sulfonyl-bridged dimeric congeners sulfadixiamycin A–C **135–137** were isolated. From a biosynthetic perspective a sulfonyl-linkage is unusual and it was postulated that a direct flavin-mediated SO₂ incorporation was involved.⁹⁶ Other aspects of the biosynthesis of the xiamycins and the cyclisation cascades were elucidated by the biomimetic synthesis of key intermediates.⁹⁷

Two other endophytic *Streptomyces* spp., also obtained from the stem of the mangrove *Bruguiera gymnorrhiza*, led to three bacterial caryolanes bacaryolane A–C **138–140**. These are mirror images of typical plant-derived caryolanes.⁹⁸ The other *Streptomyces* sp. endophyte yielded a series of divergolide⁹⁹ congeners **141–146**.¹⁰⁰ A thiazine **147** and two thiazoles **148** and **149** were isolated from a mangrove sediment-derived *Actinomycetospora chlora*. This is the first reported natural occurrence of a 5-hydroxy-3-phenyl-4H-1,3-thiazine-4-one core.¹⁰¹

Derived from mangrove sediment-sourced actinomycetes were **150** (ref. 102) and preQ₀,¹⁰³ **151** (first-time natural product)¹⁰⁴ while **152–154** came from an endophyte of the sea-grass *Salicornia* sp.¹⁰⁵ A tidal mud-flat *Streptomyces* sp. was the source of the hormaomycins B **155** and C **156**, which each contain the unusual structural features (4Z)-propenyl-proline, 3-(2-nitrocyclopropyl)-alanine, 5-chloro-1-hydroxypyrrol-2-carboxylic acid and 3-methylphenylalanine only found before in hormaomycin.^{106,107}

A further mud-flat Streptomyces produced the dilactone-tethered, pseudo-dimeric peptides mohangamide A **157** and B **158**. Apart from the dilactone-tethering, another interesting feature of these metabolites was the acyl chain-bearing dihydro-pyridine. A four-step derivatisation approach was used to determine the absolute configuration at C-62 of mohangamide A **157**.¹⁰⁸ Also isolated from a tidal mud-flat or saltern *Streptomyces*

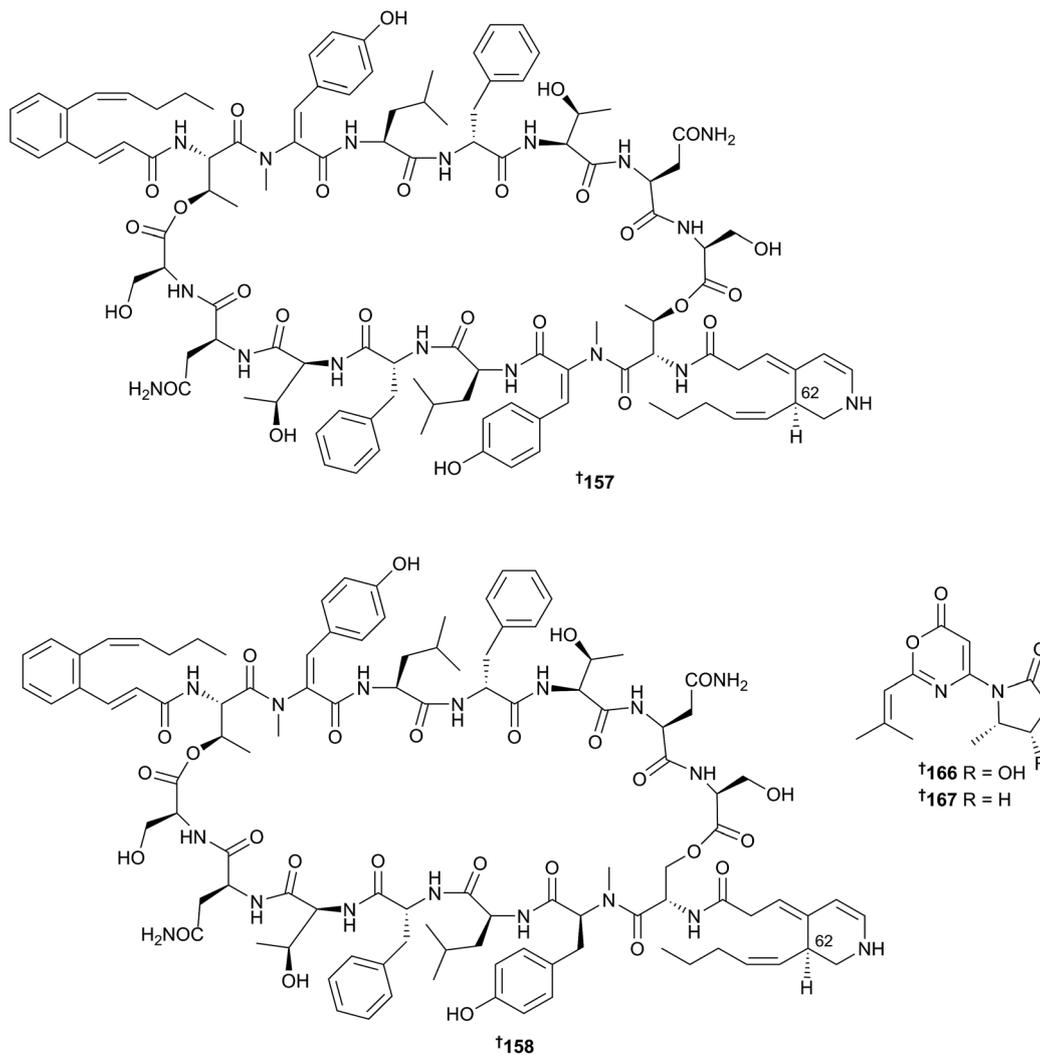




sp. were **159**, **160** (ref. 109) and **161–165**,^{110,111} while the salinazones A **166** and B **167** are first examples of a natural alkaloid with an oxazinone-pyrrolidione core.¹¹²

A number of successful synthetic and biosynthetic studies have been realised. These included peptide-based targets such as marthiapeptide,^{113,114} the disulfide-containing peptide thiochon-drilline C,^{115,116} bogorol A and the more thermodynamically-favoured (*Z*) isomer,^{117,118} the siderophores amphibactin-T¹¹⁹ and moanachelin ala-B.^{120,121} The first synthesis of fradcarbazole¹²² was by semi-synthesis¹²³ from staurosporine.¹²⁴ Also successfully synthesised were the nitrosporeusines,^{125,126} fijiolide A,^{127,128} marinisporolide^{129,130} and splenocin B.^{131,132} A new route to isoquinolines was developed for the synthesis of mansouramycin^{133,134} and a total synthesis and full stereochemical assignments have been completed for heronapyrroles A **168** and B **169**.^{135,136} A further synthesis of bacillamide B¹³⁷ has reconfirmed the absolute configuration as (*S*) and that the specific optical rotation is negative.¹³⁸ The unusual anthracycline marmoycin¹³⁹ has been successfully synthesised and fluorescent microscopy studies indicated that it accumulates in the lysosomes and not the cell nucleus.¹⁴⁰ The synthesis of immunoaffinity fluorescent probes of chlorizidine A¹⁴¹ established that two cytosolic proteins, part of the glycolytic cycle, were the targets for chlorizidine,¹⁴² while studies on the mechanism of action of thalassospiramide¹⁴³ confirmed that the nanomolar activity of this group of lipopeptides against human calpain 1 protease can be ascribed to the rigid 12-membered ring containing the α,β -unsaturated amide moiety that is conserved across the group.¹⁴⁴ Annotations of the draft genome sequence of the *Streptomyces* sp. producing akaeolide¹⁴⁵ and lorneic acid¹⁴⁶ identified type 1 PKS clusters and the PKS origins were supported by ¹³C-labeling studies.¹⁴⁷ The biosynthetic gene cluster for the production of the marformycins,¹⁴⁸ *mfn*, has been identified from *Streptomyces drozdowiczii* and encodes six NRPS's and related proteins for the assembly of the depsipeptide core structure.¹⁴⁹ Two papers addressed heronamide¹⁵⁰ biosynthesis. Firstly, the gene cluster for heronamide F was identified from a deep-sea *Streptomyces* sp. and the presence of a β,γ -migrated diene system in the side-chain confirmed by ¹³C-labeling studies.¹⁵¹ The second paper was a theoretical examination of the proposed transannular [6 + 4] cycloaddition proposed as a step in the biosynthesis of heronamide A. The DFT computational results support that proposal and suggest that the cycloaddition is highly stereoselective giving one product, but proceeds *via* a ambimodal transition state that can lead to both the observed [6 + 4] and unobserved [4 + 2] products with the [4 + 2] product being less stable (5.2 kcal mol⁻¹).¹⁵² Structurally, anthracimycin and chlorotonil are virtually identical but were isolated from a *Streptomyces* sp.^{153,154} and *Sorangium cellulosum*,¹⁵⁵ a myxobacterium, respectively. Chlorotonil differs from anthracimycin in that all sp³ stereocenters are inverted, there is an additional methyl group and a *gem*-dichloro entity. The two biosynthetic gene clusters have been compared in two papers published side-by-side. Both compounds are formed by *trans*-AT PKS pathways and clusters in the chlorotonil genome readily explain the chlorination and methylation pattern. In each case the decalin ring system is formed by a spontaneous [4 + 2] cycloaddition and it is proposed that the alternative stereochemistries are





in part a consequence of the orientation of the C16 methyl group pre-organising the PKS-bound intermediate prior to the [4 + 2] cycloaddition.^{156,157} The biosynthesis of two similar *Salinispora pacifica* metabolites, salinopyrone and pacificanone,¹⁵⁸ was unexpectedly correlated with the large PKS cluster from *Micromonospora carbonacea*¹⁵⁹ that produces the macrolide rosamicin¹⁶⁰ and illustrates how domain and module skipping can give rise to polyketide product diversity.¹⁶¹ From a study of splenicin¹³¹ biosynthesis the new aromatic CoA-linked extender unit, benzylmalonyl-CoA, was identified and provides a link between amino acid and CoA-linked extender units and opens access to the bio-engineering of polyketide carbon scaffolds.¹⁶² To reach the conclusion that indole-C-3 methylation of *cyclo*-L-Trp-L-Trp precedes indole-C-3' prenylation and transfer of a second methyl to the *N'* position in the biosynthesis of the nocardioazine alkaloids¹⁶³ required bioinformatics analysis, bioinspired syntheses and MS metabolomics profiling.¹⁶⁴ Target-directed genome mining is a new strategy for the discovery of new biosynthetic

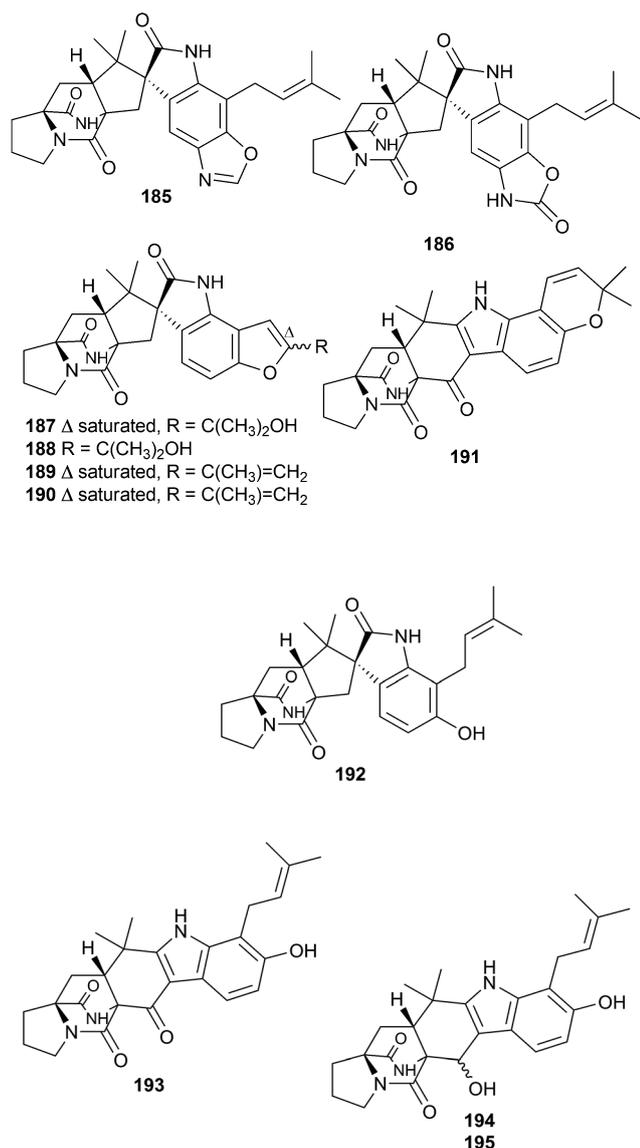
pathways and the concept was developed around an analysis of the pan-genome of 86 *Salinispora* bacterial genomes. The strategy operates by querying the genomes for duplicated housekeeping genes that are co-localised with biosynthetic gene clusters.¹⁶⁵ The initial development of cytological screening of natural product extracts using a high content imaging approach to generate phenotype fingerprints has been extended from the original 312 extracts¹⁶⁶ to over 5000 pre-fractionated extracts from marine Actinobacteria and demonstrated the role that untargeted cytological screening can play in ascertaining the pathways and the mechanisms disrupted and so leading to a targeted selection of extracts based on a potential mode of action.¹⁶⁷

3.2 Marine-sourced fungi (excluding from mangroves)

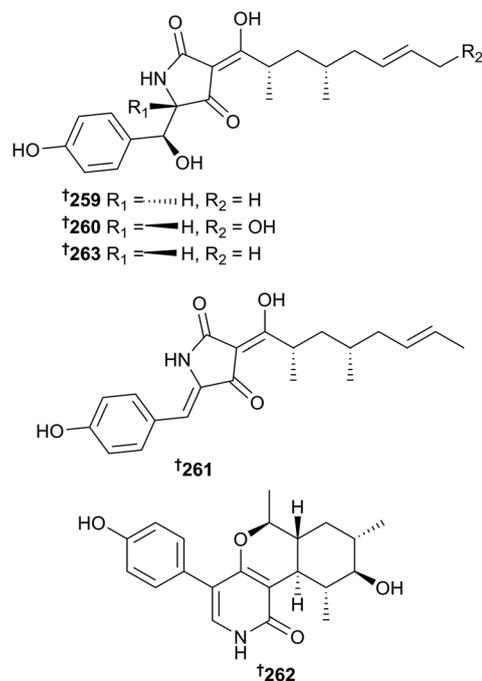
Studies of fungi continue to be on the rise with 371 new compounds reported in 2015 compared to 318 in 2014 and 223 in 2013. A number of new metabolites have been obtained from the genera *Acremonium* (benzophenones **170–172** (ref. 168)), *Alternaria*



(tricycloalternarenes **173** and **174**,¹⁶⁹ and a spiro decalin derivative **175** (ref. 170)), *Arthrinium* (alkaloids **176–178** (ref. 171) and cytochalasins **179–183**).¹⁷² Of these, arthrinium A **179** was claimed as new but is a known natural product derivative¹⁷³ and ketocytochalasin **183** (ref. 173) is a first time MNP.¹⁷² Citromycesin analogue **184** was obtained from an *Ascomyza* sp.,¹⁷⁴ while as usual, the genus *Aspergillus* has been well studied. Of particular note was a continuing study into the biosynthesis of the prenylated indole alkaloids notoamides,¹⁷⁵ stephacidins¹⁷⁶ and versicolamide B.¹⁷⁷ Feeding of [¹³C]₂ racemic 6-*epi*-notoamide T¹⁷⁸ to *Aspergillus* sp.¹⁷⁹ cultured in liquid media resulted in incorporation into versicolamide B and also into seven new metabolites **185–191**, which were not produced under normal culture conditions. The same incorporation experiment on agar medium resulted in production of four additional new metabolites, **192–195**. All were produced as racemic mixtures. It was suggested that addition of excess precursor to the cultures activated expression of dormant tailoring genes.¹⁸⁰



Other metabolites produced by *Aspergillus* species included spiculisporic acid analogues **196** and **197**,¹⁸¹ phenyl ether derivatives **198–202**, of which dehydrocyclopeptide¹⁸² **201** and viridicatin¹⁸² **202** were obtained as first time MNPs,¹⁸³ polyketide **203** and decaline derivative **204**,¹⁸⁴ alkaloids **205–207**,¹⁸⁵ **208–210**,¹⁸⁶ indole diterpenoids **211** and **212**,¹⁸⁷ isocoumarin **213**, cyclohexapeptide **214** and pyripropene derivative **215**,¹⁸⁸ peptides **216** and **217**,¹⁸⁹ **218**,¹⁹⁰ hydroxyphenylacetic acid derivative **219**,¹⁹¹ alkaloids **220** (also synthesised)¹⁹² and **221–225**,¹⁹³ the steroids **226**, 2-*O*-methylbutyrolactone I **227** (aspernolide C)¹⁹⁴ and 2-*O*-methylbutyrolactone II¹⁹⁵ **228** (last two as new MNPs),¹⁹⁶ meroterpenoids **229–232**,¹⁹⁷ alcohols **233–250**,¹⁹⁸ alkaloid **251**,¹⁹⁹ xanthone **252**, alkaloid **253** (ref. 200) and dihydroisocoumarin **254**.²⁰¹ The stereochemistry of 5'-hydroxyasperentin²⁰² was established as (3*R*,10*R*,13*S*,14*S*) **255** by X-ray crystallography.²⁰¹ New metabolites were isolated from the genera *Auxarthron* (triterpene glycoside **256** (ref. 203)) and *Beauveria* (co-culture with *Penicillium*) (citrinin derivatives **257** and **258** (ref. 204)). Several new tetramic acids, chaunolidine A–C **259–261** and a pyridinone, chaunolidone **262** were obtained from an Australian *Chaunopycnis* sp.²⁰⁵ Additionally, the absolute configuration of the co-isolated tetramic acid F-14329, previously obtained from terrestrial *Chaunopycnis*²⁰⁶ and *Tolypocladium*²⁰⁷ species, was established as **263** and is a first time MNP. Chaunolidone **262** possessed selective and potent cytotoxicity to the NCI-H460 cell line.²⁰⁵ Interestingly, compounds with the same planar structures as chaunolidines A **259** and C **261** were simultaneously reported as metabolites of the terrestrial fungus *Tolypocladium cylindrosporum*.²⁰⁸

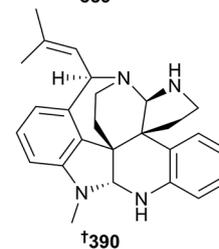
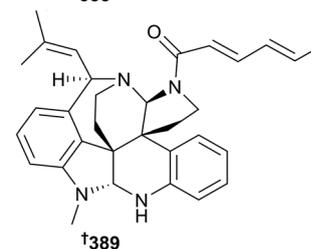
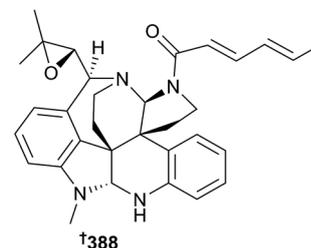
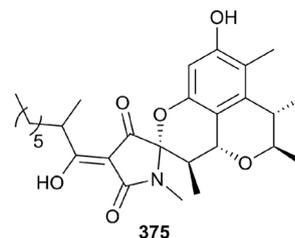
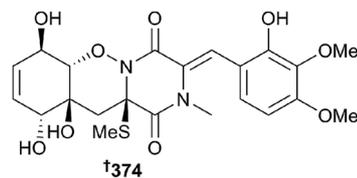
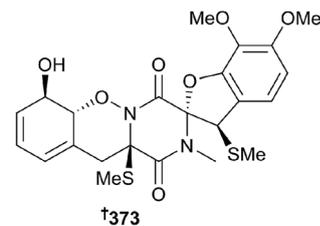


