Natural Product Reports

REVIEW

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Marine natural products††

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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 review[1] 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.

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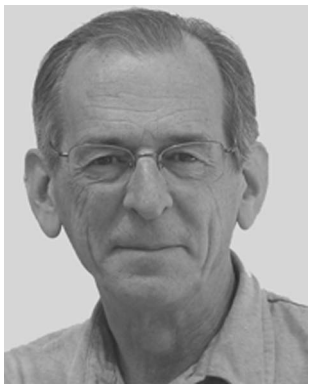
2 Reviews

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 compounds[6] and antiviral agents[7] have been described. There have been surveys of anticancer compounds from marine sponges[8] and microalgae,[9] while the bioactivities of specific classes of MNPs such as peptides,[10,11] polyacetylenes,[12] indole alkaloids,[13] and halogenated compounds[14] 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 activity[16] and antifouling properties.[17] MNPs from marine cyanobacteria[18] 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 MarinLit[24] continues to be updated and has been the principal source of information for this review.

3 Marine microorganisms and phytoplankton

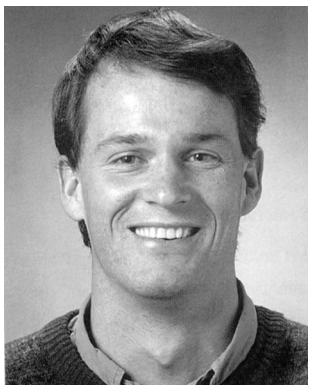
3.1 Marine-sourced bacteria

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

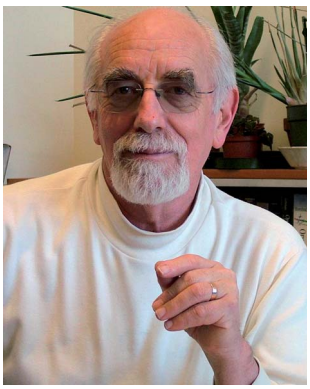


John Blunt obtained his BSc (Hons) and PhD degrees from the University of Canterbury, followed by postdoctoral appointments in Biochemistry at the University of Wisconsin–Madison, and with Sir Ewart Jones at Oxford University. He took up a lectureship at the University of Canterbury in 1970, from where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

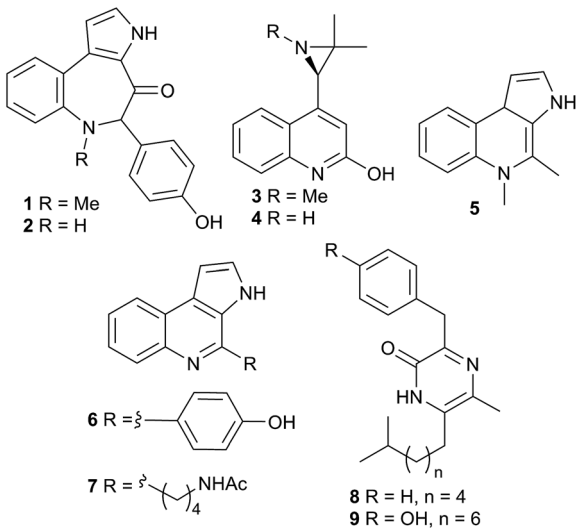


Brent Copp received his BSc (Hons) and PhD degrees from the University of Canterbury, where he studied the isolation, structure elucidation and structure–activity relationships of biologically active marine natural products under the guidance of Professors Blunt and Munro. He undertook postdoctoral research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



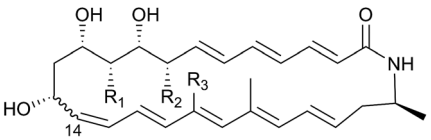
Murray Munro, Emeritus Professor in Chemistry at the University of Canterbury, has worked on natural products right through his career. This started with diterpenoids (PhD; Peter Grant, University of Otago), followed by alkaloids during a postdoctoral spell with Alan Battersby at Liverpool. A sabbatical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



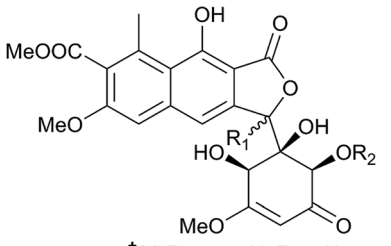
Michèle Prinsep received her BSc (Hons) and PhD degrees from the University of Canterbury, where she studied the isolation and structural elucidation of biologically active secondary metabolites from sponges and bryozoans under the supervision of Professors Blunt and Munro. She undertook postdoctoral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

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]

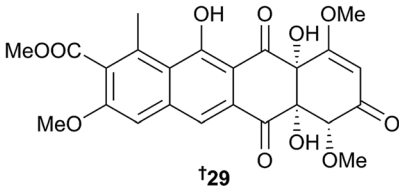


The putative BGC for the fluostatins from *Micromonospora rosaria*[30] was expressed heterologously in *Streptomyces coelicolor* and led to the isolation of fluostatin L ***17*** and a fluostatin heterodimer ***18***,[31] while investigation of another *Micromonospora* sp. resulted in isolation of a 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 *Norcadiopsis* 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 tetracenomycin (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



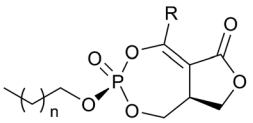
†26 R_1 = ▬ H, R_2 = H
†27 R_1 = ▬ H, R_2 = Me
†28 R_1 = ┈ H, R_2 = Me



†29

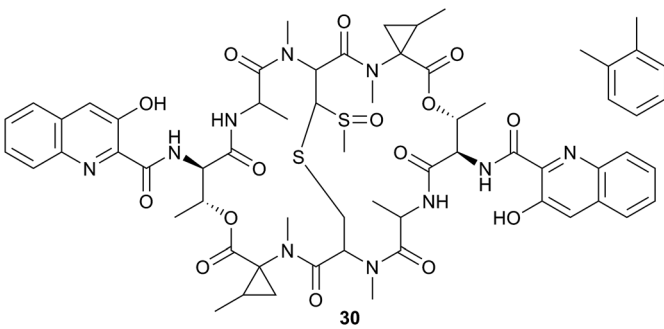
components and new derivatives of known compounds (methylation, hydroxylation, *etc.*). Molecular networking coupled with genome sequence data allowed for the rapid correlation between a BGC and the resultant secondary metabolite (pattern-generation). In this example it was found that the cluster NPRS40 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] Sioxanthin **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 sioxanthin is also unusual as the carotenoid biosynthesis genes are non-clustered in the *Salinospora* genomes.[41]

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]



†32 n = 13, R = *n*Bu
†33 n = 12, R = *n*Bu
†34 n = 11, R = *n*Bu
†35 n = 12, R = *i*Bu
†36 n = 11, R = *i*Bu
†37 n = 13, R = *n*Pr
†38 n = 12, R = *n*Pr
†39 n = 11, R = *n*Pr
†40 n = 13, R = Et
†41 n = 12, R = Et
†42 n = 11, R = Et

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



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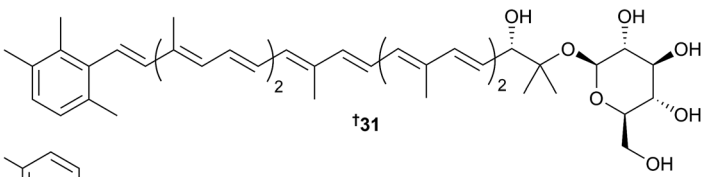
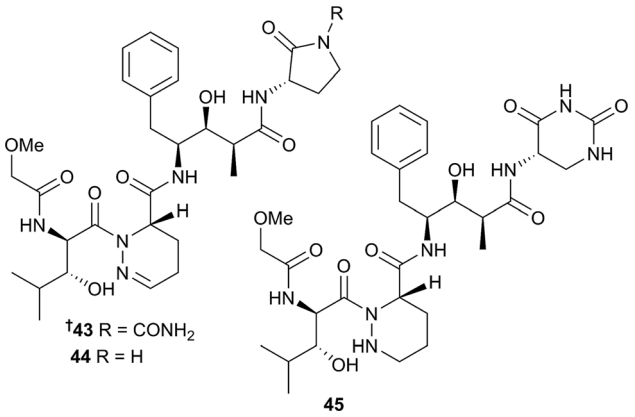


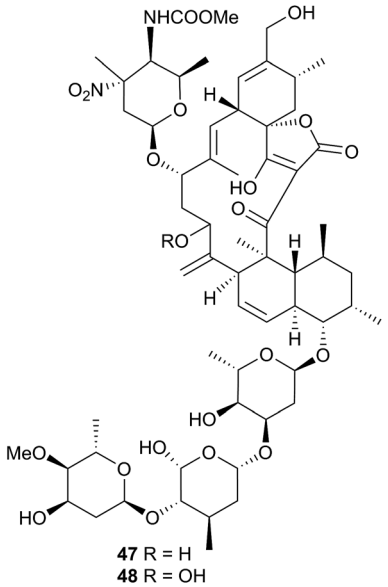
†31

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 investigation. Each contained a similar suite of compounds so only *S. bangulaensis* 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]

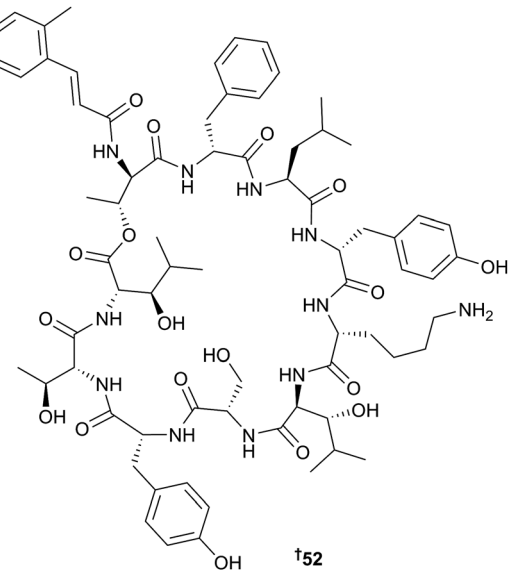
Another major screening effort was against >33 000 extracts from 5036 cultivatable Costa Rican marine



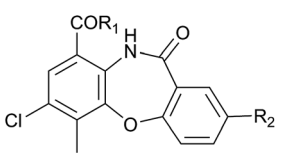
microorganisms to discover activators of the apoptotic arm of unfolded protein response (UPR). High levels of UPR signaling characterize many human cancers. The screening led to the discovery of three further lobophorin[47–50] congeners ***46***, **47** and **48** from a *Streptomyces* sp. and, subject 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 $^{13}C/^{15}N$ abundance the growth media used peptone and yeast extract and $^{15}NH_4Cl$ and [U-^{13}C]-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 HNCO, 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]

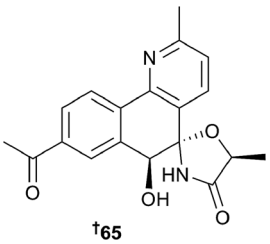


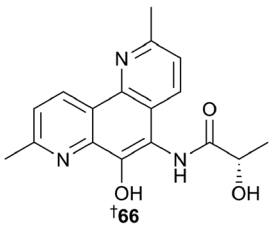
New ansamycin analogues ***53–55*** were obtained from a mutant strain of *S. seoulensis*,[55] and further ikarugamycin[56] derivatives (tetramic acid macrolactams) ***56–58*** were isolated from a *S. zhaozhouensis.*[57] A combination of gene inactivation and complementation, synthetic substrates and 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]

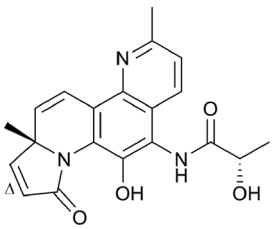


Marine Actinobacteria continue to surprise with the versatility of their biosynthetic machinery. Phylogenetic studies have

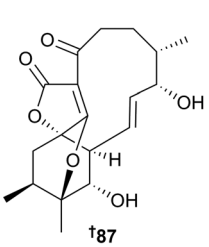
led to the identification of 13 distinct marine actinomycete groups. The chemical investigation from one of these groups, a member of the family Streptomycetaceae, led to the isolation of two new classes of marine alkaloid, represented by actinobenzoquinoline **65**, and the actinophenanthrolines A–C **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]

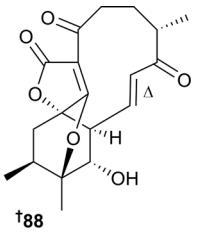

†**65**

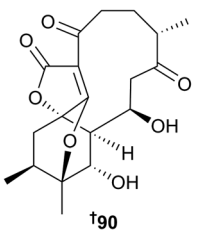

†**66**

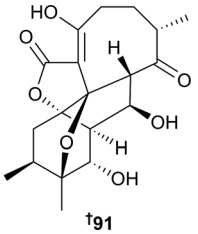

†**67** Δ saturated
68

Further bohemamine 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 abyssomicin[70] 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]

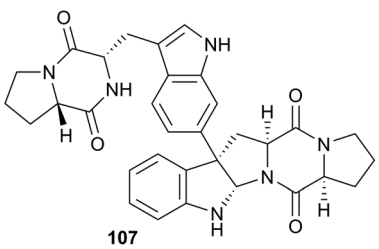

†**87**


†**88**
†**89** Δ saturated


†**90**

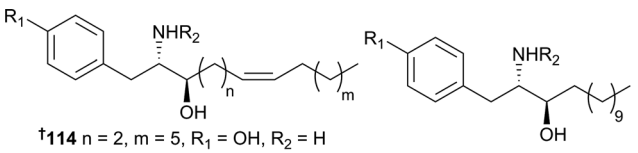

†**91**

A number of other compounds of lower molecular weight were also isolated from actinomyctes 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 properties[79] and an incompletely characterized cyslabdan-like compound ***106***.[80] Anti-dormant mycobacterial properties were reported for the known terrestrial antibiotic nybomycin[81] isolated, in this instance, from a marine Streptomycete. 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, Nocardiopsis, 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 isonaseseazine B **107**, a stereoisomer of naseseazine B.[83,84]