An OSMAC approach was utilised in the isolation of polyketides **264** and **265** from *Cladosporium sphaerospermum*²⁰⁹ and other metabolites obtained from *Cladosporium* species included



diketopiperazines **266** and **267**,²¹⁰ bicyclic lactam **268** (ref. 211) and polyketides **269** and **270**.²¹² New metabolites isolated from the genera *Corynepsoa* included chromone derivatives **271–282** (ref. 213) while *Dichotomomyces* spp. produced the thio-diketopiperazines **283–285**, (**284** (ref. 214) and **285** (ref. 215) as first time MNPs),²¹⁶ and steroids **286–288**.²¹⁷ From *Emericella* spp. the polyketides **289–296** (ref. 218) and lactones **297–300** (ref. 219) were characterised while the isopimarane **301** (ref. 220) came from an *Epicoccum* sp. and a *Eurotium* sp. gave the prenylated indole diketopiperazines **302–316**.²²¹ The co-isolated alkaloid neoehinulin B^{222,223} was shown to be a potent inhibitor of H1N1 virus and a panel of other influenza virus strains through binding to viral hemagglutinin disrupting the attachment of viruses to host cells.²²¹ Further new metabolites were obtained from the genera *Gliomastix* (macrolides **317–321** (ref. 224)), *Graphium* (thiodiketopiperazines **322–329**,²²⁵ **330** and **331** (ref. 226)) and *Hypocrea* (furan derivatives **332**, **333** and cyclopentenone derivatives **334–338**).²²⁷ Two of these compounds, *N*-isobutyl-2-phenylacetamide²²⁸ **337** and *N*-(2-methylbutyl)-2-phenylacetamide²²⁹ **338** were first time NPs.²²⁷ New natural products were isolated from the genera *Lophiostoma* (merosesquiterpenoids craterellin D **339** and craterellin A²³⁰ **340**; first marine isolation for the latter),²³¹ and *Nectria* (monoterpenoid α -pyrones **341** and **342**).²³² Of these, nectriapyrone D²³² **342** was simultaneously isolated from a terrestrial fungus as gulpyrone B.²³³ The genera *Neosartorya* and *Paecilomyces* also yielded new metabolites (alkaloids **343** and **344**,²³⁴ meroditerpene **345** and alkaloids **346** and **347** (ref. 235) and butenolide derivatives **348** and **349**,²³⁶ alkaloids **350** and **351**,²³⁷ **352** and **353** (ref. 238) and octaketide spiroketals **354–357** (ref. 239)). The genus *Penicillium* was, as always, a prolific source of new metabolites, including bithiodiketopiperazines **358** and **359**, sesquiterpenes **360** and **361**,²⁴⁰ phenolic bisbolanes **362–364** and nor-bisbolane **365**,²⁴¹ benzoic acid derivative **366**,²⁴² citrinin derivatives **367–370** and tetramic acid analogues **371** and **372**.²⁴³ A culture of *P. adametzioides* was the source of the dithiodiketopiperazine derivatives peniciadametizine A **373**, with the unique spiro[furan-2,7'-pyrazino[1,2-*b*][1,2]oxazine] skeleton, along with an analogue, peniciadametizine B **374**, both inhibitors of the plant pathogenic fungus *Alternaria brassicae*.²⁴⁴ Penicitrinine A, **375** also with a unique spiro skeleton, was obtained from *P. citrinum* and was cytotoxic to a wide range of tumour cell lines. It also induced apoptosis and suppressed metastasis.²⁴⁵

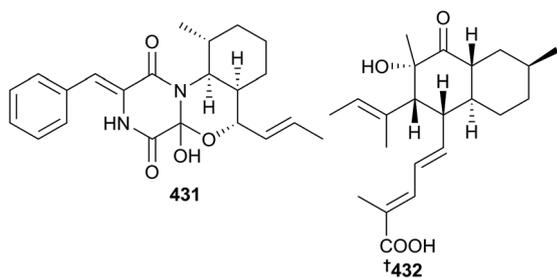
Phthalide derivatives **376** (ref. 246) (first time MNP) and **377**, isopatulin²⁴⁷ **378** (first time MNP),²⁴⁸ and oxindole alkaloids **379–386** were also isolated from the *Penicillium* genus.²⁴⁹ Another oxindole alkaloid **387** was claimed as new and named cyclopiamide I²⁴⁹ but had already been reported in 2014 as aspergilline D.²⁵⁰ The current report does however represent the first marine isolation.²⁴⁹ The gene cluster from *Penicillium expansum* responsible for biosynthesis of the indole alkaloids communesins²⁵¹ has been identified. In the process, three new metabolites, communesin I–K **388–390** were isolated. The investigation confirmed that communesins originate from L-tryptophan *via* coupling of tryptamine and aurantioclavine.²⁵²



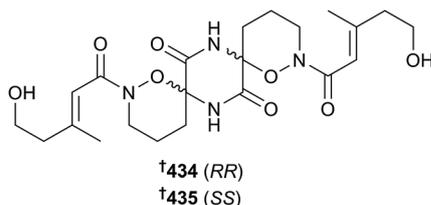
Further metabolites isolated from the genus *Penicillium* include meroterpenes **391** and **392**,²⁵³ alkaloids **393**,²⁵⁴ **394–396**,²⁵⁵ diphenylmethanone derivative **397**,²⁵⁶ phenolic enamide **398** and meroterpenoid **399**,²⁵⁷ azaphilone derivatives **400–402** and diphenyl ether derivatives **403** and **404**.²⁵⁸ The planar structure of **404** appears in a screening library²⁵⁹ but no source is given for the compound. Chromones **405–409**,²⁶⁰ sesquiterpenes **410–413**,²⁶¹ merosesquiterpenes **414** and **415**,²⁶² 1,4-diazepane **416**,²⁶³ tanzawaic acids **417–420**,²⁶⁴ diketopiperazine **421**,²⁶⁵ polyketides **422–426**,²⁶⁶ spiroindoline alkaloids **427** and



428,²⁶⁷ and azaphilone derivatives **429** and **430** (ref. 268) were also obtained from *Penicillium* species. *P. vinaceum* was the source of penicillivinacine **431**, which exhibited potent anti-migratory activity against the highly metastatic breast cancer cell line MDA-MB-231.²⁶⁹ A sponge-derived *Penicillium* sp. yielded the fusarielin analogue **432** when grown axenically but co-culture of this strain with another *Penicillium* strain obtained from the same sponge elicited production of the known compounds norlichexanthone²⁷⁰ and monocerin²⁷¹ **433** (first time MNP), neither of which was detected in the individual axenic cultures of the two strains.²⁷²

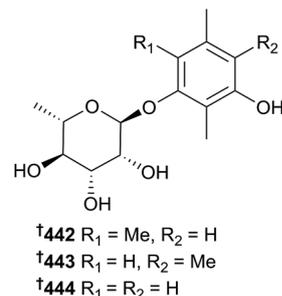


A soft coral-related *Pestalotiopsis* sp. was the source of enantiomeric alkaloid dimers (+)- and (-)-pestaloxazine A **434** and **435**.²⁷³ These mixed polyketide-cyclopeptide metabolites (PKS-NRPS hybrids) possessed a unique, symmetric spiro [oxazinane-piperazinedione] skeleton and the racemate and each enantiomer exhibited Enterovirus 71 (EV71) activity but **434** was more selective and more potent.²⁷³

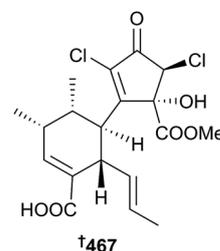


The genus *Pestalotiopsis* yielded a number of other new metabolites, including meroterpenoids **436** and **437**, isocoumarin **438**, phenol **439** (ref. 274) phthalide derivative **440**,²⁷⁵ 5'-O-acetyl uridine²⁷⁶ **441** (ref. 275) (new NP) and pestarhamnos A-C **442–444**.²⁷⁷ The pestarhamnos were obtained through cultivation on a modified medium which contained equal concentrations of sodium chloride and potassium bromide in an expectation of producing brominated analogues of the previously isolated pestalochlorides.^{278,279} Interestingly, no brominated analogues were detected but pestalochlorides C and D²⁷⁹ were isolated along with pestarhamnos A-C **442–444**.²⁷⁷

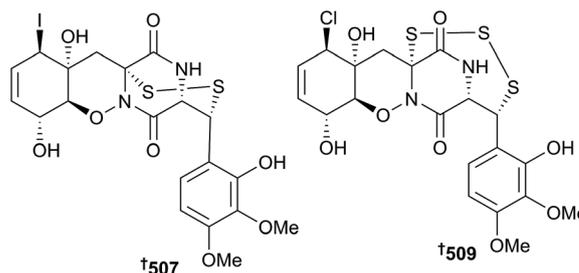
Other fungal genera to yield new metabolites included *Phaeosphaeria* (polyketides **445** and **446**),²⁸⁰ *Phoma* (cytochalasin derivatives **447–449**, cytochalasin B6 (ref. 281) **450** (first NP isolation)),²⁸² *Pleosporales* (pleosporalins A-G **451–457**),²⁸³ *Pseudoallescheria* (chlorinated benzofurans **458** and **459**,²⁸⁴ pseudellones A-C **460–462** (ref. 285)) and *Pseudogymnoascus* (nitrated asteric acid derivatives **463–466**).²⁸⁶ The ascidian-derived *Roussoella* sp. produced roussoellatide **467**, a dichlorinated polyketide with an unprecedented skeleton and



experiments with $[1-^{13}\text{C}]$, $[2-^{13}\text{C}]$ - and $[1,2-^{13}\text{C}]$ -acetate suggested that biosynthesis proceeds from two pentaketides that each undergo Favorskii rearrangement prior to being joined by an intermolecular Diels–Alder reaction.²⁸⁷



New metabolites were also obtained from the genera *Simplicillium* (diketopiperazine **468** and furanone²⁸⁸ **469**; the latter a first time MNP²⁸⁹), *Spicaria* (isobenzofurans as acetylated derivatives **470–473**),²⁹⁰ *Spiromastix* (polyphenols **474–484**),²⁹¹ *Stachybotrys* (meroterpenoid sulfate **485**,²⁹² sesquiterpenoid **486** and xanthone derivatives **487** and **488** (ref. 293)), *Talaromyces* (sesquiterpene-conjugated amino acids **489–492**,²⁹⁴ diphenyl ether derivatives **493–495** and tenellic acid methyl ester (first time MNP)²⁹⁵ **496**,²⁹⁶ oxaphenalenone dimers **497** and **498** and isopentenyl xanthone **499** (ref. 297)) and *Trichobotrys* (tetramic acid derivatives **500–505**).²⁹⁸ A red algal-derived *Trichoderma* species produced gliovirin,²⁹⁹ pre-trichodermamide A³⁰⁰ and the related trichodermamide A³⁰¹ when grown on a freshwater medium, chlorinated derivatives trichodermamide B³⁰¹ and DC1149B³⁰² **506** when cultured in natural seawater and a new iodinated derivative **507** (ref. 303) when cultured in a freshwater medium supplemented with sodium iodide. A brominated analogue, DC1149R³⁰² **508** was obtained with sodium bromide supplementation to the freshwater medium and isolated for the first time as a natural product.³⁰³ Cultivation of the strain in seawater supplemented with dimethylsulfoxide (DMSO) yielded the trithio-derivative, chlorotrithio-brevamide **509**.³⁰⁴ Decalin derivatives **510–512**,³⁰⁵



lipids **513–520** (ref. 306) and octaketides **521** and **522** (ref. 307) were also obtained from the genus *Trichoderma*.

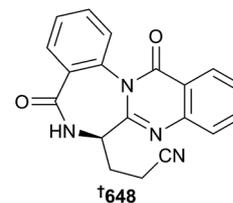
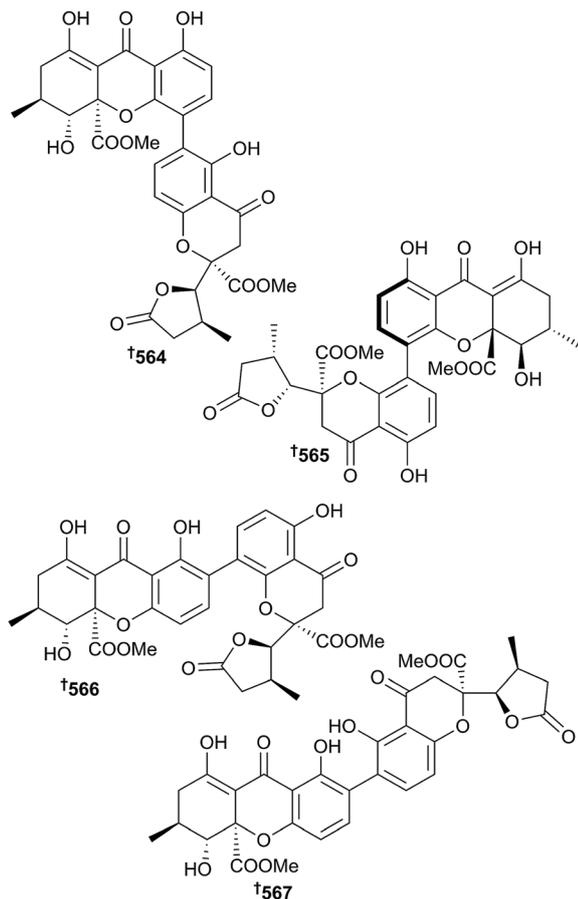
The genus *Truncatella* was the source of some isoprenylated cyclohexanols **523–536**,³⁰⁸ while an antibiotic polyketide **537** and ascosetin³⁰⁹ **538** were obtained from a fungus of the Lindgomycetaceae family.³¹⁰ Synthesis of the octaketide ascospiroketal A, originally obtained from *Ascochyta salicorniae*,³¹¹ via a Ag^I-promoted cyclisation cascade, revised the stereochemistry to **539** and indicated that the structure of ascospiroketal B³¹¹ should also be revised accordingly.^{312,313} Remisporine A was originally obtained from *Remispora maritima* and spontaneously dimerises to form remisporine B.³¹⁴ Comparison of the calculated and measured ECD spectra of remisporine B suggested a revision of configuration. By extension the configuration of natural product remisporine A should be changed to **540**.³¹⁵ The structure of trichodermatide A, originally obtained from *Trichoderma reesei*,³¹⁶ has been revised to **541**, a C-10 epimer of the structure originally proposed via synthesis and X-ray structure analysis of a synthetic intermediate of trichodermatide A.³¹⁷ Total synthesis of the proposed structure of the cyclic hexapeptide similanamide, obtained from *Aspergillus similanensis* associated with the sponge *Rhabdormia* sp.¹⁸⁸ and comparison of the NMR data of the synthetic compound with those of the natural product, has indicated that similanamide is in fact identical to PF1171C,³¹⁸ a hexapeptide previously obtained from an unidentified soil ascomycete.³¹⁹ *Clonostachys rosea* was the source of a new natural product, 4-methyl-(6*E*,8*E*)-hexadecadienoic acid **542**, previously known only from methanolysis of a metabolite of the mushroom *Microporellus subsessilis*.³²⁰ This fatty acid inhibited growth of MCF-7 cells and down-regulated the lipogenic enzymes acetyl CoA carboxylase (ACC) and fatty acid synthase (FAS).³²¹ Acetylglutotoxin G³²² **543** was obtained for the first time as a MNP as was the known synthetic open-chain hemisuccinimide **544**,³²³ (*Penicillium copticola*) which was named penicillimide.³²⁴ Alternariol-9-methyl ether 3-*O*-sulfate **545**, previously obtained from *Alternaria* sp., an endophyte of the Egyptian medicinal plant *Polygonum senegalense*,³²⁵ was obtained for the first time from the marine environment from endophytic *Alternaria alternata*.³²⁶ The norditerpenes aspewentin A–C (*Aspergillus wentii*³²⁷) have been synthesised³²⁸ as have the prenylated indole alkaloids, (+)-notoamide I (*Aspergillus* sp.)³²⁹ and (–)-17-hydroxy-citrinalin B (*Penicillium citrinum*)³³⁰ via a unified strategy.³³¹ Herbarins A and B originally obtained from *Cladosporium herbarum*³³² have been synthesised via a multi-step procedure and both displayed antioxidant properties.³³³ Starting from the sugar D-lyxose, total synthesis of cochliomycin C^{334,335} has been achieved.³³⁶ Total synthesis of the macrolide dendrodolide K³³⁷ (*Dendrodochium* sp.) has been accomplished from a commercially available substrate by a convergent strategy³³⁸ and other dendrolides (F, G, I, J and L³³⁷) have also been synthesised via a unified strategy employing ring-closing metathesis.³³⁹ A unified strategy was also employed in the total synthesis of luteoalbusins A and B,³⁴⁰ indole diketopiperazines isolated from sediment-derived *Acrostalagmus luteoalbus*.³⁴¹ In addition to the new compound

talaromycin C,²⁹⁶ purpactins A,³⁴² C³⁴² and penicillide³⁴³ exhibited potent antifouling activity against settlement of *Balanus amphitrite* larvae²⁹⁶ as did altertoxin I, a metabolite of both terrestrial³⁴⁴ and marine³⁴⁵ *Alternaria alternata*.³⁴⁶ A number of known cyclic dipeptides, cyclo(Gly-L-Pro),³⁴⁷ cyclo(L-Ala-L-Pro),³⁴⁸ cyclo(D-Ala-L-Pro),³⁴⁹ cyclo(L-4-Hyp-L-Pro)³⁵⁰ and cyclo(L-Hyp-D-Phe)³⁵¹ were reisolated from *Eupenicillium brefeldianum* and induced extracellular alkalinisation and hydrogen peroxide production in plant cell suspensions, indicating their potential as induced systemic resistance (ISR) elicitors.³⁵² Viridicatol, a metabolite of *Aspergillus versicolor*,³⁵³ has been obtained from *Penicillium* sp. as an anti-inflammatory agent, inhibiting the nuclear factor-kappa B (NF-κB) pathway in LPS-stimulated RAW264.7 and BV2 cells.³⁵⁴ Spiromastixones are chlorodepsidone metabolites of *Spiromastix* sp.³⁵⁵ which strongly inhibit cholesterol uptake and stimulate cholesterol efflux to apolipoprotein A1 (ApoA1) and high-density lipoprotein (HDL) in RAW264.7 macrophages.³⁵⁶ FGFC1 (fungi fibrinolytic compound 1),³⁵⁷ a metabolite of *Stachyotrys longispora*³⁵⁸ has potential as a thrombolytic agent since it induces thrombolysis in a rat model of acute pulmonary thromboembolism without associated bleeding.³⁵⁹ Several studies have explored production of the lipopeptides scopularides A and B³⁶⁰ produced by *Scopulariopsis brevicaulis* (also known as *Microascus brevicaulis*). One study, the first proteome study of a marine fungus, determined that production levels of scopularides were not caused by changes in secondary metabolism, but by complex changes in primary metabolism.³⁶¹ Other studies^{362,363} resulted in assembly of the genome of the fungus. Analysis of carbohydrate-active enzymes within a gene cluster led to the postulation that *S. brevicaulis* originated from a soil fungus which came in contact with the marine sponge *Tethya aurantium*.³⁶³