107

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

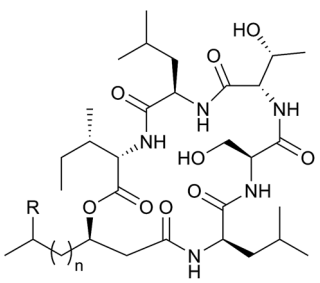
110 from a sediment-derived *Bacillus licheniformis*,[86] and two lipopeptides ***111*** and ***112*** that differ only in the chain-length of the 3-hydroxy fatty acid.[87] A cyclic tetrapeptide ***113*** was isolated from the culture broth of a *Staphylococcus* sp.[88] A number of papers reported new 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 baumanni*. 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] AntiBase[89]). Of the 10 vitroprocines subsequently isolated, vitoprocines A–C **114–116** were most active against *A. baumanni*.[90]



†**114** n = 2, m = 5, R_1 = OH, R_2 = H
115 n = 1, m = 8, R_1 = OH, R_2 = H
117 n = 2, m = 7, R_1 = OH, R_2 = Ac
119 n = 2, m = 5, R_1 = OH, R_2 = Ac
120 n = 2, m = 9, R_1 = OH, R_2 = Ac
121 n = 5, m = 2, R_1 = R_2 = H
123 n = 2, m = 5, R_1 = R_2 = H

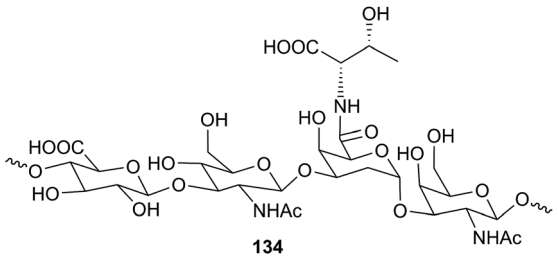
116 R_1 = OH, R_2 = H
118 R_1 = OH, R_2 = Ac
122 R_1 = H, R_2 = Ac

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 ^{13}C-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]



†**124** n = 7, R = H
†**125** n = 6, R = Me
†**127** n = 9, R = H
†**129** n = 8, R = H
†**130** n = 8, R = Me
†**131** n = 5, R = H

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]



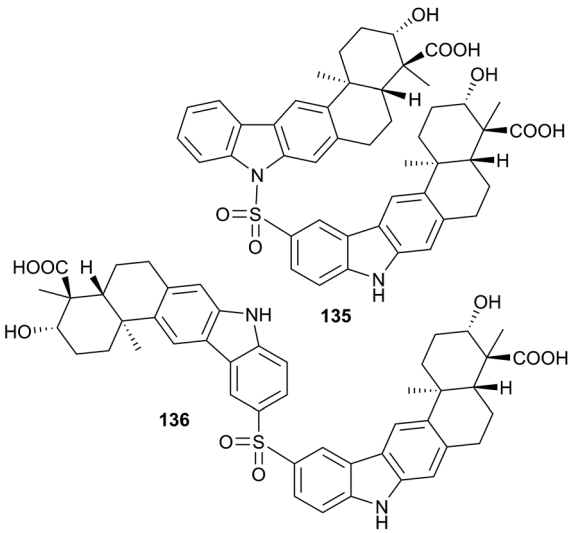
134

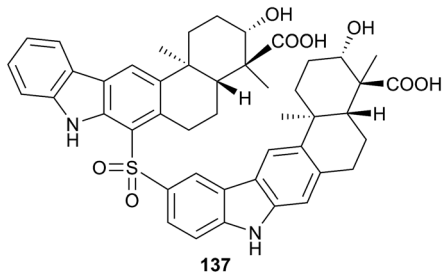
The seashore Actinobacteria derived from mangroves, seagrasses, salterns and mud-flats have been grouped separately on the grounds that as a group they have been exposed to much greater changes in temperature, submersion, salinity and sunlight than their oceanic counterparts. Following isolation of a series of the polycyclic xiamycin[94] and other indolesesquiterpenes[95] 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 SO_2 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]

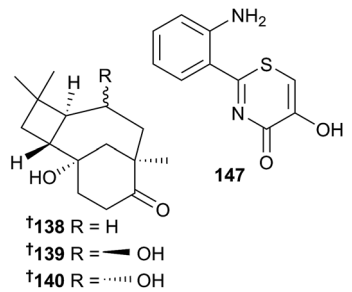
Two other endophytic *Streptomyces* spp., also obtained from the stem of the mangrove *Bruguiera gymnorrhiza*, led to three bacterial caryolanes bacaryolane A–C **138–140**. These are mirror images of typical plant-derived caryolanes.[98] The other *Streptomyces* sp. endophyte yielded a series of divergolide[99] 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-4*H*-1,3-thiazine-4-one core.[101]

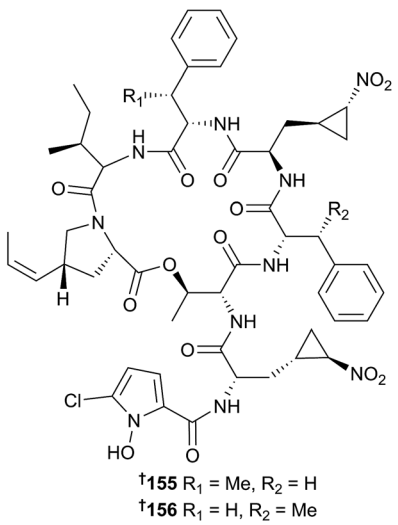
Derived from mangrove sediment-sourced actinomycetes were ***150*** (ref. 102) and preQ$_0$,[103] ***151*** (first-time natural product)[104] while ***152–154*** came from an endophyte of the sea-grass *Salicornia* sp.[105] A tidal mud-flat *Streptomyces* sp. was the source of the hormaomycins B **155** and C **156**, which each contain the unusual structural features (4*Z*)-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 Streptomycete 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 dihydropyridine. 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*



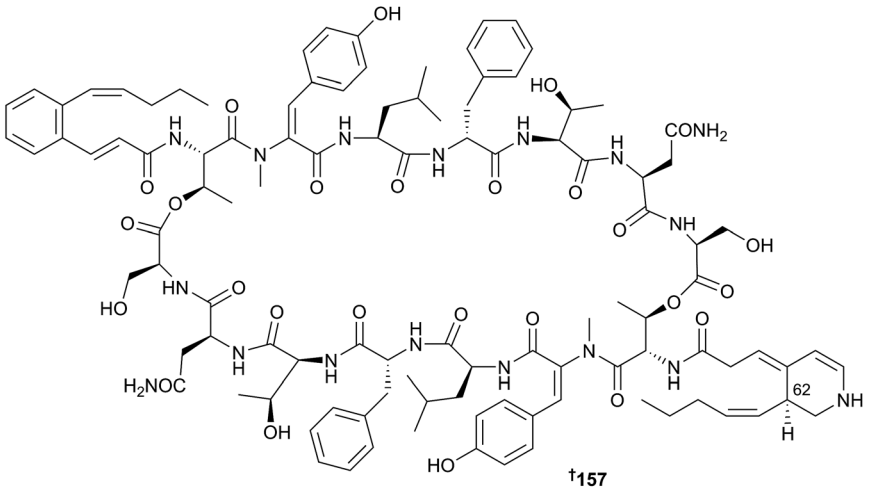






sp. were ***159***, ***160*** (ref. 109) and ***161–165***,[110,111] while the salinazinones A **166** and B **167** are first examples of a natural alkaloid with an oxazinone-pyrrolidione core.[112]

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 thiochondrilline C,[115,116] bogorol A and the more thermodynamically-favoured (*Z*) isomer,[117,118] the siderophores amphibactin-T[119] and moanachelin ala-B.[120,121] The first synthesis of fradcarbazole[122] was by semi-synthesis[123] 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 B[137] has reconfirmed the absolute configuration as (*S*) and that the specific optical rotation is negative.[138] The unusual anthracycline marmoycin[139] 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 A[141] established that two cystolic proteins, part of the glycolytic cycle, were the targets for chlorizidine,[142] while studies on the mechanism of action of thalassospiramides[143] 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 akaeolide[145] and lorneic acid[146] identified type 1 PKS clusters and the PKS origins were supported by ^{13}C-labeling studies.[147] The biosynthetic gene cluster for the production of the marformycins,[148] *mfn*, has been identified from *Streptomyces drozdowiczi* and encodes six NRPS's and related proteins for the assembly of the depsipeptide core structure.[149] Two papers addressed heronamide[150] 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 ^{13}C-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 sp^3 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



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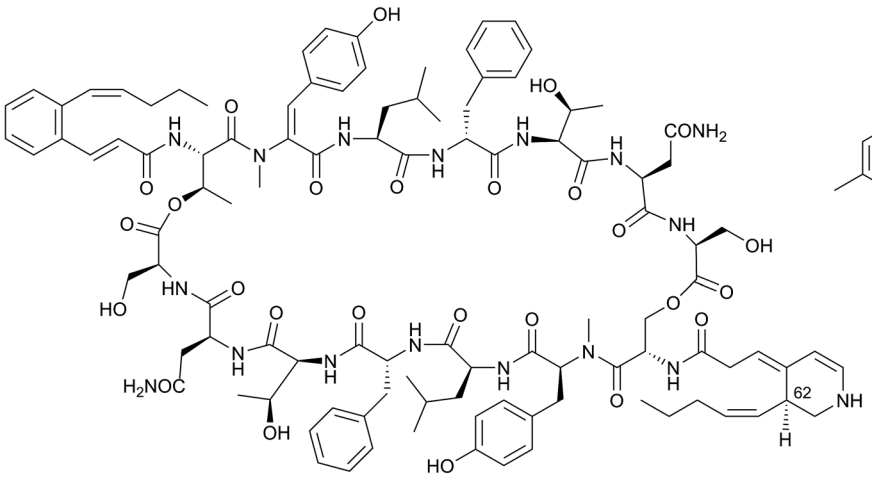

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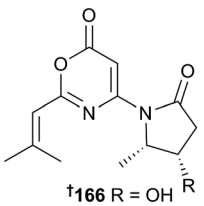


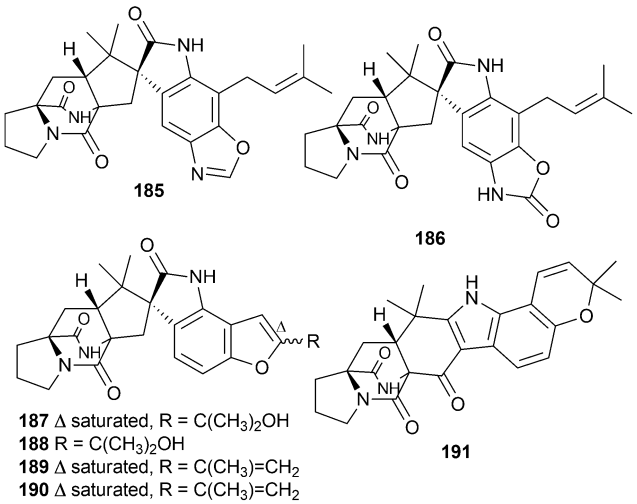
†166 R = OH
†167 R = H

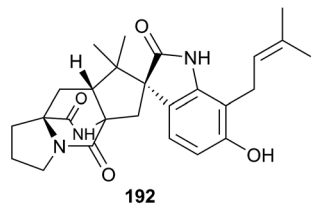
in part a consequence of the orientation of the C16 methyl group pre-organising the PKS-bound intermediate prior to the [4 + 2] cycloaddition.[156,157] The biosynthesis of two similar *Salinispora pacifica* metabolites, salinipyrone and pacificanone,[158] was unexpectedly correlated with the large PKS cluster from *Micromonospora carbonacea*[159] that produces the macrolide rosamicin[160] and illustrates how domain and module skipping can give rise to polyketide product diversity.[161] From a study of splenocin[131] 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 alkaloids[163] 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 *Salinospora* 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 extracts[166] 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]

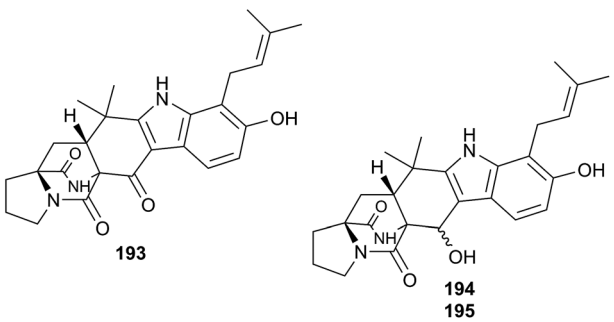
3.2 Marine-sourced fungi (excluding from mangroves)