3.3 Fungi from mangroves

There has been a continued increase in the number of new metabolites reported from mangrove-associated fungi (127 in 2015 vs. 103 in 2014), with the majority coming from endophytic species. An *Alternaria* sp. yielded cyclohexanone, cyclopentanone and xanthone derivatives **546–549** (ref. 364) and the genus *Aspergillus* was the source of many new metabolites including meroterpenoids **550–553**,³⁶⁵ polyketides **554–556**,³⁶⁶ indole diketopiperazines **557–559**,³⁶⁷ isochromanone derivatives **560–563** (ref. 368) and the versixanthones **564–567** and **568** and **569**.³⁶⁹ The absolute configurations of these xanthone-chromanone dimers were established by a combination of techniques, including chemical conversions. A solvent-induced retro-oxa-Michael reaction was particularly helpful and indicated that **568** and **569** may in fact be artefacts of isolation. All of the versixanthones exhibited cytotoxicity at some level against several HTCLs and versixanthone E **568** was an inhibitor of topoisomerase I.³⁶⁹ Further metabolites obtained from the *Aspergillus* genus include dinaphthalenone derivatives **570–573**,³⁷⁰ lumazine peptide **574**,³⁷¹ cyclohexanone-furan derivative **575**, isocoumarin derivatives **576–578** and **579** (ref. 372) (first marine isolation)³⁷³ and polyene **580**.³⁷⁴





New metabolites were obtained from the genera *Botryosphaeria* (isocoumarin **581** (ref. 375)), *Cladosporium* (dimeric tetralone **582** (ref. 376)), *Daldinia* (hydronaphthalenone **583** (ref. 377)), *Eurotium* (indole-diketopiperazine **584** (ref. 378)), *Eutypella* (cytochalasans **585** and **586** (ref. 379) (new NP) and **587**),³⁸⁰ *Fusarium* (α -pyrones cladobotrin V **588** (ref. 381) and **589**,³⁸² cyclic depsipeptides **590** and **591** (ref. 383)), *Lophiostoma* (phenalenone derivatives **592–600** and sesterterpene bipolarenic acid **601** (ref. 384)), *Meyerozyma* (depsidones **602–606** (ref. 385)), *Nigrospora* (acetamidopentane derivative **607** and phenalenone derivative **608** (ref. 386)) and *Paradictyoarthrinium* (hydroanthraquinones **609** and **610** (ref. 387)). The genus *Penicillium* was also the source of a number of new metabolites including polyketide decalins **611–616**,³⁸⁸ sulfide diketopiperazines **617–621**,³⁸⁹ pyrrole-4,5-dione derivative **622**,³⁹⁰ polyketides **623–625** and **626** (ref. 391) (isolated for the first time as a NP) and compound **627**,³⁹² citrinin analogues **628–630**, xanthone derivative **631**,³⁹³ compounds **632** and **633**,³⁹⁴ **634** and **635**,³⁹⁵ alkaloids **636** and **637**,³⁹⁶ α -pyrones **638** and **639**, dihydroxybenzoic acid derivatives **640** and **641**, **642** and **643**,³⁹⁷ (the last two are known compounds³⁹⁸) and polyketides **644–647**.³⁹⁹ Pinazaphilone A reported in this paper³⁹⁹ is identical with pinophilin F **402** (ref. 258) reported in Section 3.2. An unusual benzodiazepine alkaloid **648** with a terminal cyano group was also obtained

from a *Penicillium* sp. but was inactive towards a panel of HTCLs.⁴⁰⁰

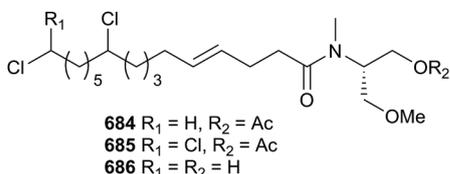
Further metabolites were obtained from the genera *Pestalotiopsis* (prenylated phenols **649** and **650** (ref. 401)), *Phomopsis* (purine derivative **651** and octadecadiene derivative **652**,⁴⁰² first isolation as a NP),⁴⁰³ *Setophoma* (polyketides **653**,⁴⁰⁴ **654** and **655**, **656**,⁴⁰⁵ **657** and **658**, **659** (ref. 406)) and *Stemphylium* (aromatic sulfates **660** and **661** (ref. 407)). Stemphol⁴⁰⁸ **662** was obtained as a first time MNP.⁴⁰⁷ Several studies reported metabolites from species that were unidentified or only partially classified. Sesquiterpenoids **663** and **664** (ref. 409) and coumarin **665** (ref. 410) were obtained from unidentified species (the latter from a mixed culture of two species) and spirodioxynaphthalenes **666–670** (ref. 411) were obtained from a species of the order Pleosporales. Torribiellin B⁴¹² was isolated for the first time as a MNP and the absolute configuration established as **671**.⁴¹³ Synthesis of penicillenols B1 (ref. 414) and B2 (ref. 414) determined the stereochemistry of each as **672** and **673** respectively.⁴¹⁵ Synthesis of the proposed structures of cephalosporolides H⁴¹⁶ and I⁴¹⁶ has revised the configuration at C-6 of each to (*R*) (**674** and **675**) but discrepancies for some ¹³C NMR chemical shifts of the sidechain carbons between those reported for cephalosporolide I and the synthetic compound **675** indicate that the structure of cephalosporolide I may need further investigation.⁴¹⁷ Peniphenones A–D, polyketide metabolites of *Penicillium dipodomycicola*⁴¹⁸ have been synthesised *via* a biomimetic method⁴¹⁹ as has the *Penicillium* metabolite,⁴²⁰ (–)-penibruguieramine.⁴²¹ *Pestalotiopsis* metabolite (6*S*,1'*S*,2'*S*)-hydroxypestalotin⁴²² has been synthesised⁴²³ and the proposed structure of pestalotioprolide A⁴²⁴ has been prepared *via* total synthesis, but a mismatch between the magnitudes of optical rotation data between the reported value for the natural product and the synthetic compound indicate that the stereochemistry of the natural product requires further examination.⁴²⁵ A number of known natural products were reisolated from *Phakellia fusca* and exhibited a range of activities. Penicillenol A₁,⁴¹⁴ a tetramic acid derivative, displayed anti-TB activity whilst expansols A–F^{426,427} were potent COX-2 inhibitors and all but expansol D were also potent inhibitors of COX-1.⁴²⁸

3.4 Cyanobacteria

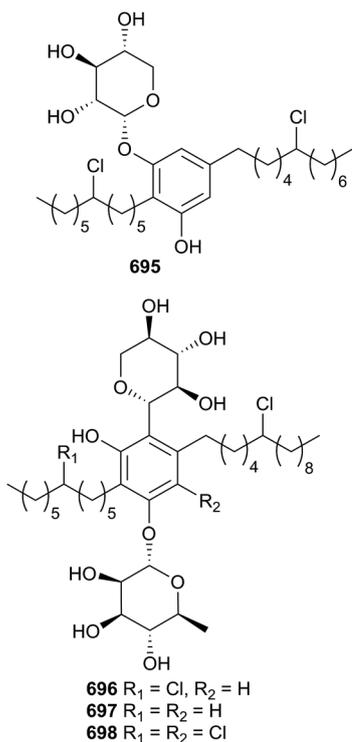
There has been an upturn in the number of new metabolites reported from cyanobacteria with 31 new metabolites reported in 2015 compared to 19 in 2014. Typical of the phylum, most of the metabolites reported were peptides. Linear lipopeptides **676** and **677** were obtained from *Anabaena torulosa*,⁴²⁹ from which the cyclic analogues laxophycins B^{430–432} and B3 (ref. 431) had



previously been obtained, posing the question as to whether the new compounds are enzymatic degradation products, isolation artefacts or true natural products.⁴²⁹ Further metabolites were obtained from the genera *Hyalidium* (new genus) (cyclic depsipeptides **678** and **679** (ref. 433)) and *Lyngbya* (lipopeptide **680** (ref. 434) and macrolides **681–683** (ref. 435)). A combination of mass spectrometric metabolic profiling and genomic analysis led to the isolation of the columbamides A–C **684–686** from *Moorea bouillonii*.⁴³⁶ These acyl amides **684–686** possessed moderate affinity for the CB₁ and CB₂ cannabinoid receptors. A similar approach was utilised in the isolation of hectoramide **687**, hectochlorins B–D **688–690** and jamaicamides D–F **691–693** from *M. producens*.⁴³⁷ The terpene alkaloid **694** was also obtained from the genus *Moorea*.⁴³⁸

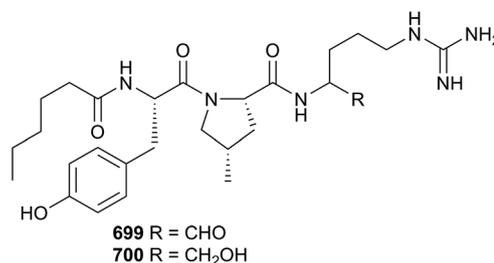


Bartolosides A–D **695–698** are chlorinated aromatic glycolipids obtained from a *Nodosilinea* species and *Synechocystis salina* respectively.⁴³⁹ Investigation of the biosynthesis of these molecules prior to completion of the structural assignment provided information that was vital to the structural elucidation of the chlorinated dialkylresorcinol core of these molecules.

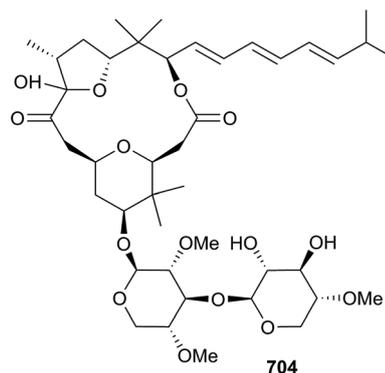


Nodularia spumigena was the source of the pseudoaeruginosins NS1 **699** and NS2 **700**, linear peptides which contain structural features of both the aeruginosins⁴⁴⁰ and the

spumigens.⁴⁴¹ Structural characterisation of these metabolites was completed through synthesis and pseudoaeruginosin NS1 **699** was a potent trypsin inhibitor.⁴⁴²



The genus *Okeania* was the source of the antimalarial polyhydroxy macrolide **701**,⁴⁴³ the macrolactone **702** (ref. 444) and the lipopeptide kurahyne B **703**.⁴⁴⁵ The related metabolite kurahyne A⁴⁴⁶ was also isolated and synthesised.⁴⁴⁵ An *Okeania* sp. was also the source of a new macrolide polycavernoside D **704**.⁴⁴⁷ Polycavernosides^{448–451} were previously implicated in fatal poisonings in the South Western Pacific and the source was ascribed to the red alga *Polycavernosa tsudai*. However, re-isolation of these metabolites from the alga has never been achieved and they bear structural resemblance to known cyanobacterial metabolites. Furthermore, polycavernoside D **704** was obtained from a Caribbean cyanobacterial sample, implying that these toxins occur over a much wider geographical range than originally thought.⁴⁴⁷



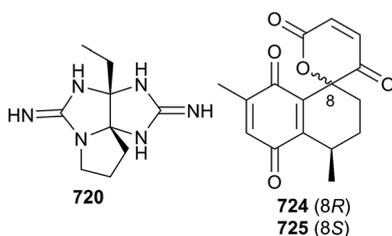
A species that is most likely a new taxon but most closely related to specimens of the *Hormoscilla* genus yielded a tetrahydroquinolinol **705** (ref. 452) whilst a species only able to be identified as a member of the Oscillatoriiales family, was the source of the polyhydroxylated macrolides **706** and **707**.⁴⁵³ Total synthesis of the cyclodepsipeptide coibamide A⁴⁵⁴ was achieved and resulted in the revision of the structure to **708** as a result of reassignment of two stereocentres.⁴⁵⁵ Two separate synthetic studies resulted in the structural revision of the lyngbyaliosides. Total syntheses of the proposed⁴⁵⁶ and correct structures (**709**) of (–)-lyngbyalioside B were completed⁴⁵⁷ and total synthesis of the (18*Z*) and (18*E*) isomers of lyngbyalioside C⁴⁵⁸ resulted in reassignment of the structures to **710** and **711** respectively.⁴⁵⁹ As a result, it was suggested that the structure of lyngbouilloside⁴⁶⁰ should likely also be reconsidered.⁴⁵⁹ Total syntheses of the



acyclic depsipeptide maedamide⁴⁶¹ and cyclodepsipeptide largamide B⁴⁶² also resulted in stereochemical revision of their structures to **712** (ref. 463) and **713** (ref. 464) respectively, the latter consistent with the revised structure previously proposed.⁴⁶⁵ Syntheses of (+)-lyngbyabellin M,^{466,467} sanctolide A^{468,469} and santacruzamate A^{470,471} were also completed, with the last not exhibiting any inhibition of histone deacetylase (HDAC), unlike the potent inhibition previously reported.⁴⁷⁰ The functions of some enzymes involved in the biosynthesis of the terminal alkyne moiety in the jamaicamides⁴⁷² were elucidated *via* both *in vitro* and *in vivo* analyses.⁴⁷³ Dereplication methods based on phylogeny and HPLC-MS were developed which showed that largazole⁴⁷⁴ was always coproduced with either dolastatin 10 (ref. 475) or symprostatin 1 (ref. 476) and that combinations of largazole and dolastatin 10 displayed cooperative activity.⁴⁷⁷

3.5 Dinoflagellates

The number of new metabolites reported from dinoflagellates has remained the same as for 2014 with 15 compounds reported in each year. The genus *Amphidinium* has yielded new metabolites, including the linear polyketide **714**,⁴⁷⁸ the macrolide **715**,⁴⁷⁹ and the linear polyketide **716**.⁴⁸⁰ Azaspiracids **717** and **718** were isolated from *Azadinium poporum*,⁴⁸¹ whilst the ladder polyether **719** was obtained from *Gambierdiscus belizeanus*.⁴⁸² Recent studies have shed some light on the biosynthetic pathway to paralytic shellfish toxins (PSTs) such as saxitoxin (STX).⁴⁸³ PSTs are known to be produced by both freshwater cyanobacteria and by dinoflagellates. Synthesis of some genetically predicted biosynthetic STX intermediates and identification of these in both a cyanobacterium and a dinoflagellate was previously reported.⁴⁸⁴ One of these intermediates has now been converted into cyclic-C' **720**, a tricyclic bisguanidine compound structurally related to STX. This metabolite was also identified in a PST-producing cyanobacterium and a dinoflagellate, suggesting that it is either a biosynthetic intermediate of STX or a shunt product of PSTs.⁴⁸⁵ Two karlotoxins **721** (ref. 486) and **722** (ref. 487) were obtained from a *Karlotodinium* sp. as new MNPs and the stereochemistry of karlotoxin 2 (ref. 488) was revised to **723**.⁴⁸⁹ The ciliate *Spirostomum teres* contains colourless extrusive organelles which function as a chemical defence.⁴⁹⁰ The tricyclic quinones spirostomin A **724** and B **725** were isolated from these organelles as a 5 : 1 diastereoisomeric mixture which was lethal to the ciliate *Paramecium caudatum* at a relatively low dose. Total synthesis of each confirmed relative configurations.⁴⁹¹



Nonacosadienes **726** and **727** were obtained as metabolites of the microalga *Emiliania huxleyi*⁴⁹² while 12β-

deoxydecarbamoysaxitoxin⁴⁹³ **728** was obtained as a first time MNP.⁴⁹⁴ Syntheses of the polyketide amphirionin-4 (ref. 495) and ciguatoxin 54-deoxyCTX1B⁴⁹⁶ have been achieved.^{497,498} Polyketide synthesis genes unique to two *Gambierdiscus* species that produce maitotoxin⁴⁹⁹ were characterised, perhaps implicating them in the biosynthesis of this metabolite.⁵⁰⁰ Studies with *Karenia brevis* showed that brevetoxin⁵⁰¹ is localised in the chloroplasts and interacts with light harvesting complex II (LHCII) and thioredoxin, so is likely implicated in non-photochemical quenching (NPQ). Differences between toxic and low toxicity *K. brevis* strains in NPQ and reactive oxygen species (ROS) production supported this.⁵⁰²

4 Green algae

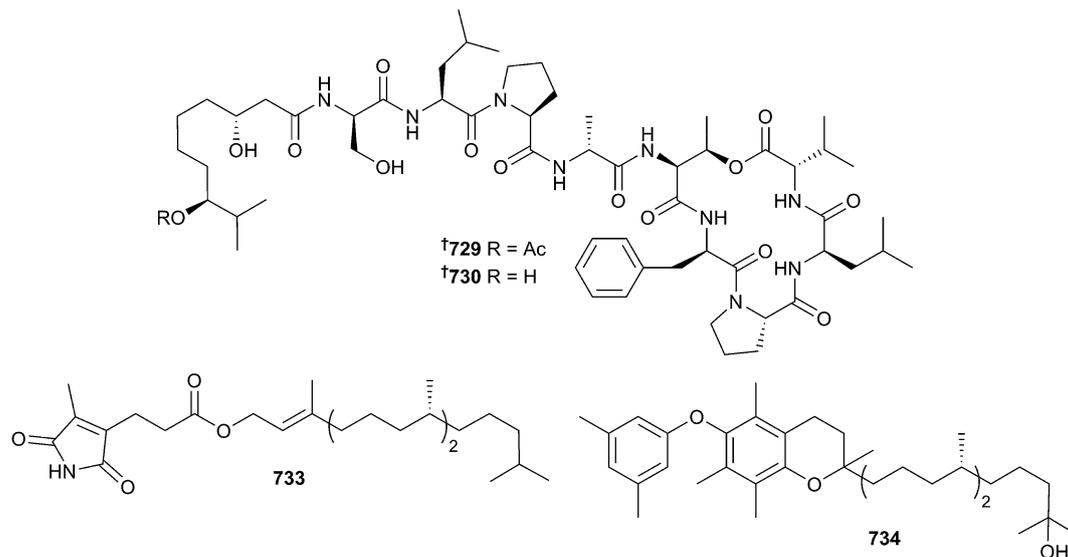
The output of new compounds from the phylum Chlorophyta for 2015 was greater than that for recent years with eight new compounds noted from three publications. Noteworthy were the cyclic lipopeptides mebamamide A **729** and B **730** from *Derbesia marina*.⁵⁰³ This is a structural class rarely found in the Chlorophyta. Also reported were diterpenoids, **731–733**, an α -tocopheroid **734**, a sterol **735** along with 12 known compounds from *Caulerpa racemosa*⁵⁰⁴ and a triterpene acid **736** from *Codium dwarkense*.⁵⁰⁵ The diterpenoid **733** and the α -tocopheroid **734** are the first natural products to contain the haematinic acid and 3,5-dimethylphenoxy motifs respectively.