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*

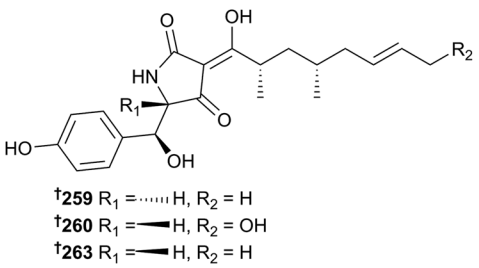
(tricycloalternarenes ***173*** and ***174***,[169] and a spiro decalin derivative ***175*** (ref. 170)), *Arthirinium* (alkaloids ***176–178*** (ref. 171) and cytochalasins ***179–183***).[172] Of these, arthrinium A ***179*** was claimed as new but is a known natural product derivative[173] and ketocytochalasin ***183*** (ref. 173) is a first time MNP.[172] Citromycetin analogue ***184*** was obtained from an *Ascomyta* 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] stephacidins[176] and versicolamide B.[177] Feeding of $[^{13}C]_2$ racemic 6-*epi*-notoamide T[178] 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]

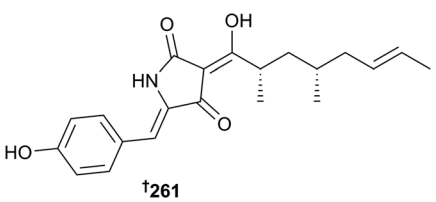


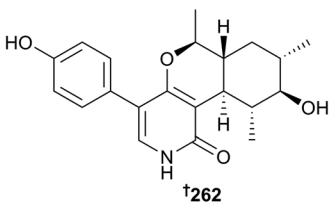




Other metabolites produced by *Aspergillus* species included spiculisporic acid analogues ***196*** and ***197***,[181] phenyl ether derivatives ***198–202***, of which dehydrocyclopeptine[182] ***201*** and viridicatin[182] ***202*** were obtained as first time MNPs,[183] polyketide ***203*** and decaline derivative ***204***,[184] alkaloids ***205–207***,[185] ***208–210***,[186] indole diterpenoids ***211*** and ***212***,[187] isocoumarin ***213***, cyclohexapeptide ***214*** and pyripyropene 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 II[195] ***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′-hydroxyasperentin[202] 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]



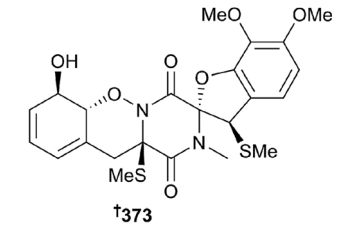




An OSMAC approach was utilised in the isolation of polyketides ***264*** and ***265*** from *Cladosporium sphaerospermum*[209] and other metabolites obtained from *Cladosporium* species included

diketopiperazines ***266*** and ***267***,[210] bicyclic lactam ***268*** (ref. 211) and polyketides ***269*** and ***270***.[212] New metabolites isolated from the genera *Corynepsora* included chromone derivatives ***271–282*** (ref. 213) while *Dichotomomyces* spp. produced the thiodiketopiperazines ***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 neoechinulin 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-phenylacetamide[228] ***337*** and *N*-(2-methylbutyl)-2-phenylacetamide[229] ***338*** were first time NPs.[227] New natural products were isolated from the genera *Lophiostoma* (merosesquiterpenoids craterellin D ***339*** and craterellin A[230] ***340***; first marine isolation for the latter),[231] and *Nectria* (monoterpenoid α-pyrones ***341*** and ***342***).[232] Of these, nectriapyrone D[232] ***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 bisthiodiketopiperazines ***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***, isopatulin[247] ***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 I[249] 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 communesins[251] 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]



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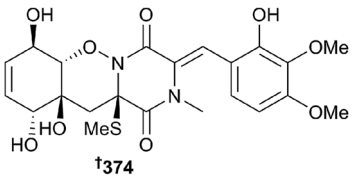
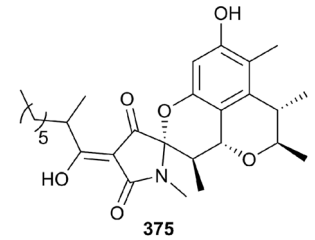


†374



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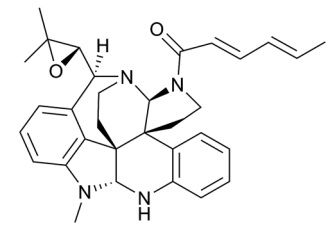

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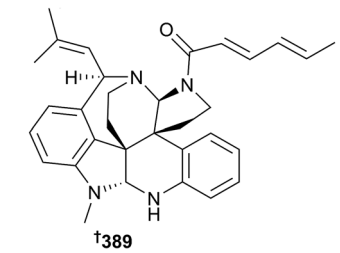
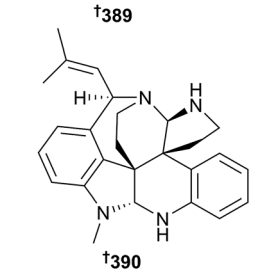


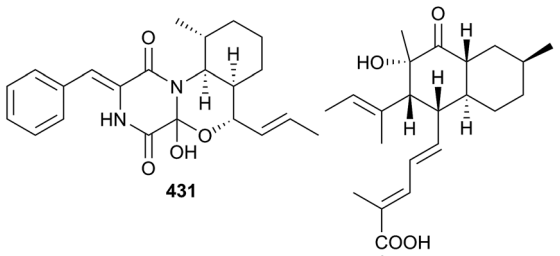
†389



†390

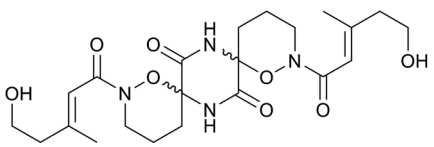
Further metabolites isolated from the genus *Penicillium* include meroterpenes ***391*** and ***392***,[253] alkaloids ***393***,[254] ***394–396***,[255] diphenylmethanone derivative ***397***,[256] phenolic enamide ***398*** and meroterpenoid ***399***,[257] azaphilone derivatives ***400–402*** and diphenyl ether derivatives ***403*** and ***404***.[258] The planar structure of ***404*** appears in a screening library[259] 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 norlichexanthone[270] and monocerin[271] ***433*** (first time MNP), neither of which was detected in the individual axenic cultures of the two strains.[272]



431 †**432**

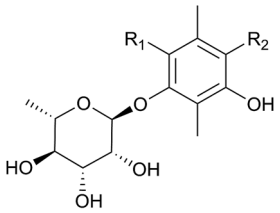
A soft coral-related *Pestalotiopsis* sp. was the source of enantiomeric alkaloid dimers (+)- and (−)-pestaloxazine A **434** and **435**.[273] These mixed polyketide-cyclopeptide metabolites (PKS-NRPS hybrids) possessed a unique, symmetric spiro [oxazinane-piperazinedione] skeleton and the racemate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



†**434** (*RR*)
†**435** (*SS*)

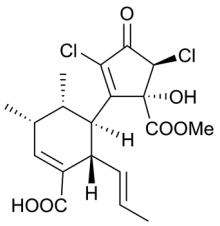
The genus *Pestalotiopsis* yielded a number of other new metabolites, including meroterpenoids ***436*** and ***437***, isocoumarin ***438***, phenol ***439*** (ref. 274) phthalide derivative ***440***,[275] 5′-*O*-acetyl uridine[276] ***441*** (ref. 275) (new NP) and pestarhamnoses A–C **442–444**.[277] The pestarhamnoses 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 pestalachlorides.[278,279] Interestingly, no brominated analogues were detected but pestalachlorides C and D[279] were isolated along with pestarhamnoses 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 asterric acid derivatives ***463–466***).[286] The ascidian-derived *Roussoella* sp. produced roussoellatide **467**, a dichlorinated polyketide with an unprecedented skeleton and



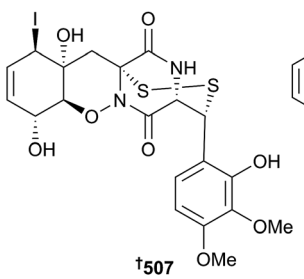
†**442** R_1 = Me, R_2 = H
†**443** R_1 = H, R_2 = Me
†**444** R_1 = R_2 = H

experiments with [1-^{13}C]-, [2-^{13}C]- and [1,2-^{13}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]

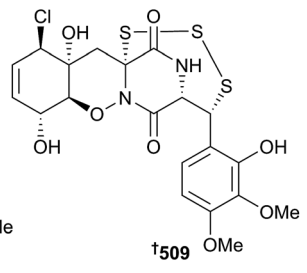


†**467**

New metabolites were also obtained from the genera *Simplicillium* (diketopiperazine ***468*** and furanone[288] ***469***; the latter a first time MNP[289]), *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 dervatives ***500–505***).[298] A red algal-derived *Trichoderma* species produced gliovirin,[299] pre-trichodermamide A[300] and the related trichodermamide A[301] when grown on a freshwater medium, chlorinated derivatives trichodermamide B[301] and DC1149B[302] ***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, DC1149R[302] ***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, chlorotrithiobrevamide **509**.[304] Decalin derivatives ***510–512***,[305]



†**507**



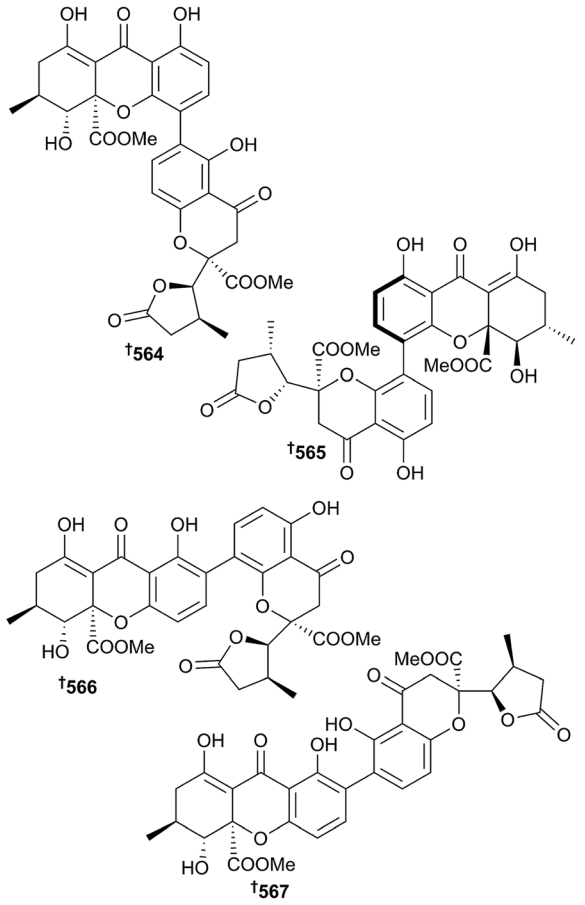
†**509**

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

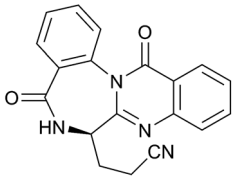
The genus *Truncatella* was the source of some isoprenylated cyclohexanols ***523–536***,[308] while an antibiotic polyketide ***537*** and ascosetin[309] ***538*** were obtained from a fungus of the Lindgomycetaceae family.[310] Synthesis of the octaketide ascospiroketal A, originally obtained from *Ascochyta salicorniae*,[311] *via* a Ag^{I}-promoted cyclisation cascade, revised the stereochemistry to ***539*** and indicated that the structure of ascospiroketal B[311] 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 *Rhabdermia* 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] Acetylgliotoxin G[322] ***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 synthesised[328] 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 K[337] (*Dendrodochium* sp.) has been accomplished from a commercially available substrate by a convergent strategy[338] and other dendrolides (F, G, I, J and L[337]) 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] C[342] and penicillide[343] exhibited potent antifouling activity against settlement of *Balanus amphitrite* larvae[296] as did altertoxin I, a metabolite of both terrestrial[344] and marine[345] *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 antiinflammatory 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 *Stachyhotrys 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 B[360] 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 cylohexanone, 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] isochromane 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 dinapthalenone 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* (indolediketopiperazine ***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 compounds[398]) and polyketides ***644–647***.[399] Pinazaphilone A reported in this paper[399] 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]

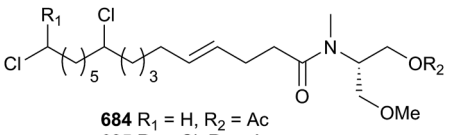


Further metabolites were obtained from the genera *Pestalotiopsis* (prenylated phenols ***649*** and ***650*** (ref. 401)), *Phomopsis* (purine derivative ***651*** and octadecadiene derivative ***652***;[402] first isolation as a NP),[403] *Setophoma* (polyketides ***653***,[404] ***654*** and ***655***, ***656***,[405] ***657*** and ***658***, ***659*** (ref. 406)) and *Stemphylium* (aromatic sulfates ***660*** and ***661*** (ref. 407)). Stemphol[408] ***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. Torrubiellin B[412] 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 H[416] and I[416] has revised the configuration at C-6 of each to (*R*) (***674*** and ***675***) but discrepancies for some ^{13}C 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 dipodomyicola*[418] have been synthesised *via* a biomimetic method[419] as has the *Penicillium* metabolite,[420] (−)-penibruguieramine.[421] *Pestalotiopsis* metabolite (6*S*,1′*S*,2′*S*)-hydroxypestalotin[422] has been synthesised[423] and the proposed structure of pestalotioprolide A[424] 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 A_1,[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

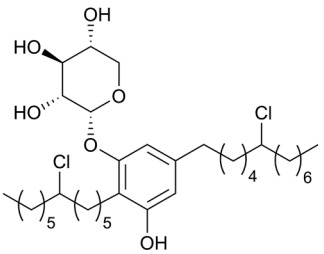
There has been an upturn in the number of new metabolites reported from cyanobacteria with 31 new metabolites reported in 2015 compared to 19 in 2014. Typical of the phylum, most of the metabolites reported were peptides. Linear lipopeptides ***676*** and ***677*** were obtained from *Anabaena torulosa*,[429] 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 CB_1 and CB_2 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]



684 R_1 = H, R_2 = Ac
685 R_1 = Cl, R_2 = Ac
686 R_1 = R_2 = H

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.