The structure and absolute configuration of nigricanoside A, isolated in 2007 from *Avrainvillea nigricans*,⁵⁰⁶ has been established by enantioselective total synthesis as **737**, correcting aspects of the previously reported configurations.⁵⁰⁷ Originally isolated as the dimethyl ester, nigricanoside A was reported to inhibit the proliferation of several cancer cell lines (IC₅₀ 3 nM), but the synthetic material, identical in all respects to the natural sample, was inactive. The natural material was ~90% pure and it is now suggested that the potent bioactivity of nigricanoside A was associated with a related, co-eluting minor metabolite with sub-nanomolar activity.⁵⁰⁷ An efficient and cost-effective method for the production of kahalalide congeners for advanced biological testing is based on the selective hydrolysis of *N*-protected kahalalide F isolated from nuisance blooms of *Bryopsis pennata*.⁵⁰⁸ By combining virtual- and structure-based ligand screening approaches, a database of >100 caulerpin analogues was efficiently evaluated *in silico* for potential inhibitory activity against monoamine oxidase B,⁵⁰⁹ while astaxanthin and other algal carotenoids have been the focus of many studies and reviews.^{510–518}

5 Brown algae

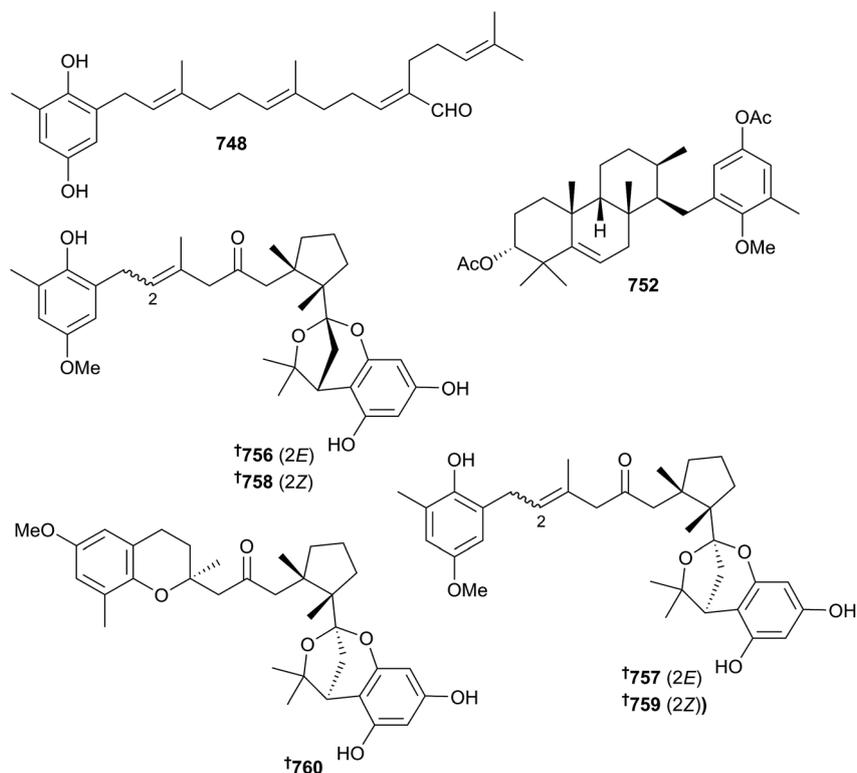
The level of interest in brown algae in 2015 was comparable to recent years with 33 new compounds reported from 12 papers out of a total of 54 papers and reviews on brown algae. Not atypically the chemistry was dominated by terpenoids and meroterpenoids with two dolastanes, **738** and **739**, four xenicanes, **740–743** and two cytotoxic sterols **744** and **745** isolated from *Canistrocarpus cervicornis*,^{519,520} *Dictyota plectens*,⁵²¹ and *Cystoseira trinodis*⁵²² respectively. The compounds of mixed biosynthesis was a tranche comprised of a chromene, **746**





(*Homoeostrichus formosana*),⁵²³ five acyclic meroditerpenoids 747–750, (*Sargassum paradoxum*)⁵²⁴ 751 (*Cystophora retroflexa*, *C. subfarinata*, *Sargassum* cf. *fallax*),⁵²⁵ four cyclic meroditerpenoids 752 (*Stypodium flabelliforme*),⁵²⁶ 753–755 (*Stypodium zonale*)⁵²⁷ and the cyclophloketal A–E, 756–760, hybrid meroditerpenoids from *Cystoseira tamariscifolia*.⁵²⁸ The cyclophloketal, 756–760, each incorporated an *O*-methyltoluquinol and a phloroglucinol with the cyclic diterpene and are the first examples of meroterpenoids with the rarely found 2,7-dioxabicyclo[3.2.1]octane backbone.⁵²⁸ The proposed, unprecedented *syn-cis-anti* arrangement for the A/B/C ring system in the cyclic

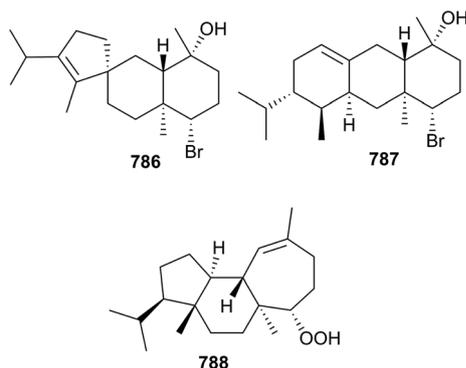
meroditerpenoid, *O,C(3)-seco-9-ene-6 β -taondiol* 752 was based on NOESY data and supported the notion that the folding patterns of the presumed biosynthetic precursor, 2-geranylgeranyl-6-methylhydroquinone, are flexible during biosynthesis leading to different classes of metabolites related to the taondiol group.^{528–531} The isolation and characterisation of >20 acyclic meroditerpenoids from a collection of seven Australian brown algae (and one red alga) included five new diterpenoids (747, 748, 749–751). This is an excellent example of the use of HPLC-NMR for the isolation and identification of unstable compounds (see 748 as a representative example).^{524,525}



The non-terpenoid brown algal compounds are represented by the polyketides, **761–770**, from *Lobophora variegata*.⁵³² When considered as a group their biosynthetic origins can be rationalised by involvement of a non-acetate starter acyl-CoA, most likely a dodecanoic acid unit, and type III polyketide synthases.^{533,534} The absolute configuration for the acyclic diterpenoid elegandiol,^{535,536} **771**, was unequivocally re-established as (*S*) using VCD. This insightful paper outlines the approaches necessary for using VCD in the determination of absolute configuration.⁵³⁷ The first asymmetric synthesis of (–)-dolastatrienol (14-hydroxydolasta-1(15),7,9-triene)⁵³⁸ was reported⁵³⁹ along with a concise synthesis of dictyodendrins A and F.⁵⁴⁰ Additionally, there were many papers and reviews dealing with the biological properties of brown algal polyphenolics^{541–557} and carotenoids.^{15,558–562}

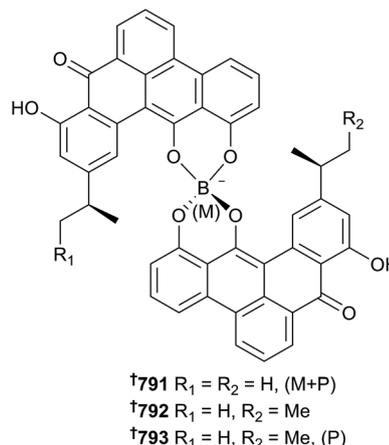
6 Red algae

In 2015 twelve papers reported 33 new or revised structures from red algae. Of these papers, six described compounds from *Laurencia* spp. Twenty of the 33 compounds encompassed the typical structural types of fatty acid derivatives **772** and **773**,⁵⁶³ **774**,⁵⁶⁴ **775**,⁵⁶⁵ oxosqualenoids **776–779**,⁵⁶⁶ sesquiterpenoids **780** and **781**,⁵⁶⁷ **782**,⁵⁶⁸ **783**,⁵⁶⁹ **784–785**,⁵⁷⁰ diterpenoids **786–788**,⁵⁷¹ **789**,⁵⁷² and the mycosporine-like amino acid **790**.⁵⁷³ The rearranged diterpenoids spirophaerol **786** anthrasphaerol **787** and corfusphaeroxide **788** from *Sphaerococcus coronopifolius* have unprecedented tricyclic skeletons.⁵⁷¹



The remaining 13 compounds, the borolithochromes **791–803**, were a series of polyketide-derived spiroborate pigments from samples of a more than 150-million-years-old Jurassic putative red alga *Solenopora jurassica*. The representative structures of borolithochromes G **791**, H1 **792** and H2 **793** are shown here. The presence of boron in these structures as bis-six-membered spiroborates is unprecedented among present-day boron-containing natural products.

The rather unusual benzo[*gh*]tetraphene ligands have never been seen in any fossil compounds, and only recently a study⁵⁷⁴ of the anaerobic bacterium *Clostridium beijerinckii* revealed a polyketide antibiotic clostrubin A with similarities to the ligands in the borolithochromes. It was suggested that the fossil pigments may originally have been produced by an ancient bacterium, or



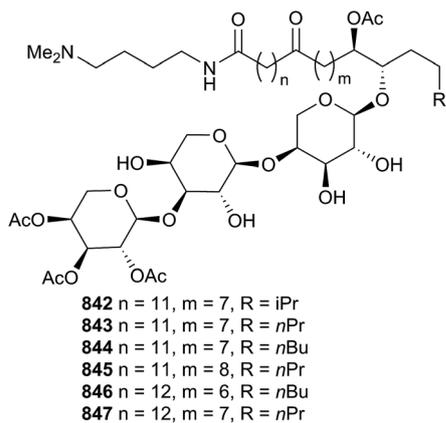
have originated from bacteria that degraded the dead organic material of *S. jurassica*. In this remarkable piece of work, all structures were determined on samples of 6–57 μg, utilizing micro- and microcryo-probe NMR spectroscopy. Chiralities were established by comparison of experimental NMR shifts and CD spectra with results from DFT calculations.⁵⁷⁵ Syntheses of plocamenone and isoplocamenone have confirmed their structures⁵⁷⁶ and established their absolute configurations.⁵⁷⁷ Total syntheses of the proposed structures of microcladallenes A, B and C⁵⁷⁸ confirmed the structures of A and B but indicated that microcladallene C could not be correct.⁵⁷⁹ Additional studies on bis(2,3-dibromo-4,5-dihydroxyphenyl)-methane (*Rhodomela larix*)⁵⁸⁰ and bis(2,3-dibromo-4,5-dihydroxybenzyl) ether (*Odonthalia corymbifera*)⁵⁸¹ have revealed significant activities in a range of assays, all indicating the potential of these compounds for development as anticancer agents.^{582–584} Studies on eight brominated indoles from *Laurencia brongniatii*⁵⁸⁵ have revealed that some of them constitute a new class of relatively potent naturally occurring aryl hydrocarbon receptor (AhR) agonists.⁵⁸⁶

7 Sponges

The number of new sponge-derived metabolites described in 2015 (291) has remained relatively static when compared to previous years, with terpenoid compounds (130) being particularly dominant in number. A variety of ceramides **804–806**,⁵⁸⁷ cerebrosides **807–815** (ref. 588) and **816–833**,⁵⁸⁹ and lysosphingolipids **834** and **835** (ref. 590) were reported from *Spheciospongia vagabunda*, *Aulosaccus* sp. and *Spirastrella purpurea*, respectively, while the genera *Biemna*, *Callyspongia*, *Haliclona* and *Xestospongia* yielded taurinated **836**,⁵⁹¹ polyunsaturated **837–839**,⁵⁹² **840** (ref. 593) and brominated **841** (ref. 594) fatty acids. *Stelletta* sp. provided six new glycosidated fatty acids stellettoside A1–B4 **842–847**. The structures of these *N,N*-dimethylputrescine-derivatives were established using a combination of advanced spectroscopic and degradative studies. The mixture of **842** and **843** was inactive against HeLa cells yet the mixture of **844–847** was cytotoxic (IC₅₀ 9 μM).⁵⁹⁵

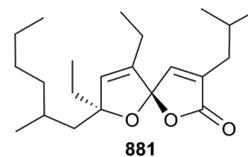
Polyacetylenes were found in extracts of *Callyspongia implexa* **848**,⁵⁹⁶ *Petrosia* sp. **849–851**,⁵⁹⁷ *Halichondria* sp. **852–854**,⁵⁹⁷ *Pleroma* sp. **855–861**,⁵⁹⁸ and *Xestospongia* sp. **862** and **863**.⁵⁹⁹ The nanomolar-scale isolation of mollenynes B–E **864–867** from



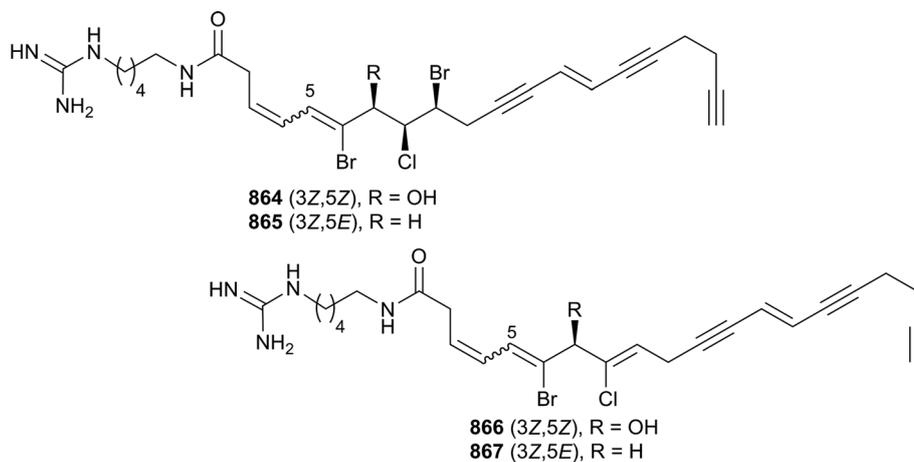


Spirastrella mollis posed several challenges. First, the extremely low yields of isolated compound imposed limitations on acquiring usable NMR spectra, and second, unequivocal placement of the chlorine and bromine atoms upon the carbon backbone was difficult due to the similarity in ^{13}C chemical shifts. The former issue was resolved by use of a cryogenically-cooled NMR microprobe while the latter exploited a new band-selective HSQC experiment for enhanced resolution by only detecting a small region of the ^{13}C dimension. This facilitated the observation of the $^{35}Cl/^{37}Cl$ isotopic effect that causes a splitting of a chlorinated ^{13}C resonance of around 1 Hz. The biosynthesis of these compounds could involve an unusual “dyotropic shift” of Cl and Br atoms, which would also account for the observed inversion of configurations within the series.⁶⁰⁰

contained spiroplakortone **881**. This modestly cytotoxic compound (IC_{50} 37.5 μM against L5178Y mouse lymphoma) has an unprecedented spirocyclic core ring system and it suggested that it is formed *via* a hybrid polyketide/amino acid biosynthetic pathway. The structure of **881** was solved by a comprehensive combination of spectroscopic and computational studies to establish the configuration of the spiro-center.⁶⁰⁶



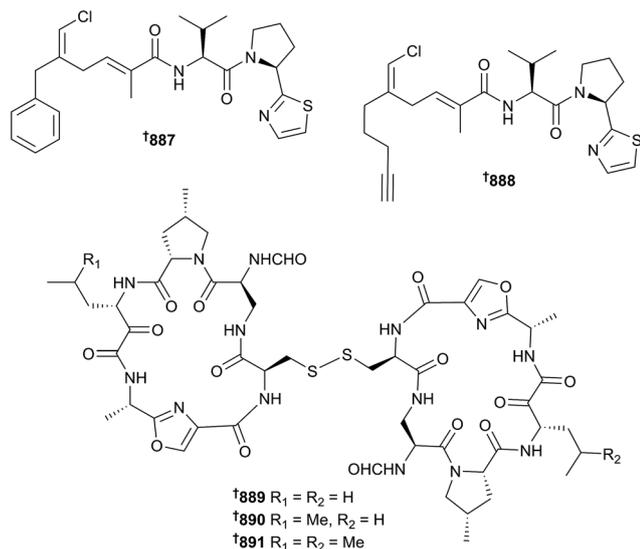
An unidentified sponge yielded two aromatic bases **882** and **883**,⁶⁰⁷ while a mixture of Thoretid and Verongid sponges was the source of a new isoascorbic acid derivative **884**, although this was speculated to be of fungal origin.⁶⁰⁸ *Euryspongia* sp. from Okinawa yielded eurydiene **885** (ref. 609) while an Australian *Drarmacidon* sponge contained triphenyl **886**.⁶¹⁰ Smenothiazoles A **887** and B **888** are two chlorinated thiazoles isolated from *Smenospongia aurea* (Little Inagua, Bahamas). These metabolites are of mixed PKS/NRPS origin that bears significant resemblance to the cyanobacterial compound jamaicamide B.⁴⁷² Both compounds showed *in vitro* inhibition of four solid HTCLs in the 1–100 nM range, and could selectively induce apoptosis in some cell lines *via* cell cycle blockage in the G_0G_1 phase.⁶¹¹



The known fungal metabolites gibepyrone C **868** and F **869** (ref. 601) were isolated from the marine environment for the first time.⁶⁰² Sponges of the *Plakortis* genus are well known producers of methyl and ethyl branched polyketide peroxides. Studies of *P. angulospiculatus* **870–872**,⁶⁰³ *Plakortis* sp. **873–875** (ref. 604) and *P. bergquistae* **876–880** (ref. 605) were reported in 2015. Of note was the investigation of *P. simplex* which

A surprisingly small number of peptides and depsipeptides were reported in 2015, given sponges are normally prolific reservoirs of such compounds. The α -ketoleucine or α -ketonorvaline-containing dimeric cyclopentapeptides nazumazoles A–C **889–891** (*Theonella swinhoei*) were detected as an exceedingly broad peak using ODS-HPLC and were isolated as an inseparable mixture. A significant number of degradative





experiments were used to establish the dimeric structures, each joined through a single disulfide linkage. The mixture was cytotoxic to the P388 cell line (IC₅₀ 0.86 μM).⁶¹² Four collections of *Callyspongia aerizusa* from three different locations in Indonesia were sources of callyaerins I–M **892**, **893**, **894**, **895** and **896**. These new congeners were inactive against both *M. tuberculosis* and two HTCLs, even though related compounds were active in low μM concentrations, providing intriguing SAR. The re-isolation of callyaerins D **897**, F **898** and G **899**,^{613,614} previously isolated in vanishingly small quantities, allowed for complete structural elucidation which necessitated structural revisions as shown.⁶¹⁵

Stelletapeptins A **900** and B **901** are hybrid NRPS/PKS decapeptides isolated from *Stelletta* sp. Structures were established using a combination of degradation studies and comprehensive NMR experiments. Both exhibited anti-HIV activity in HIV_{RF}-infected human T-lymphoblastoid cells with EC₅₀'s of 23 and 27 nM, respectively, with cytotoxicity vs. the parent cell lines only observed at 367 and 373 nM, giving a large degree of selectivity.^{616,617} Macrolides were significantly reduced in numbers with just one report in 2015. Phormidolides B **902** and C **903** were isolated from a Petrosidae sponge (Pemba, Tanzania). Difficulties in assigning the relative configuration around the macrolide core necessitated the synthesis of three diastereomers of the lactone ring as a change in only one centre completely altered the NMR data for the entire ring system. Both compounds were cytotoxic to three HTCLs in the μM range.⁶¹⁸ *Hemimycala arabica* and *Acanthella cavernosa* were sources of hemimycalins **904** and **905** (ref. 619) and diketopiperazines **906** and **907**.⁶²⁰

Both enantiomers **908** and **909** of spirocyclic spirorotulactone were isolated from *Fascaplysinopsis*. X-ray studies suggested the presence of a racemate, prompting the researchers to separate the compounds *via* chiral chromatography. The absolute configuration of each stereoisomer was

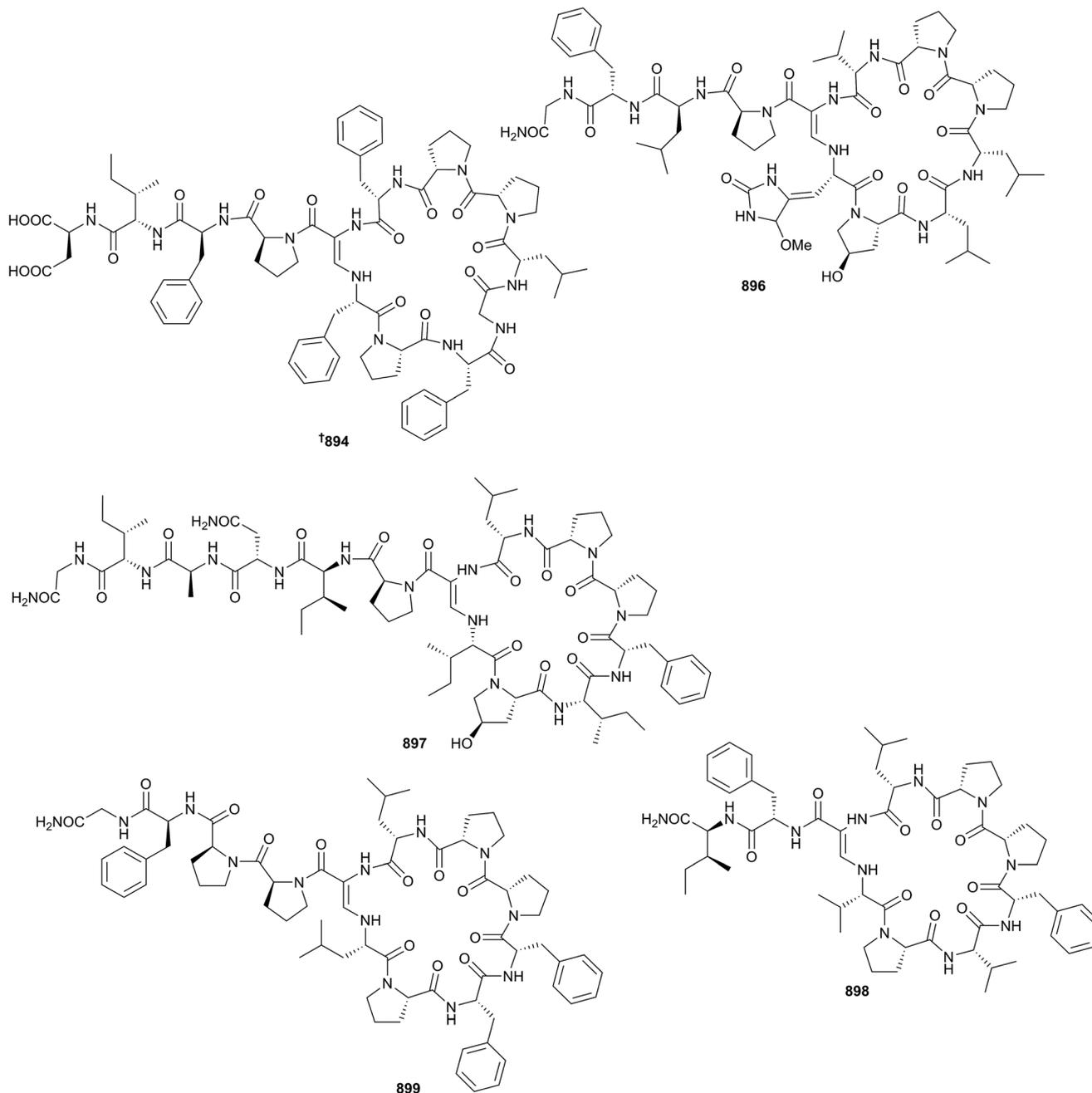
determined by comparison of calculated and experimental ECD spectra. While both compounds inhibited IL-2 production at 15 μM , the dextrorotatory isomer was much more active than the levorotatory, while neither was cytotoxic at 50 μM vs. four HTCLs. A plausible biogenesis from tryptophan, glyoxal and dimethyl urea was proposed.⁶²¹

Three diamine-type alkaloids **910–912** were isolated from Indonesian *Neopetrosia*⁶²² and *Acanthostrongylophora*⁶²³ sponges, while a *Neopetrosia* sp. also yielded two nucleosides **913** and **914**, one of which was also synthesised.⁶²⁴ Indole alkaloids were isolated from *Ircinia* **915** and **916**,⁶²⁵ *Plakortis* **917** and **918** (ref. 626) and *Spongia* **919** and **920** (ref. 627) sponges. An *Aaptos* sponge yielded three aaptamine alkaloids **921–923**.⁶²⁸ A *Biemna* sp. was the source of two pyridoacridines *N*-hydroxymethylisocystodamine **924** and neolabuanine **925**. The structure assigned to **925** had previously been incorrectly attributed to labuanine A;⁶²⁹ the current study determined that this isolate was in fact ecionine A.⁶³⁰ Both compounds induced similar levels of cellular differentiation of human leukaemia tumour cells to normal erythrocytes at similar levels (ng mL⁻¹) to doxorubicin.⁶³¹

Guanidine-type alkaloids have been isolated from *Biemna laboutei* **926–930**,⁶³² *Pseudoaxinella reticulata* **931–934**,⁶³³ *Monanchora arbuscula* **935–940** (the synthesis of **935** was also achieved),⁶³⁴ and *M. pulchra* **941–943**,⁶³⁵ while oroidin-type pyrrolo-alkaloids were sourced from the genera *Stylissa* **944** and **945** (ref. 636) and *Agelas* **946** (synthesis also completed),⁶³⁷ **947** and **948**,⁶³⁸ **949–951**,⁶³⁹ **952–956**.⁶⁴⁰ A series of bromotyrosine-derived compounds were reported from a member of the Verongida **957** and **958**,⁶⁴¹ *Pseudoceratina arabica* **959–961**,⁶⁴² *P. purpurea* **962** and **963**,⁶⁴³ *Acanthodendrilla* sp. **964**,⁶⁴⁴ *Suberea* sp. **965–967** (ref. 645) and *Aplysina lacunosa* **968–970**.⁶⁴⁶ As always, prenylated metabolites dominate the compounds reported from sponges. Isolated meroterpenoids include **971–976**,⁶⁴⁷ **977–984**,⁶⁴⁸ and **985–987** (ref. 649) from *Dysidea* sponges. A novel approach was taken to promote the production of several “natural products”. Homogenised *Verongula rigida*, a sponge with known potent oxidative potential, was added to homogenised *Smenospongia aurea* and *S. cerebriformis* and incubated in ethanol for one week. LC-MS guided isolation of the *Smenospongia* extracts yielded several new 4,9-friedodrimane meroterpenoids **988–995**. Whilst **992–995** are likely artefacts of the ethanol incubation, the other new compounds are all likely true biochemically-produced metabolites. The fused iminoquinone moiety of **990** and **991** is unprecedented in known natural products. Compounds **989–991** and **995** were moderately cytotoxic to two HTCLs.⁶⁵⁰ Puupehenol **996** (*Dactylospongia* sp.) exhibited pronounced anti-inflammatory activity. The known compound puupehenone⁶⁵¹ was also isolated. Exposing **996** to mild acid (CDCl₃) at slightly elevated temperatures (30 °C) resulted in quantitative conversion of puupehenol to puupehenone, suggesting the latter is actually an artefact of isolation.⁶⁵²

A series of adociaquinone compounds **997–1002** was reported from an Indonesian *Xestospongia* sp.,⁶⁵³ while meroditerpenoids **1003–1005**,⁶⁵⁴ **1006**,⁶⁵⁵ **1007** and **1008** (ref. 656) were isolated from *Agelas nakamurai*, *Strongylophora strongylata*,



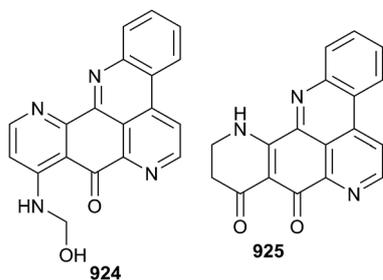
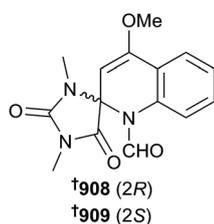
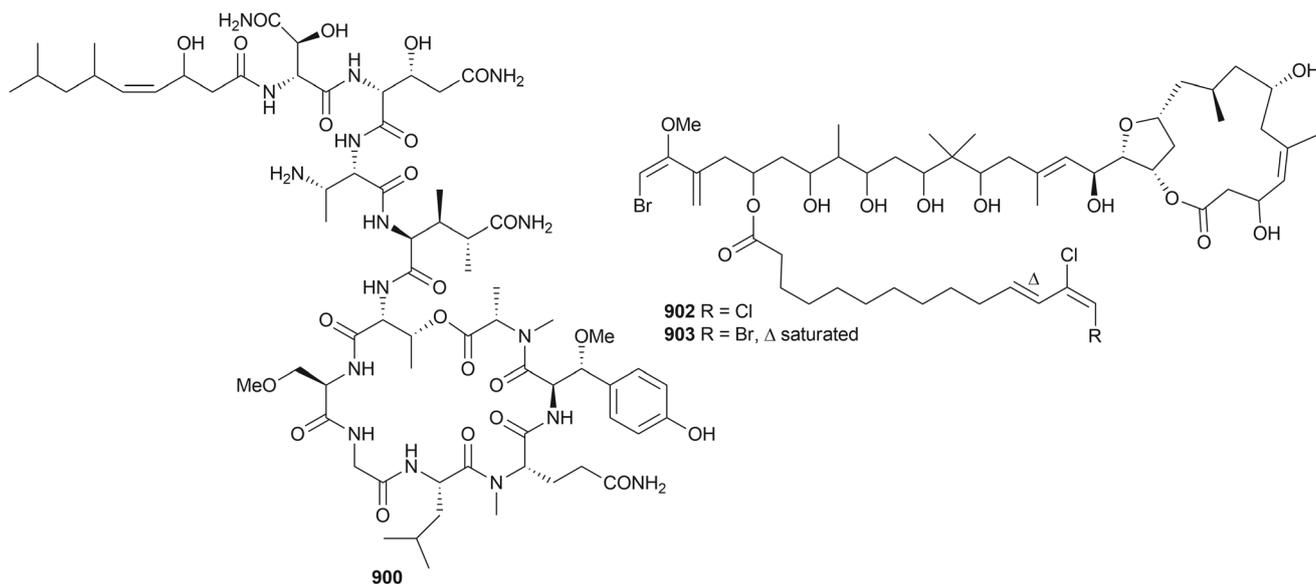


and *Petrosia cortica* respectively. Sesquiterpenoids **1009** and **1010**,⁶⁵⁷ and **1011–1013** (ref. 658) were isolated from *Dysidea fragilis* and **1014–1018** from *Halichondria* sp.,⁶⁵⁹ while three farnesylacetone derivatives **1019–1021** were reported from *Diacarnus megaspinorhabdosa*.⁶⁶⁰ *Niphates* and an unidentified Dictyoceratid sponge were the sources of **1022** (ref. 661) and **1023–1025**,⁶⁶² respectively. Monamphilectines B **1026** and C **1027** are potent antimalarial β -lactams (IC₅₀ 44.5 and 43.3 nM vs. *P. falciparum*, respectively) isolated from *Svenzea flava* and were both synthesised from a known diisocyanide.⁶⁶³

Investigation of *Hamigera tarangaensis* revealed a series of brominated nitrogenous hamigeran diterpenoids **1028–1036**. All incorporated an amino acid as part of the nitrogen

heterocycle although stereochemical arguments required the inclusion of *allo*-isoleucine in **1035** and **1036** implying the intriguing possibility of a joint sponge/prokaryotic biogenesis.⁶⁶⁴ Sponges remain prolific producers of sesterterpenoids. Sarcotragin C **1037** was isolated from *Sarcotragus* sp.⁶⁶⁵ while a manoalide congener **1038** and several luffalides **1039–1044** came from *Luffariella variabilis*⁶⁶⁶ and *Luffariella* sp.,⁶⁶⁷ respectively. Two suvanine sesterterpenoid salts **1045** and **1046** were found from *Coscinoderma* sp.⁶⁶⁸ A large number of scalaranes **1047–1051**,⁶⁶⁹ **1052** and **1053**,⁶⁷⁰ **1054–1058**,⁶⁷¹ **1059** and **1060**,⁶⁷² **1061–1071**,⁶⁷³ **1072** and **1073** (ref. 674) were reported from five different sponge genera, *Carteriospongia*, *Hyattella*, *Ircinia*, *Phyllospongia* and *Spongia* respectively. Other new



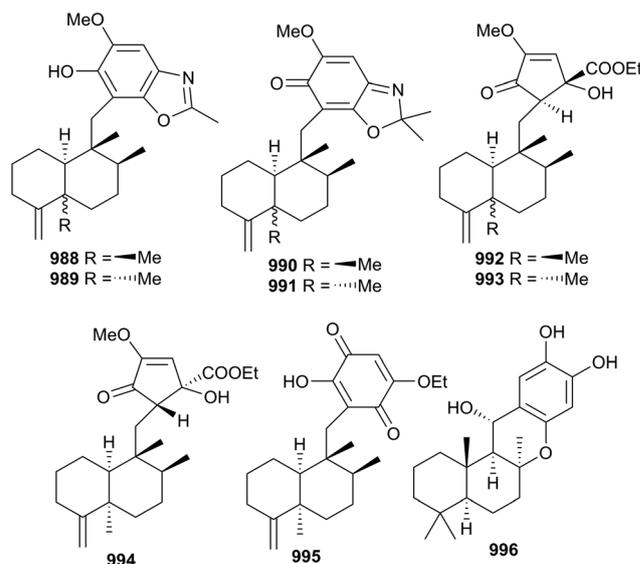


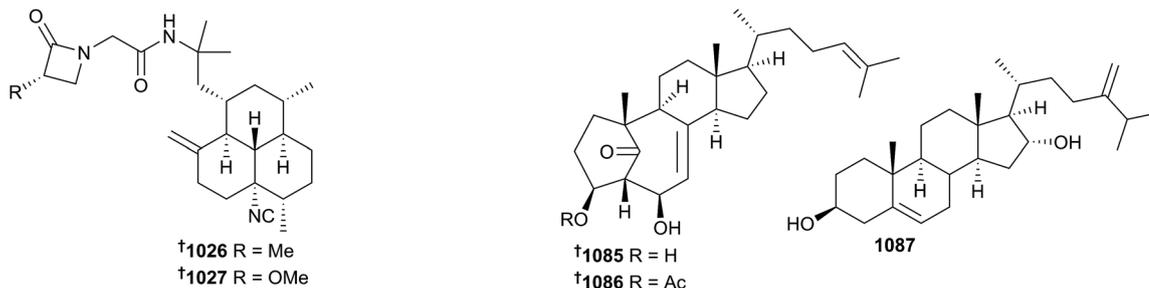
sesterterpenoids were **1074** and **1075** (*Clathria gombawuiensis*)⁶⁷⁵ and **1076** (*Haliclona* sp.) sourced from Korean collections.⁶⁷⁶

Several new sterols and their degradation products have also been reported from sponges. Epoxide-**1077** and peroxide-**1078–1079** containing sterols were found from *Biemna*⁵⁹³ and *Monanchora*⁶⁷⁷ sponges, respectively, while highly derivatized sterols were isolated from *Dragmacidon australe* **1081** (ref. 610) and *Polymastia boletiformis* **1082** and **1083**.⁶⁷⁸ A new 9,11-secosterol **1084** came from a Korean *Ircinia* sp.⁶⁷⁹ The first naturally occurring bicyclo[4,3,1]-A/B ring system steroids, monanchosterol A **1085** and B **1086**, were isolated along with a third sterol **1087** from *Monanchora* sp. (Gageo Is., Korea). The biogenesis of the ring-contracted compounds was suggested to begin from a common

4 β ,5 β -epoxysterol. The only other report of such a ring system is from a synthetic study published by Barton in the 1980s.⁶⁸⁰ While **1085** was toxic to RAW264.7 cells (IC₅₀ 65 μ M), both **1086** and **1087** were not, but instead were immunomodulatory inhibiting mRNA expression of IL-6 by \sim 70% at 10 μ M even though monanchosterols A and B only differ by a single acetylation.⁶⁸¹

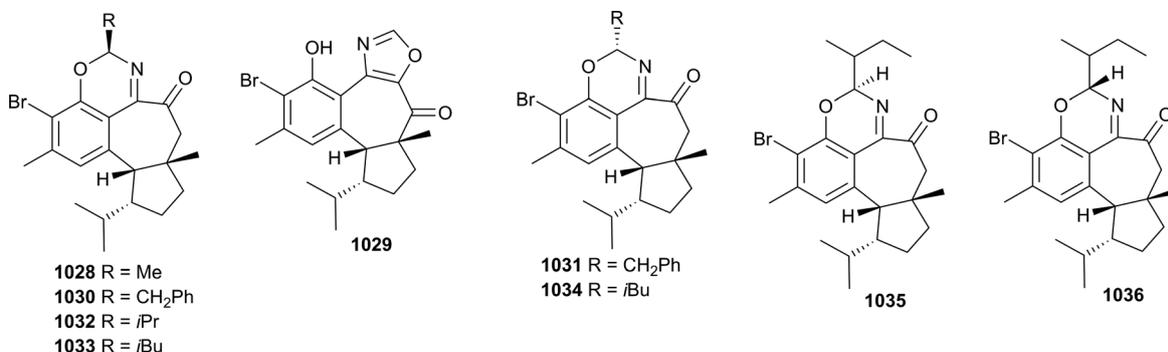
A nortriterpenoid-saponin **1088**,⁶⁷⁵ and nine other triterpenoids **1089–1096** (ref. 682) and **1097** (ref. 683) were reported in 2015. Additionally, the new compounds stelletins N–P **1098–1100** were isolated from *Stelletta tenuis*⁶⁰² although the name stellettin N had been used previously for a different structure.⁶⁸⁴ The





absolute configuration of psammalyisin A **1101** (ref. 685) (isolated in the current study from *Aplysinella strongylata*) was established from detailed comparison of calculated and experimental ECD data in conjunction with NMR studies including Mosher's analysis,⁶⁸⁶ while the absolute configuration of eurypongins A **1102** (*Eurypongia* sp.) was also determined using chiroptical techniques.⁶⁸⁹ Inconsistencies in NMR data reported for two sponge sterols isolated from *Neofibularia nolitangeri*⁶⁸⁷ with those isolated from Japanese edible mushrooms necessitated structural revision to **1103** and **1104**.⁶⁸⁸ Hepatitis B infection poses a major human health risk. Two sponge-derived polybrominated biphenyls^{689,690} isolated from Indonesian *Dysidea* species were found to possess hepatitis antiviral activity with selectivity indices of 12.8–18.2.⁶⁹¹ Transcriptomic analysis of HepG2 hepatocarcinoma cells treated with both *Crambe crambe* metabolites crambescins C1 (ref. 692) and A1 (ref. 693) showed that the former protects against cytotoxic oxidative damage by induction of metallothionein, while the latter is ineffective.⁶⁹⁴ The bastadin-class of bromotyrosine compounds, in particular bastadin-6,⁶⁹⁵ suppress foam formation in macrophages *via* inhibition of cholesterol-ester formation, and may have application in the treatment of atherosclerosis.⁶⁹⁶ Panicein A hydroquinone⁶⁹⁷ (*Haliclona mucosa*) inhibits the efflux of doxorubicin by the Hedgehog receptor Patched and enhances the anticancer efficacy of the drug.⁶⁹⁸ A hypothesis put forward over a decade ago that marine isonitriles and isothiocyanates may exert the antiplasmodial activity *via* interference of heme detoxification⁶⁹⁹ has been corroborated. The mode of action of these compounds was assessed using a scaled-down version of Egan's β -hematin assay demonstrating that marine isonitriles inhibit β -

hematin crystallisation and supported by *ab initio* calculations of the stability of the isonitrile complexes bound to iron in heme.⁷⁰⁰ Gracilins A, H and L^{701,702} along with tetrahydroaplysulphurin-1,⁷⁰³ all isolated from *Spongionella* sp., were found to modulate mitochondrial function in neuroblastoma cells by regulating storage of calcium entry in a similar manner to cyclosporine A *via* binding to cyclophilin D.⁷⁰⁴ Okadaic acid (OA), a potent marine cytotoxin that inhibits protein phosphatases, was originally isolated from *Halichondria okadai* but later identified as being produced by the dinoflagellate *Prorocentrum lima* and actively bioaccumulated by the sponge.⁷⁰⁵ The role and mechanism of OA accumulation by *Halichondria* has not yet been established. Exposure of an extract of *H. okadai* to OA indicated strong binding to two proteins, OA Binding Proteins (OABP) 1 and 2. While unsurprisingly OABP1 is a protein phosphatase, OABP2 is not. The X-ray crystal structure of OABP2.1 obtained from *H. Okadai* bound to OA showed that it has significant binding affinity for OA and has a limited homology to known protein scaffolds. Surprisingly, the global fold of OABP2.1 was most similar to the jellyfish Ca²⁺-binding photoprotein aequorin. Ca²⁺ does not displace OA from its binding site, suggesting a different mechanism for OA release by the sponge.⁷⁰⁶ A comprehensive LCMS analysis of 253 *Aplysina* sponges comprising ten different morphologies showed that the sponge secondary metabolome correlates better with the sponge phenotype, described by invertebrate morphology, rather than the microbiome.⁷⁰⁷ The ability of 26 sponges to inhibit bacterial quorum-sensing without cytotoxic activity was investigated. The extract of *Ircinia felix* was found to be the most potent inhibitor of