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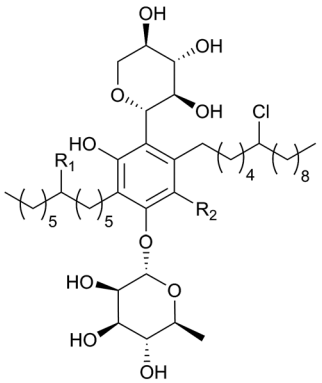
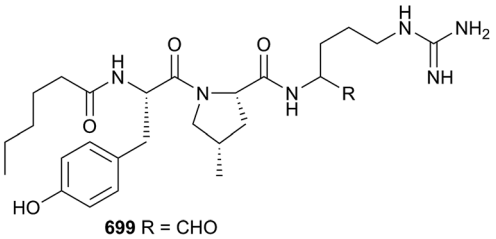


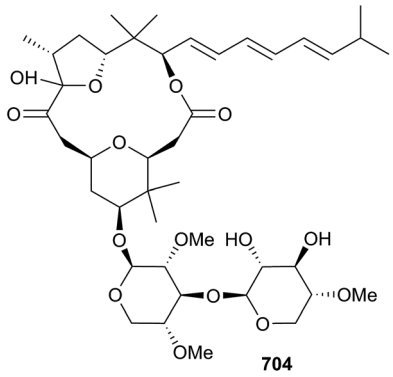
696 R_1 = Cl, R_2 = H
697 R_1 = R_2 = H
698 R_1 = R_2 = Cl

Nodularia spumigena was the source of the pseudoaeruginosins NS1 **699** and NS2 **700**, linear peptides which contain structural features of both the aeruginosins[440] and the spumigens.[441] Structural characterisation of these metabolites was completed through synthesis and pseudoaeruginosin NS1 **699** was a potent trypsin inhibitor.[442]



699 R = CHO
700 R = CH_2OH

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 A[446] 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, reisolation 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]



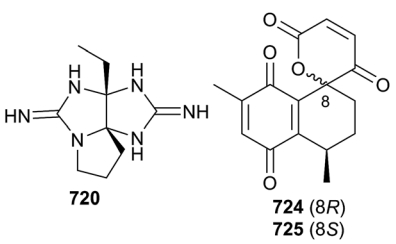
704

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 Oscilliatoriales family, was the source of the polyhydroxylated macrolides ***706*** and ***707***.[453] Total synthesis of the cyclodepsipeptide coibamide A[454] 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 lyngbyalosides. Total syntheses of the proposed[456] and correct structures (***709***) of (−)-lyngbyaloside B were completed[457] and total synthesis of the (18*Z*) and (18*E*) isomers of lyngbyaloside C[458] resulted in reassignment of the structures to ***710*** and ***711*** respectively.[459] As a result, it was suggested that the structure of lyngbouilloside[460] should likely also be reconsidered.[459] Total syntheses of the

acyclic depsipeptide maedamide[461] and cyclodepsipeptide largamide B[462] 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 jamaicamides[472] were elucidated *via* both *in vitro* and *in vivo* analyses.[473] Dereplication methods based on phylogeny and HPLC-MS were developed which showed that largazole[474] was always coproduced with either dolastatin 10 (ref. 475) or symplostatin 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 *Karlodinium* 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 *Paramedcium caudatum* at a relatively low dose. Total synthesis of each confirmed relative configurations.[491]



720 **724** (8*R*) **725** (8*S*)

Nonacosadienes ***726*** and ***727*** were obtained as metabolites of the microalga *Emiliania huxleyi*[492] while 12β-deoxydecarbamoylsaxitoxin[493] ***728*** was obtained as a first time MNP.[494] Syntheses of the polyketide amphirionin-4 (ref. 495) and ciguatoxin 54-deoxyCTX1B[496] have been achieved.[497,498] Polyketide synthesis genes unique to two *Gambierdiscus* species that produce maitotoxin[499] were characterised, perhaps implicating them in the biosynthesis of this metabolite.[500] Studies with *Karenia brevis* showed that brevetoxin[501] 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]

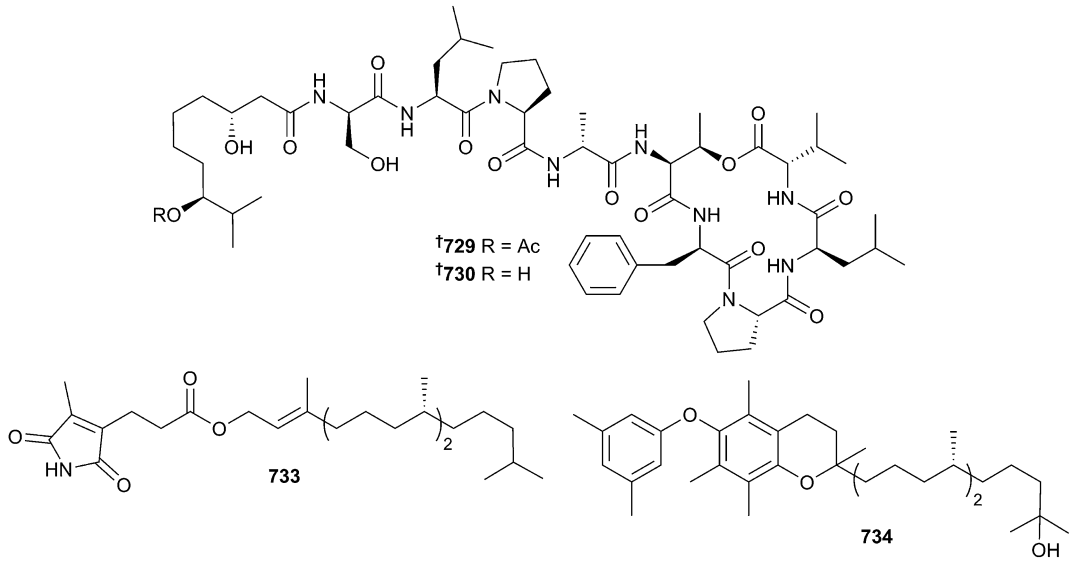
4 Green algae

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.