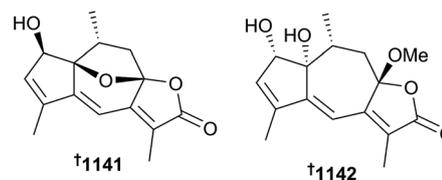


quorum-sensing with the activity linked to the felixinin furanosesquiterpenoid class.^{708–710} Chemical examination of adult and bud larvae of the chemically-defended sponge *Tethya maza* indicated that the sterol composition of both were largely similar, suggesting that the larvae are also defended during reproduction.⁷¹¹ First total syntheses were reported for many compounds including the lipids motualevic acid F, (*E*)- and (*Z*)-antazirine,^{712–714} mycalol (revised to **1105**)^{715–717} and myrmekioside A,^{718,719} and polyacetylenes callispongynic acid,^{720,721} phosphiodyn A and placotylenes A.^{722–725} The structure of plakinidone has been corrected to **1106**; the compound is highly sensitive to air oxidation. The compound's relative configuration was also determined,^{726,727} while the relative configuration of the C-36 to C-42 portion of hemicalide **1107** was also solved by synthesis.^{728,729} Total syntheses of polyketides gracilioether B and C^{730,731} and hippolachnin,^{732,733} mycothiazole,^{734–736} aromatic renieramycin I,^{737,738} and peptides cyclocinamide A,⁷³⁹ corticiamide B,^{740–742} stylissamide X^{743,744} and stylissatin A^{745,746} have all been realised. The total synthesis of yaku'amide A **1108**, including eight possible stereoisomers of its core region, required revision of structure, and also that of congener B **1109**.^{747,748} Macrolides are attractive targets for synthesis with the construction of tulearin A,^{749,750} mycalolide B,^{751,752} and muironolide A **1110** being completed, the latter requiring a structural revision.^{753,754} Pyridines nakinadine D–F,^{755,756} indoles scalaridine A,^{757,758} dragmacidin D **1111**,^{759–761} dendridine A,^{762,763} and guanidine batzelladine B^{764,765} are alkaloid compounds that have all been synthesised. Although the stereoselective synthesis of palau'amine has been achieved before,⁷⁶⁶ the construction of the ABDE tetracyclic core in one cascade step is a very significant improvement in the production of this important marine metabolite.⁷⁶⁷ Clavatadine A,^{768,769} aplysinellamides A and B,^{770,771} and 11-deoxyfistularin-3 (ref. 772 and 773) were synthesised for the first time. Meroterpenoids that had initial total syntheses are panicein A,^{774,775} dictyoceratins A⁷⁷⁶ and C,^{777–779} and neopetrosiquinones A and B.^{780,781} The structure of siphondictyal B⁷⁸² has been revised to **1112**, based upon total synthesis. The biomimetic conversion of siphondictyal B to liphagal⁷⁸³ via a stable *o*-quinone methide supports a novel biogenetic proposal.⁷⁸⁴ The sesquiterpenoids aignopsanoic acid A, methyl aignopsanoate and isoaignopsanoic acid A⁷⁸⁵ have been synthesised, with absolute configurations and that of the related compound microcionin-1 **1113** (ref. 786) established.⁷⁸⁷ Several diterpenoids have succumbed to total synthesis: *viz.* spongio-lactone^{788,789} debromohamigeran E,^{790,791} and kalihinol B.^{792,793} While the racemic synthesis of ambliol A had earlier been achieved,^{794,795} the first enantioselective synthesis has established the absolute configuration as **1114**.⁷⁹⁶ The total syntheses of the ses-terterpenoids phorbin A,^{797,798} luffarins L and I,^{799–801} salmahyrtisol A⁸⁰² and hippospongide A^{803,804} have been finalised.

8 Cnidarians

The low number of new compounds reported from cnidarians in 2015 (143) is 40% below the previous decadal average. The chemistry of cnidarians is typically dominated by compounds of terpenoid origin. In 2015 there were a limited number of alkaloids isolated from both soft and hard corals, including the anxiolytic

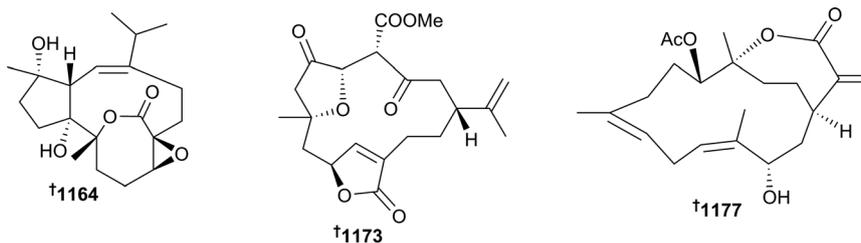
ceramide **1115** (*Sarcophyton auritum*),⁸⁰⁵ the diaminopropyl analogue **1116** (*Paraplexaura* sp.),⁸⁰⁶ and new examples of zoanthenamines **1117–1123** from the hard coral *Zoanthus kuroshio*.⁸⁰⁷ The simple cinnamate ester **1124** was isolated from *Sarcophyton ehrenbergi* and the structure confirmed and absolute configuration assigned by stereoselective synthesis.⁸⁰⁸ A series of seventeen sesquiterpenes were reported, comprised of a himachalene-type peroxide **1125** (*Litophyton arboretum*),⁸⁰⁹ cyclopentenones **1126** (*Sinularia sandensis*)⁸¹⁰ and **1127** and **1128** (*Sinularia acuta*),⁸¹¹ eudesmane-type **1129** (*Sinularia gaweli*),⁸¹² subergane-type **1130** (*Subergorgia suberosa*),⁸¹³ monocyclic and bicyclic germacrenes **1131** (*Sarcophyton glaucum*)⁸¹⁴ and **1132** and **1133** (*Capnella* sp.),⁸¹⁵ caryophyllanes **1134** and **1135** (*Rumphella antipathies*),⁸¹⁶ and guaiane lactones **1136–1140** (*Menella kanisa*)⁸¹⁷ and **1141** and **1142** (*Menella woodin*).⁸¹⁸ Of note was the use of a diverse array of computational techniques, including calculated ¹³C NMR chemical shifts, optical rotation and ECD to determine the structures and absolute configurations of **1141** and **1142**.



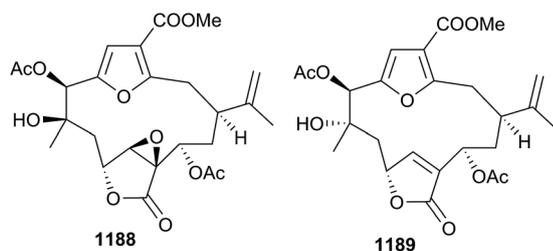
Of four tocopherol-derived metabolites **1143** and **1144** (ref. 819) and **1145** and **1146**,⁸²⁰ hirsutocospiro A **1143** exhibited strong anti-inflammatory activity and cladophenol glycosides A **1145** and B **1146** exhibited mild cytotoxicity towards three HTCLs. Thirty-one cembrane-related metabolites reported from cnidarians in 2015 included **1147** (*Sarcophyton glaucum*),⁸¹⁴ epoxynephthenols **1148–1150** (field-collected *Nephtea colum-naris*),⁸²¹ columnariols A **1151** and B **1152** (cultured *N. colum-naris*),⁸²² sarcophine and ehrenbergol congeners **1153–1157** (*Sarcophyton ehrenbergi*),⁸²³ *cis*-cyclopropylated casbanes sinularcasbane G–L **1158–1163** (*Sinularia* sp.),⁸²⁴ sarcophelegans A–D **1164–1167** (*Sarcophyton elegans*),⁸²⁵ tricyclic **1168** (*Sarcophyton solidum*),⁸²⁶ pyrans **1169** and **1170** (*Sarcophyton trocheliophorum*)⁸²⁷ and **1171** (*Litophyton arboretum*),⁸⁰⁹ hydroperoxycembranoid **1172** (*Sarcophyton trocheliophorum*),⁸²⁸ and **1173–1177** (*Sinularia sandensis* and *S. flexibilis*).⁸²⁹ X-ray studies were used to determine the complete structural and stereochemical characterization of sarcophelegan A **1164**,⁸²⁵ cembranoid **1173** and isosinulaflexiolide K **1177**.⁸²⁹ X-ray studies were also used to confirm the structures and configuration of previously reported cembranoids sarsolilide B (*Sarcophyton trocheliophorum*)^{826,830} pukalide (*Leptogorgia alba*)⁸³¹ and dendronpholide F (*Dendronephthya* sp.)^{829,832} The trivial name epoxynephthenol assigned to **1150** (ref. 821) has been used previously.⁸³³

A series of nitrogenous diterpenoids and sesquiterpenoids **1178–1187** were reported from *Cespitularia taeniata* – the absolute configuration of cespilamide A **1178** was established by a combination of MM2 modeling and Mosher's analysis.⁸³⁴

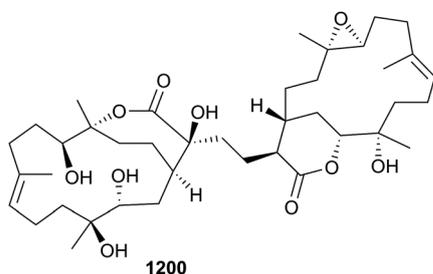




Rare examples of cembranoid 7,8-diols **1188** and **1189** were isolated from *Sinularia gaweli*.⁸¹² The structure assigned **1188** is the (–)-enantiomer of the known cembranoid leptodiol acetate (*Leptogorgia* sp.),⁸³⁵ while **1189** was found to be a potent inhibitor of pro-inflammatory iNOS production in LPS-stimulated murine macrophages.

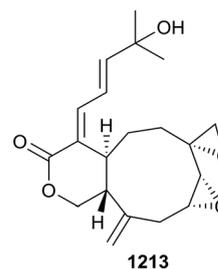


Norcembranoids **1190** and **1191** (*Sinularia numerosa*)⁸³⁶ were unfortunately given the trivial names sinumerolide A and (7*E*)-sinumerolide A, names previously attributed to cembranoids reported from the same organism.⁸³⁷ From a structural point of view, the metabolites are simply methyl ether variants of the previously reported ethyl ether leptocladolide A and its (7*E*) isomer.⁸³⁸ A mildly cytotoxic norcembranoid **1192** was isolated from cultured specimens of *S. numerosa*.⁸³⁹ Six α -methylene- γ -lactone cembranoids **1193–1198**, epoxide **1199** and bis-cembranoid sinulaflexiolide L **1200** were reported from *Sinularia flexibilis*.⁸⁴⁰ The structure and relative configuration of **1200** and absolute configuration of known co-metabolite sinulflexolide⁸⁴¹ were secured by X-ray studies.



Cytotoxic and anti-inflammatory bis-cembranoids glaucumolide A **1201** and B **1202** were isolated from cultured specimens of *Sarcophyton glaucum*,⁸⁴² while of sarcophytolides M **1203** and N **1204**, only the former exhibited cytotoxicity to a panel of HTCLs.⁸⁴³ Eight new briarane-skeletoned diterpenes were reported in 2015 (briarenolides K **1205**, L **1206** (ref. 844)

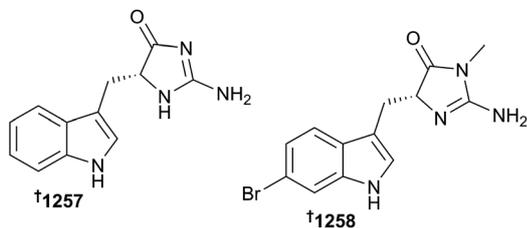
and U–Y **1207–1211**,⁸⁴⁵ *Briareum* sp.; dichotellide V **1212**,⁸⁴⁶ *Dichotella gemmacea*). All the briarenolides were found to inhibit production of the pro-inflammatory inducible nitric oxide synthase (iNOS), while briarenolides U–Y also inhibited the product of COX-2 in LPS-stimulated macrophage cells. Of the remaining nine diterpenes, three were xenicanes (**1213–1215**, unnamed, *Xenia* sp.),⁸⁴⁷ and six were eunicellins (**1216** and **1217**,⁸⁴⁸ *Muricella sibogae*; **1218–1221**,⁸⁴⁹ *Cladiella hirsuta*). Of note was that the structure of **1213** was secured by X-ray studies.



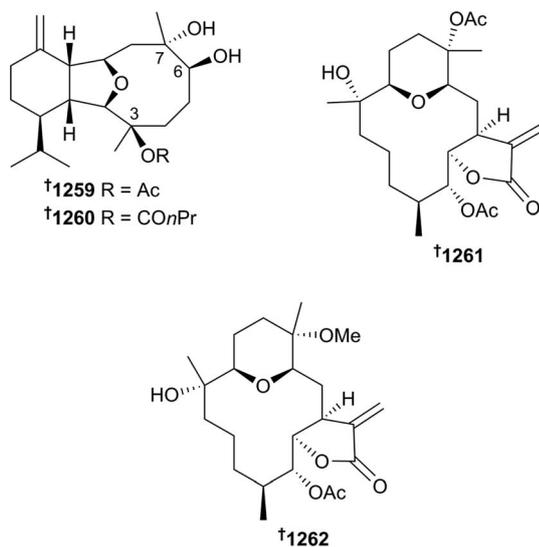
From the cnidarians a variety of steroids were isolated that included pregnane glycosides (**1222** and **1223**, *Cladiella hirsuta*),⁸²⁰ *seco*-sterols (**1224–1229**, *Subergorgia suberosa*)⁸⁵⁰ a *seco*-ketosterol hydroperoxide **1230** (*Litophyton arboretum*),⁸⁰⁹ ketosterols (**1231–1233**, *Subergorgia rubra*),⁸⁵¹ hydroxylated/polyhydroxylated sterols (**1234–1237**, *Sinularia acuta*);⁸¹¹ **1238–1243**, *Palythoa tuberculosa*;⁸⁵² **1244–1249** and known **1250**, *Klyxum flaccidum*;⁸⁵³ **1251–1254**, *Menella woodin*;⁸⁵⁴ **1255**, *Dichotella gemmacea*⁸⁵⁵) and a steroidal glycoside (**1256**, *Sinularia nanolobata*).⁸²⁰ The C-24 configuration of **1250** was corrected by comparison with related MNPs. Investigation of MNP chemistry of sea anemones has identified two new imidazolones **1257** and **1258** from the sea anemone *Heteractis aurora*.⁸⁵⁶ Absolute configurations were assigned by stereoselective synthesis of the corresponding enantiomers, with the magnitudes of optical rotation observed indicating the natural products had been isolated as scalemic (partially racemic) mixtures. Further studies of toxins from anemones has revealed two new examples of HCRG polypeptides (>6 kDa) from *Heteractis crispa*,⁸⁵⁷ the toxicity of the α -pore-forming toxin equinatoxin II depends upon its ability to assemble into oligomers on the cell surface,⁸⁵⁸ while *N*-terminus modified analogues of the 35-residue disulfide-rich toxin ShK from *Stichodactyla helianthus* showed enhanced selectivity towards voltage-gated potassium channel Kv1.3 *versus* other subtypes, making them of clinical interest for the treatment of autoimmune diseases.^{859,860} A comprehensive sequence



alignment study of cnidarian toxins suggests a common origin of sodium channel and a subtype of potassium channel toxins in sea anemones and that pore-forming toxins have evolved under strong evolutionary constraints.⁸⁶¹

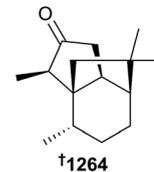


As noted in last year's review,¹ clarification of the structures of cladiellin diterpenes including the sclerophytins (*Sclerophyllum capitalis*)⁸⁶² is an ongoing issue. Based upon re-analysis of NMR data Friedrich and Paquette in 2002 proposed a number of structural revisions.⁸⁶³ Synthesis of the purported structure of sclerophytin F as well as three diastereomers, combined with re-examination of published NMR data, has led to the conclusion that sclerophytins E and F are in fact the same compound **1259**.⁸⁶⁴ The study concluded that all sclerophytins share the sclerophytin A skeleton with variation of acylation at the C-3 and C-6 positions and that the C-3 configuration inversions proposed by Friedrich and Paquette are incorrect. The structure of lithophytin E (*Litophyton* sp.)⁸⁶⁵ should be corrected to the C-7 epimer **1260**. The structures and absolute configurations of (+)-uprolide F diacetate **1261** and (+)-uprolide G acetate **1262** (*Eunicea mammosa*)⁸⁶⁶ have been revised (again)⁸⁶⁷ and confirmed by total synthesis.^{868,869}



A stereodivergent synthesis of four diastereomers has established the structure and absolute configuration of solandelactone I (*Solanderia secunda*)⁸⁷⁰ to be **1263**,⁸⁷¹ while total synthesis of the enantiomer has led to correction of absolute configuration of (–)-suberosanone (*Isis hippuris*)⁸⁷² to **1264**.⁸⁷³ The structures of clavulolactones II and III⁸⁷⁴ (*Clavularia*

viridis),⁸⁷⁵ tubastrine⁸⁷⁶ (*Tubastrea aurea*)⁸⁷⁷ as well as ascidians^{878,879}) and breitfussin A and B^{880,881} (*Thuiaria breitfussi*)⁸⁸² have been confirmed by total synthesis.



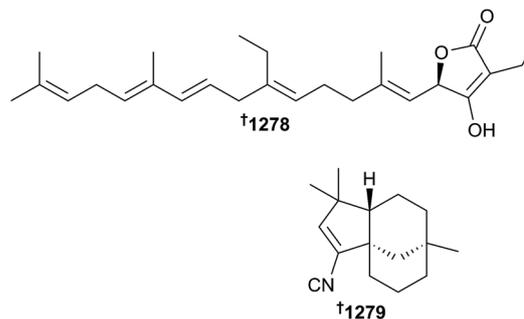
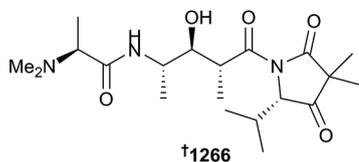
Further biological studies of lipids and sterols from *Eunicea fusca* and *Eunicea* sp. have identified some to exhibit anti-biofilm action in the absence of antimicrobial effects,⁸⁸³ alcyonolide-type diterpenes (*Cespitularia* sp.) exhibit cytotoxicity towards HCT-116 cells *via* induction of caspase 3/7 activity and suppress pro-inflammatory iNOS and COX-2 gene expression,⁸⁸⁴ cembranoids exhibit peroxisome proliferator-activated receptor transactivational effects,⁸⁸⁵ antiprotozoal activities,⁸⁸⁶ anti-osteoporotic and antioxidant activities,⁸⁸⁷ hepatocellular carcinoma cell migration and invasion,⁸⁸⁸ and antiproliferative activity through activation of the transforming growth factor-beta (TGF- β) pathway.⁸⁸⁹ Excavatulide B, a briarane diterpenoid originally isolated from *Briareum excavatum*, exhibits anti-inflammatory and analgesic effects *in vitro* and in *in vivo* models.⁸⁹⁰ Two sesquiterpenes, (*Z,E*) and (*E,E*)-germacrones, constituents of the gorgonian *Phyllogorgia dilatata*, are odiferous volatiles with fragrant, marine and slightly woody odours with citrus aspects.⁸⁹¹ Finally, amphidinolide P, originally reported from the marine dinoflagellate *Amphidinium* sp., was isolated from the octocoral *Stragulum bicolor* and also in its predator, the nudibranch *Marionia limceana*.⁸⁹² A likely artificial methyl acetal derivative of amphidinolide P was also isolated from the octocoral.

9 Bryozoans

There were five reports (containing 9 compounds) of new metabolites isolated from bryozoans in 2015 compared to three reports (containing 18 compounds) in 2014, so interest in this understudied phylum continues to increase very slowly. The tribrominated alkaloid kororamide B **1265** was isolated from *Amathia tortuosa*, along with kororamide A⁸⁹³ and convolutamines I⁸⁹⁴ and J.⁸⁹⁴ All four compounds induced a phenotypic signature in a cell line derived from a Parkinson's disease patient indicative of effects on vesicular trafficking, a process recently implicated in the disease.⁸⁹⁵ The tripeptide janolusimide B **1266** is the first peptide to be isolated from a bryozoan and was obtained from *Bugulina flabellata*.⁸⁹⁶ Janolusimide B is an *N*-methyl analogue of janolusimide,⁸⁹⁷ which was isolated from a Mediterranean nudibranch, *Janolus cristatus*, a known predator of bryozoans. Hydrolysis, derivatisation and stereo-selective synthesis of fragments were utilised to establish the stereochemistry.⁸⁹⁶ Four new bryostatins,⁸⁹⁸ bryostatin 21 **1267**, and 9-*O*-methylbryostatins 4, 16 and 17 **1268–1270** were obtained from *Bugula neritina* although it is probable that **1268–1270** are artefacts since the solvent used for extraction was



methanol.⁸⁹⁹ The known synthetic compound *p*-methylsulfonylmethyl-phenol^{900,901} **1271** was obtained as a first time NP and monoheneicosanoin⁹⁰² **1272** was obtained as a new MNP from *Cryptosula pallasiana*.⁹⁰³ Synthesis of amathamide F originally obtained from *Amathia wilsoni*⁹⁰⁴ has confirmed the revision of the structure proposed in 2011 (ref. 905) (**1273**).⁹⁰⁶

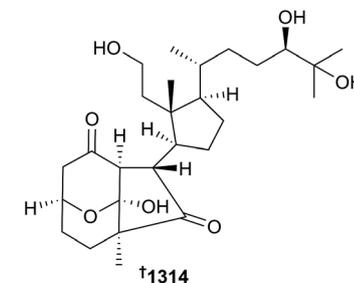


10 Molluscs

The number of new metabolites reported from molluscs (43) is a substantial increase in the average number reported per year over the past decade. Azaspiracids 7–10 **1274–1277** were isolated from extracts of the mussel *Mytilus edulis* and the structures characterised by NMR and mass spectrometry.⁹⁰⁷ Azaspiracid 8 was approximately an order of magnitude more cytotoxic towards Jurkat T lymphocytes than either of azaspiracids 9 and 10. The neurotoxic effects of azaspiracid 1 have been investigated using PC12 cells, whereby exposure induced early differentiation and down-regulation of the neurospecific intermediate filament protein peripherin.⁹⁰⁸ Crystal structures of pinnatoxins A and G bound to acetylcholine-binding protein, a surrogate for their cellular nAChR target, have identified the attributes required for tight binding and receptor subtype selectivity.⁹⁰⁹ Electrophysiological and competition binding experiments have identified that 13-desmethyl spirolide C is a potent but relatively non-selective ligand of nAChRs while 13,19-didesmethyl spirolide C is more selective of the muscular-type receptor.⁹¹⁰ Both MNPs interacted weakly with muscarinic AChRs. Further investigation of the unusual occurrence of tetrodotoxin in New Zealand collections of the nudibranch *Pleurobranchaea maculata* has led to the metabolite being detected in mucin cells, the mantle, gonad tissue and the digestive gland of the nudibranch as well as in the larvae and eggs but not in the gelatinous egg cases.⁹¹¹ These findings suggest the toxin is of dietary source and may play a defensive role in the nudibranch. Nudibranchs were the sources of a homosesterterpene **1278** (*Charcotia granulosa*),⁹¹² a series of antimalarial isocyanato and isothiocyanato sesquiterpenes **1279–1283** (*Phyllidia ocellata*),⁹¹³ scalarane sesterpenes **1284** and **1285** (*Glossodoris hikuerensis*) and diterpene **1286** (*Goniobranchus albonares*),⁹¹⁴ norscalaranes **1287–1296** and spongian diterpenes **1297–1305** (*Dorisprismatica* (= *Glossodoris*) *atromarginata*).⁹¹⁵ Granuloside **1278** is the first example of a linear homosesterterpene.⁹¹² Absolute configuration was assigned by comparison of experimental and calculated ECD data. The structure and absolute configuration of 2-isocyanoclovone **1279** was secured by X-ray crystallographic analysis of a formamide derivative.⁹¹³

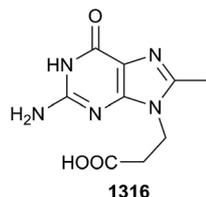
Two studies of sea hares identified eight new dactylomelane diterpenes **1306–1313** from a Greek collection of *Aplysia depilans*,⁹¹⁶ while a Japanese collection of *A. kurodai* was the source of modestly cytotoxic 9,11-secosteroid aplysiasecoesterol A

1314.⁹¹⁷ The absolute configuration of **1314** was established by comparison of calculated and experimental ECD data using a simplified model of the tricyclic γ -diketone core of the MNP and by modified Mosher's analysis.



Re-examination of extracts of *Elysia crispa* (Venezuela) has led to the characterisation of (–)-phototridachiahypopyrone **1315**,⁹¹⁸ a molecule previously speculated to be a MNP based upon its biomimetic photochemical formation from the related metabolite tridachiahypopyrone.⁹¹⁹ Surface-assisted mass spectrometry, whereby on-surface solvent extraction of small molecules onto nanostructured or porous silicon surfaces, has been used to image the distribution of choline esters, brominated indoles and lipids in the tissue of the mollusc *Dicathais orbita*.⁹²⁰ 6-Bromohypaphorine (*Hermisenda crassicornis*), previously known as a sponge^{921,922} and tunicate metabolite,⁹²³ is a mild agonist of human $\alpha 7$ nAChR but shows no effect on muscle-type nAChR from *Torpedo californica*.⁹²⁴ Dolastatin 16 obtained by total synthesis⁹²⁵ was found to be inactive, in contrast to the potent cytotoxicity towards HTCLs originally attributed to the MNP (*Dolabella auricularia*).⁹²⁶ New examples of M- and T-superfamily peptides were isolated from Indian collections of *Conus araneosus*⁹²⁷ and *C. figulinus*⁹²⁸ while analysis of venom duct cDNA from *C. litteratus*⁹²⁹ and *C. marmoreus*⁹³⁰ prompted the cloned expression or chemical synthesis and subsequent biological evaluation of new peptides. Highly detailed transcriptome analysis of *C. episcopatus* identified over 3300 novel full-length conotoxin precursors which represented 9 known and 16 new gene superfamilies.⁹³¹ Six novel cysteine frameworks were identified, providing impetus for further toxin discovery in *Conus* snails. Two studies in particular reported metabolites that expand the chemical repertoire of *Conus* molluscs. In the first of these, a simple guanine derivative, guananine **1316** was isolated from *C. gualanensis* and the structure confirmed by synthesis.⁹³² Compound **1316** exhibited potent paralytic activity in mice, mimicking the activity of the crude venom extract.

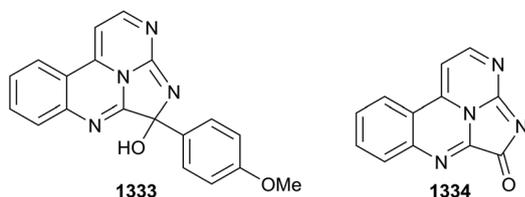




A small library of analogues representing desmethyl and/or propionate sidechain positional isomers were all devoid of activity. At the other molecular weight extreme, a specialised insulin Con-Ins G1, bearing post-translational modifications characteristic of conotoxins, *e.g.* hydroxyproline and γ -carboxyglutamate, was isolated from the venom of the fish-hunting *C. geographus*.⁹³³ The protein, which has greater sequence similarity to fish insulins than to mollusc versions, elicits hypoglycemic shock in fish, facilitating prey capture by the snails distended false mouth, the so-called 'net strategy'. Further variants were discovered upon closer examination of the venom extract by MS. A selenocysteine analogue of Con-Ins G1 was synthesised and was found to induce similar effects including being active when added to the water column. Fish-like insulin sequences were also identified in another fish-hunting species, *C. tulipa*, that also uses the net strategy, whereas sequences were absent in harpoon-method fish hunters.⁹³³

11 Tunicates (ascidians)

The eighteen new tunicate-derived natural products presented in this review is the second lowest annual count since 2002. The metabolites reported included a meroterpenoid **1317**,⁹³⁴ an array of halogenated alkaloids **1318–1323** (ref. 935) and **1324**,⁹³⁶ taurine amides **1325–1327**,⁹³⁷ purines **1328–1331**,⁹³⁸ a new pyridoacridine **1332** (ref. 939) and two unusual tetracyclic-cored alkaloids **1333** and **1334**.⁹⁴⁰ Noteworthy were the isolation, structure elucidation, synthesis and biological evaluation of eudistidines A **1333** and B **1334** (*Eudistoma* sp., Palau).⁹⁴⁰ A four-step condensation/cyclisation reaction sequence afforded both natural products, allowing confirmation of their structures. Eudistidine A was found to inhibit an essential protein–protein interaction (p300-HIF-1 α) required for HIF-1 α (hypoxia-inducible factor 1) activation: such inhibitors could find therapeutic use as antitumour agents by acting to down-regulate the expression of hypoxia-selective genes.



An expeditious total synthesis of shishijimicin A⁹⁴¹ has been reported,⁹⁴² confirming the structure and opening the door for further biological evaluation of this potentially cytotoxic enediyne. The structure of tunichrome Sp-1 (ref. 943) has been confirmed by total synthesis⁹⁴⁴ and a new catalytic asymmetric synthetic route to (–)-perophoramidine⁹⁴⁵ has been disclosed.⁹⁴⁶ Cell-cycle arrest at

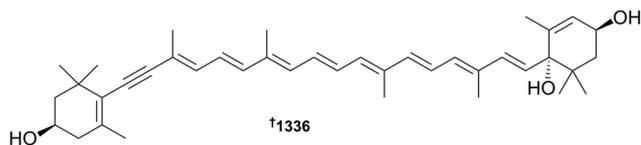
the G₂/M phase and induction of apoptosis in HeLa cells⁹⁴⁷ was observed for the ascidian alkaloid eudistomin H,⁹⁴⁸ while eusynstyelamide B⁹⁴⁹ also induces G₂/M phase arrest, causes double strand breaks in DNA and is a topoisomerase II poison.⁹⁵⁰ Further investigation of clavamin A, a C-terminal amidated 23 residue antimicrobial peptide,⁹⁵¹ has identified it to exhibit no cytotoxicity and to be active *in vivo* and in a wound healing model of *S. aureus* infection.⁹⁵² Preliminary investigation of anti-angiogenic activity in myxoid liposarcomas has identified trabectedin (Yondelis[®], Et-743) as an upregulator of inhibitors of matrix metalloproteinases TIMP-1 and TIMP-2, and of TSP-1, a key regulator of angiogenesis-dependent dormancy.⁹⁵³ For several decades, didemnin B and related analogues have been the subject of numerous clinical trials, ultimately resulting in dehydrodidemnin B (Aplidine) being granted orphan drug status towards acute lymphoblastic leukemia. Gene-expression mapping has identified didemnin B to be a dual inhibitor of palmitoyl-protein thioesterase (PPT1) and eukaryotic translation elongation factor 1 alpha 1 (EEF1A1), the combination of which leads to apoptosis and antineoplastic activity.⁹⁵⁴ Gene expression data from cancer cell lines that were either sensitive or resistant to didemnin B identified four gene biomarkers that correlated with sensitivity to the natural product. These biomarkers, associated with epithelial-derived cell lines and also some colorectal, breast and lung cell lines, could be of use in predicting the likelihood of patient response to didemnin B or analogues in a therapeutic setting. Synthetic analogues related to the polyandrocaramines⁹⁵⁵ were found to be inhibitors of H₂S production by cystathionine beta-synthase,⁹⁵⁶ and SAR studies have been reported for thiaplidiacquinones A and B⁹⁵⁷ (various biological targets),⁹⁵⁸ cadiolides A–C^{959,960} (antibacterial),^{961,962} rubrolides⁹⁶³ (photosynthesis inhibitors),⁹⁶⁴ meridianins⁹⁶⁵ (antimalarial and antituberculosis),⁹⁶⁶ isogranulatimide⁹⁶⁷ (cytotoxicity),⁹⁶⁸ and lamellarins⁹⁶⁹ (cytotoxicity).⁹⁷⁰

12 Echinoderms

The twenty-seven new metabolites reported from echinoderms in this review is just over half the average number reported per annum over the last decade. A new carotenoid **1335** was reported from *Plesiocolochirus minutus*, with absolute configuration assigned by a combination of ECD and NOESY analysis,⁹⁷¹ while the structure of 3'-epigobiusxanthin (Crown-of-thorns *Acanthaster planci*)⁹⁷² has been corrected to that of 6'-epigobiusxanthin **1336** as a consequence of stereospecific synthesis of a series of stereoisomers.⁹⁷³ The remaining metabolites reported from echinoderms were of saccharide or sterol/sterol glycoside origins and included **1337** (starfish *Asterias rollestoni*)⁹⁷⁴ **1338–1341** (starfish *Leptasterias ochotensis*),⁹⁷⁵ **1342** (sea cucumber *Holothuria moebii*),⁹⁷⁶ **1343–1347** (starfish *Echinaster luzonicus*),⁹⁷⁷ **1348–1352** (sea cucumber *Cercodemas anceps*),⁹⁷⁸ **1353** (starfish *Culcita novaeguineae*),⁹⁷⁹ **1354** (sea cucumber *Cucumaria japonica*),⁹⁸⁰ and **1355–1362** (sea cucumber *Cladolabes schmeltzii*).⁹⁸¹

In addition to these MNPs, a further series of saponins (lessinosides A–G) were reported from *Holothuria lessona*.⁹⁸² As the structures were proposed based solely upon MSⁿ data, there are few data to define the associated aglycones and so the structures



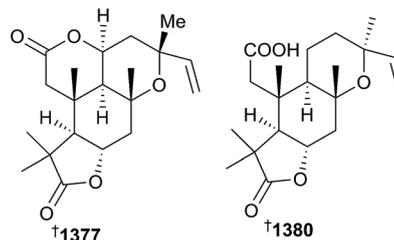
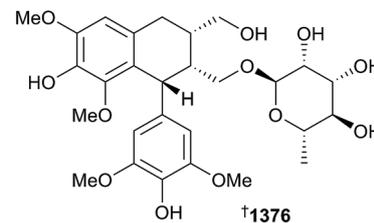


are not shown in this review. Using cladoloside C as a model (*Cladolabes schmeltzii*),⁹⁸³ chemical transformations combined with Mosher's analysis has determined C-22 as having (*R*)-configuration.⁹⁸⁴ The authors speculated that all C-22 functionalised sea cucumber glycosides may have the same (22*R*) configuration. In an important development regarding the unambiguous characterisation of complex MNPs reported from echinoderms, the structures of gangliosides GAA-7 (ref. 985) (starfish *Asterias amurensis*)⁹⁸⁶ and PNG-2A⁹⁸⁷ (starfish *Protoreaster nodosus*)⁹⁸⁸ and steroidal glycosides astrosteroside A⁹⁸⁹ (starfish *Astropecten monacanthus*)⁹⁹⁰ and linkosides A and B⁹⁹¹ (starfish *Linckia laevigata*)⁹⁹² have been confirmed by total synthesis. Further studies using purified pentahydroxynaphthoquinone echinochrome A^{993,994} have identified suppression of SERCA2A Ca²⁺ reuptake⁹⁹⁵ and improvement of exercise capacity in rats.⁹⁹⁶ A trisaccharide fragment of the starfish ganglioside LLG-3 (*Linckia laevigata*)⁹⁹⁷ promotes neurite extension in human neuroblastoma cells *via* MAPK/ERK signalling but not *via* Akt signalling.⁹⁹⁸ Polyhydroxylated sterols from the Vietnamese urchin *Diadema savignyi* induce apoptosis in HTCLs *via* inactivation of the MAPK/ERK1/2 pathway⁹⁹⁹ while sterols from the starfish *Protoreaster nodosus* were found to inhibit the production of pro-inflammatory cytokines including IL-12 p40, IL-6 and TNF- α in LPS-stimulated bone marrow-derived dendritic cells.¹⁰⁰⁰ Purified saponins from Chinese collections of *Holothuria moebii* exhibited *in vitro* cytotoxicity towards a panel of HTCLs and a total saponin fraction (mixture) inhibited CT-26 tumour growth in mice.¹⁰⁰¹ In a detailed study, the triterpene glycoside stichoposide D (*Thelenotaxanax*) was found to induce apoptosis *in vitro* in human leukemia cells through activation of CerS6 (ceramide synthase) and p38 kinase, and that similar activation properties were observed *in vivo* towards HL-60 and K562 xenografts.¹⁰⁰²

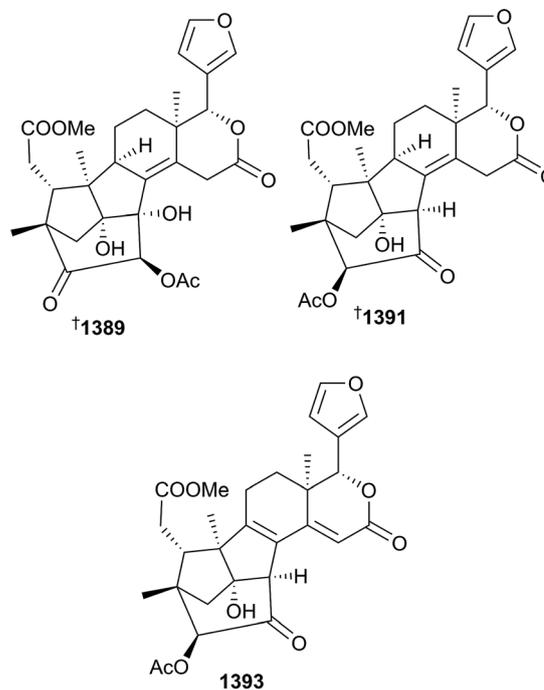
13 Mangroves

Mangroves or their associates were the sources of antiviral cyclohexylideneacetone nitriles **1363–1366** (*Bruguiera gymnorrhiza*),¹⁰⁰³ a phenolic **1367** and a diol **1368** from the fruits of *Avicennia marina*,¹⁰⁰⁴ phenolics and a cerebroside **1369–1372** (*Sonneratia ovata*),¹⁰⁰⁵ glycosides **1373** (*Kandelia candel*)¹⁰⁰⁶ and **1374–1376** (*Bruguiera gymnorrhiza*),¹⁰⁰⁷ *seco*-labdanoids **1377–1380** (*Excoecaria agallocha*),¹⁰⁰⁸ dolabrane-diterpenes **1381–1386** (*Cerriops tagal*),¹⁰⁰⁹ and limonoids **1387–1398** (ref. 1010) **1399–1401** (ref. 1011) (*Xylocarpus moluccensis* and *X. granatum*). The absolute configuration of the lignin rhamnoside **1376** was secured *via* analysis of experimental ECD data – the planar structure is identical to that of a previously reported metabolite of *Cotoneaster racemiflora* though with different magnitude and opposite sign of rotation.¹⁰¹² CD analysis and an X-ray study has led to the revision of the structure of rhizophorin A (*Rhizophora*

mucronata)¹⁰¹³ to that shown for excolide A **1377**.¹⁰⁰⁸ The structure of excolide B **1380** was also secured by X-ray analysis.



The absolute configurations of new limonoids, including thaixylomolins I **1389**, K **1391** and M **1393**, were determined by TD-DFT calculations of ECD data.¹⁰¹⁰ NMR data observed for **1391** were identical to those reported for the known phragmalin-skeletoned limonoid moluccensin J¹⁰¹⁴ – close examination of 2D NMR data requires structural correction of moluccensin J to structure **1391**. Limonoids **1389**, **1391** and **1393** exhibited mild anti-H1N1 viral activity. Further investigation of previously reported mangrove MNPs has identified the dolabrane-diterpene tagalsin C (*Cerriops tagal*)¹⁰¹⁵ to exhibit cytotoxicity *in vitro* towards a panel of haematologic cell lines, and *in vivo* towards



human T-cell leukemia xenografts, *via* a mechanism involving ROS-mediated apoptosis and cell cycle arrest.¹⁰¹⁶ In addition the phenethyl cinnamide micrometam C (*Micromelum falcatum*)¹⁰¹⁷ protects against LPS-induced reactive oxygen species in both zebrafish and macrophages,¹⁰¹⁸ and limonoids xylocensin E¹⁰¹⁹ and I¹⁰²⁰ (*Xylocarpus moluccensis* and *X. granatum*) exhibited anti-ulcer gastroprotective activities in rats, likely due to an ability to inhibit H⁺K⁺-ATPase activity.¹⁰²¹

14 Miscellaneous

A study of the sea grass *Cymodocea serrulata* has afforded an antibacterial constituent, which was attributed to the novel thiocarbonyl **1402**.¹⁰²² The spectroscopic data reported for this compound are not however consistent with the proposed structure. A new member of the cephalostatin family, cephalostatin 20 **1403**, was isolated as a minor component of extracts of the marine worm *Cephalodiscus gilchristi*.¹⁰²³ Compared to the

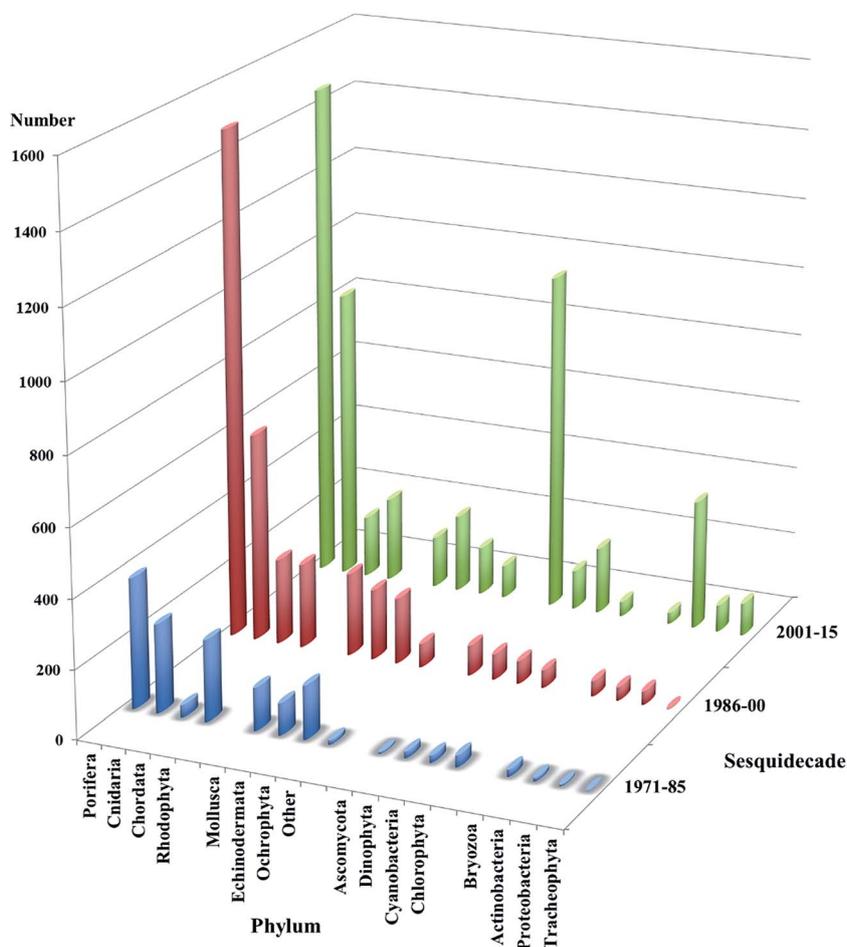
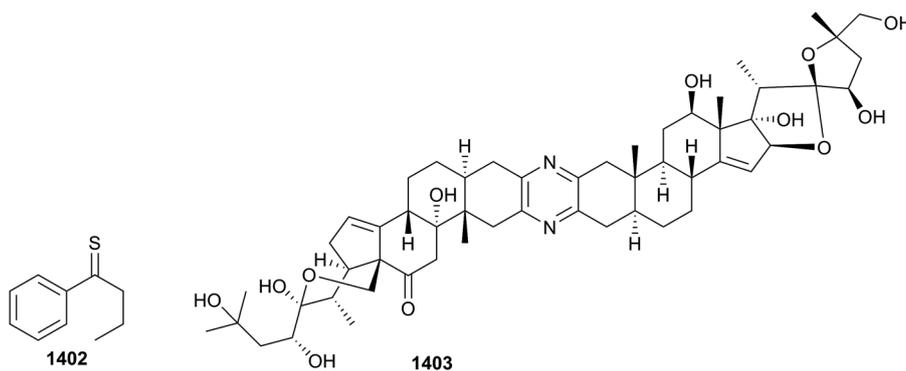


Fig. 1 The most abundantly collected phyla by sesquidecade.



more potent members of the family (cephalostatins 1–3), cephalostatin 20 was 100–1000× less cytotoxic towards a panel of HTCLs. Efforts to reduce the structural complexity of the cephalostatins and to prepare analogues from the steroid hecogenin acetate resulted in compounds lacking any cytotoxic potency.¹⁰²⁴

Site-directed mutagenesis of the plasmid used for the heterologous expression of arenicin-1, an antimicrobial peptide produced by the polychaete worm *Arenicola marina*,¹⁰²⁵ afforded a number of analogues, one of which, Val8Arg, was equipotent as an antibacterial but with diminished red blood cell haemolytic activity.¹⁰²⁶ cDNA analysis of the venom gland of the sea snake *Hydrophis cyanocinctus* led to the

identification of the first cathelicidin family antimicrobial peptide from a marine reptile.¹⁰²⁷ The peptide, Hc-CATH is a 30-mer and exhibits potent broad spectrum antimicrobial activity, *via* a mechanism related to membrane disruption and lysis. One critical step of the mechanism of light generation by cypridina luciferin, the luminescence precursor of the ostracod *Cypridina (Vargula) hilgendorffii* has been computationally modeled using structurally-simpler models.¹⁰²⁸ The peroxide intermediate cypridinid dioxetanone (CDO) can thermally decompose to generate excited oxyluciferin – CDO thermolysis *via* neutral or anionic forms were modeled, with the latter being found to be more energetically favourable in polar environments. The 33-amino-acid residue peptide

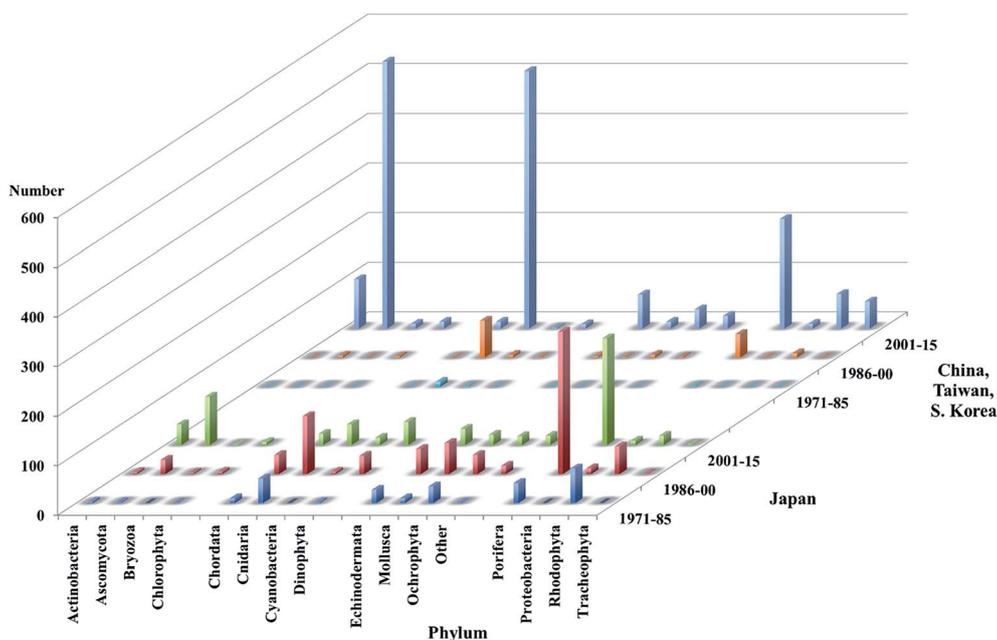


Fig. 2 Collections in Japanese waters by sesquidecade contrasted with the collections in Chinese, Taiwanese and S. Korean waters.

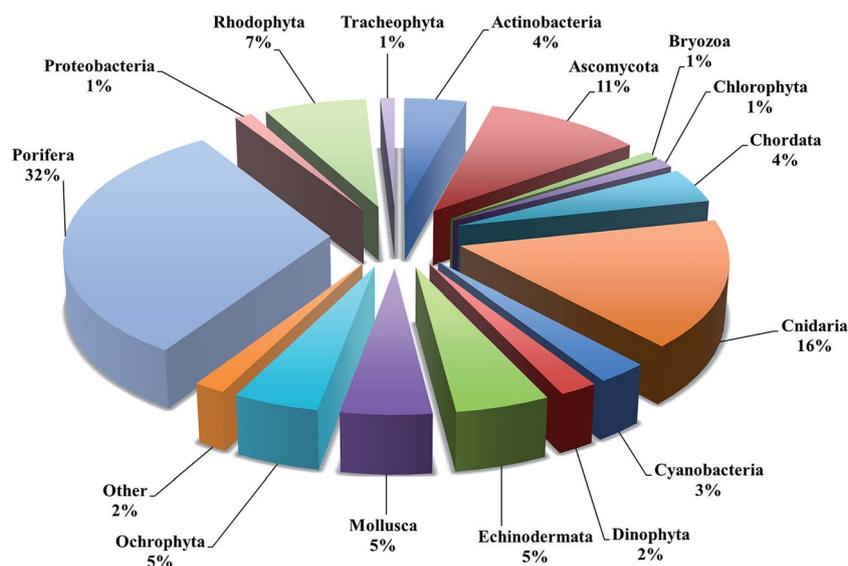


Fig. 3 Distribution of the collection effort over the period 1971–2015 by phylum.



pardaxin (flatfish *Pardachirus marmoratus*) exhibits *in vitro* and *in vivo* growth inhibition of oral squamous cell carcinoma.¹⁰²⁹ Mycosporine-like amino acids and gadusols are UV-vis protective compounds produced by a number of different species of marine organisms. Gadusol production in zebrafish is encoded by two gene products. By cloning into yeast yields of $\sim 20 \text{ mg L}^{-1}$ were obtained (5 days fermentation), opening the door to large scale production and use in commercial products.¹⁰³⁰

15 Conclusion

How things have changed over the past 45 years. In 1970 Professor G R Pettit made prophetic statements about the future for MNPs as a source of potential antineoplastic agents based on his widespread collections of marine vertebrates and invertebrates in 1968 along both coasts of North and South America and in Asia.¹⁰³¹ Through the years since he has published a myriad of papers that have confirmed his early convictions. Now, three sesquidecades on from that statement, the 600th paper in his series on anti-neoplastic agents has been published.¹⁰³² In this Conclusion we would like to acknowledge the outstanding contributions that he has made, and continues to make, to our field. In 1969 the remarkable antineoplastic properties of the ethanol/water extract from the ascidian *Ecteinascidia turbinata* were reported.¹⁰³³ Some

years later the structures of the ecteinascidins were independently published^{1034,1035} and ET-743, a bioactive research find, was transformed over the years to the anticancer drug Yondelis® (trabectedin).¹⁰³⁶ In 2015 it was established that the producer of the ecteinascidins was the γ -proteobacterial endosymbiont *Candidatus Endoecteinascidia frumentensis*.²⁵ This example is characteristic of the changes that have taken place over the past 45 years in the foci of MNP research. Three other aspects of change will be examined in this Conclusion. Firstly, the type of organism collected. Fig. 1 shows the relative abundance of the most popular 15 phyla by sesquidecade from 1971. The less commonly collected organisms are grouped as Other.¹⁰³⁷ Right from the early days of MNPs the phylum Porifera has dominated. In the 1971–1985 sesquidecade the other phyla that were collected most avidly were the Cnidaria, Rhodophyta, Ochrophyta, Mollusca, and Echinodermata. The second sesquidecade from 1986–2000 was comparable, but marked the first appearance of the Ascomycota. In the third sesquidecade there were significant changes as the Ascomycota and Actinobacteria are now in the top four most widely collected phyla. In the coming sesquidecade from 2016–2030 microbially-derived compounds will almost certainly dominate the MNP field and this will be driven by factors such as the interest in the diversity of the microbial metabolites, the relative ease of collecting marine microbes from sediments, mud-flats, salterns or as endophytes from marine invertebrates, and the

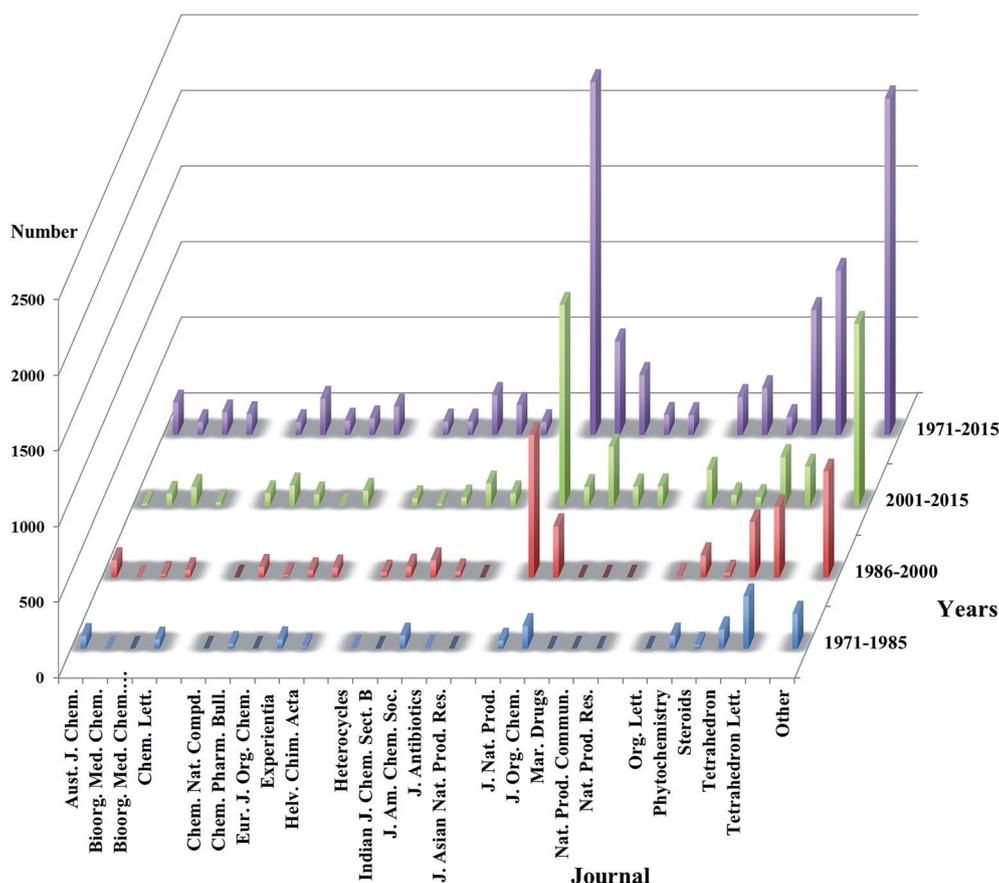


Fig. 4 The 24 most selected journals used overall for publication of new compound data for the period 1971–2015, also shown by sesquidecade.



developing technologies for extraction of genomic material from microbes and its manipulation in heterologous systems.

Research from Asian countries is now a dominant feature in MNP chemistry and was led from the start by Japan. This second aspect focuses on where the samples have been collected and in Fig. 2 the collection history of Japanese samples is examined over the three sesquidecades and compared with that of the newly emerging Asian groups collecting in Chinese, Taiwanese and South Korean waters. These collections from Asian waters now constitute about 30% of all compounds characterised and examination of Fig. 2 reveals that most of the collections from Chinese, Taiwanese and South Korean waters have taken place in the last sesquidecade with a very heavy emphasis placed on Cnidarian and microbial sources. Japanese collections have moved in that direction also, but still have a heavy emphasis on the phylum Porifera. Fig. 3 gives the perspective on the overall pattern of collections by phyla from 1971 to 2015.

The third element of change examined is who we choose to publish with. This too has changed considerably over the years as some of the most popular journals for MNP publications were not available in 1971, or alternatively have lost favour or ceased publication. In Fig. 4 the 24 most popular journals overall (cut off <85) are compared on a sesquidecade basis. The Other category combines the output from a further 309 journals that have been used on at least one occasion through the years. The choice of journal in the first sesquidecade was quite different to the latter years with the *Journal of Natural Products*, *Journal of Organic Chemistry*, *Tetrahedron*, *Tetrahedron Letters*, *Australian Journal of Chemistry* and *Phytochemistry* emerging in the second sesquidecade. By the third sesquidecade *Organic Letters* and *Marine Drugs* had appeared and have been sought after as the journal of choice in addition to the *Journal of Organic Chemistry*, *Tetrahedron*, *Tetrahedron Letters* and most notably the *Journal of Natural Products* which has gone from strength to strength. As a proportion, however, more scientists are now publishing in the Other category.

Year by year, little seems to change, but these three snapshots illustrate the actual magnitude of the changes that have occurred over the period that MNPs has been a discipline in its own right.

16 Acknowledgements

We thank Dr Helen Potter (Royal Society of Chemistry) for the provision of data used in this review, adapted from the MarinLit database with permission from the Royal Society of Chemistry.²⁴ This review is the fifteenth issue prepared by the New Zealand group of authors, and will be the last one contributed to by Professor Murray Munro, and we wish him all the best for his “retirement”. Professor Munro’s contributions have been significant, particularly ensuring that the presentations from each of the authors of the various sections have had a similar style enabling a more consistent reading experience for readers of the review. He has also been responsible for the Conclusion section (15) in each review, providing insightful comment on a range of developments and trends in MNP research over several decades. The other

authors are particularly grateful to Murray for his many contributions to these reviews, and other aspects of MNP research.

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