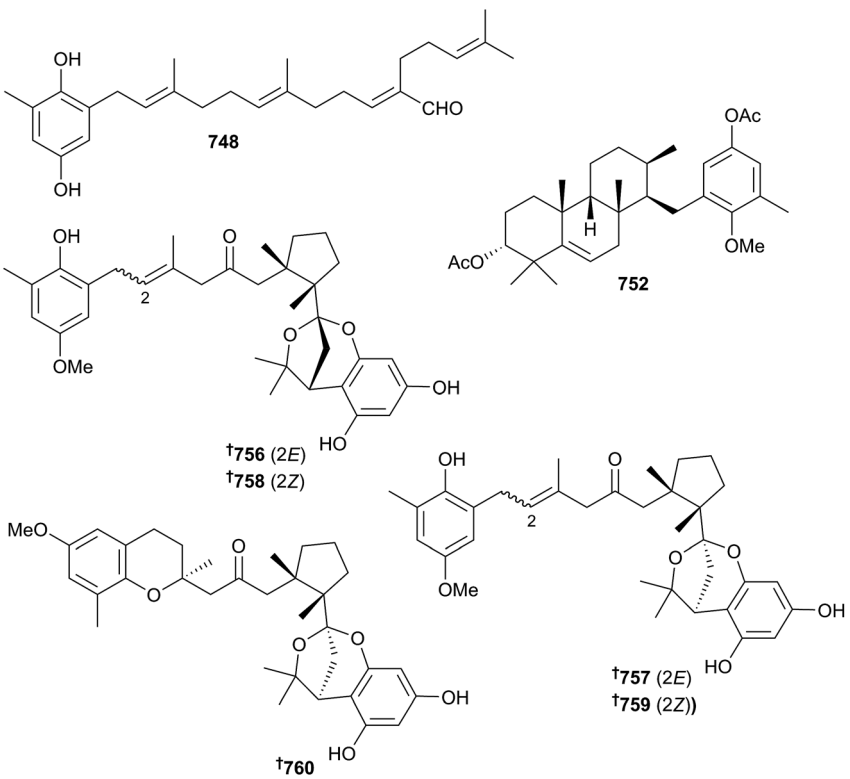
The structure and absolute configuration of nigricanoside A, isolated in 2007 from *Avrainvillea nigricans*,[506] has been established by enantioselective total synthesis as ***737***, correcting aspects of the previously reported configurations.[507] Originally isolated as the dimethyl ester, nigricanoside A was reported to inhibit the proliferation of several cancer cell lines (IC_{50} 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

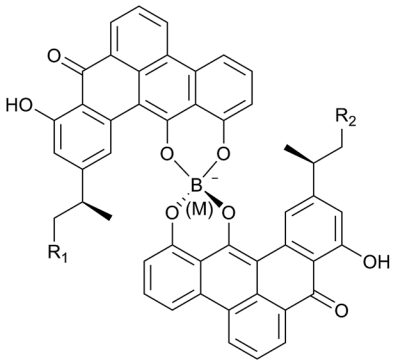
The level of interest in brown algae in 2015 was comparable to recent years with 33 new compounds reported from 12 papers out of a total of 54 papers and reviews on brown algae. Not atypically the chemistry was dominated by terpenoids and meroterpenoids with two dolastanes, ***738*** and ***739***, four 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. subfarcinata, Sargassum* cf. *fallax*),[525] four cyclic meroditerpenoids **752** (*Stypopodium flabelliforme*),[526] ***753–755*** (*Stypopodium zonale*)[527] and the cyctophloketals A–E, **756–760**, hybrid meroditerpenoids from *Cystoseira tamariscifolia.*[528] The cyctophloketals, **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-6β-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]



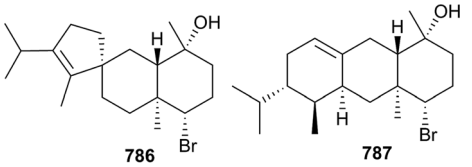
The non-terpenoid brown algal compounds are represented by the polyketides, ***761–770***, from *Lobophora variegata*.[532] When considered as a group their biosynthetic origins can be rationalised by involvement of a non-acetate starter acyl-CoA, most likely a dodecanoic acid unit, and type III polyketide synthases.[533,534] The absolute configuration for the acylic 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 reported[539] 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]

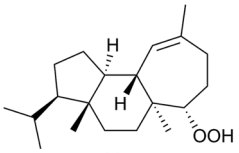


†**791** $R_1 = R_2 = H$, (M+P)
†**792** $R_1 = H$, $R_2 = Me$
†**793** $R_1 = H$, $R_2 = Me$, (P)

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 spirosphaerol **786** anthrasphaerol **787** and corfusphaeroxide **788** from *Sphaerococcus coronopifolius* have unprecedented tricyclic skeletons.[571]





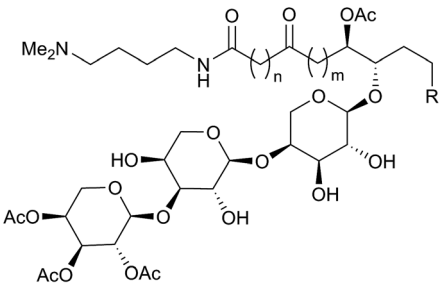
The remaining 13 compounds, the borolithochromes ***791–803***, were a series of polyketide-derived spiroborate pigments from samples of a more than 150-million-years-old Jurassic putative red alga *Solenopora jurassica*. The representative structures of borolithochromes G **791**, H1 **792** and H2 **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 study[574] 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 structures[576] and established their absolute configurations.[577] Total syntheses of the proposed structures of microcladallenes A, B and C[578] 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 (IC_{50} 9 μM).[595]

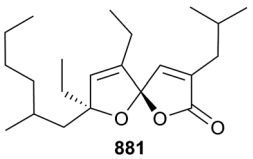
Polyacetylenes were found in extracts of *Callyspongia implexa* ***848***,[596] *Petrosia* sp. ***849–851***,[597] *Halichondria* sp. ***852–854***,[597] *Pleroma* sp. ***855–861***,[598] and *Xestospongia* sp. ***862*** and ***863***.[599] The nanomolar-scale isolation of mollenynes B–E **864–867**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



842 n = 11, m = 7, R = iPr
843 n = 11, m = 7, R = *n*Pr
844 n = 11, m = 7, R = *n*Bu
845 n = 11, m = 8, R = *n*Pr
846 n = 12, m = 6, R = *n*Bu
847 n = 12, m = 7, R = *n*Pr

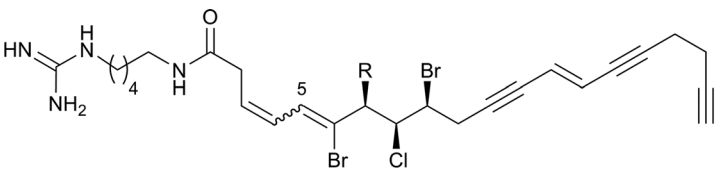
Spirastrella mollis posed several challenges. First, the extremely low yields of isolated compound imposed limitations on acquiring usable NMR spectra, and second, unequivocal placement of the chlorine and bromine atoms upon the carbon backbone was difficult due to the similarity in ^{13}C chemical shifts. 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]

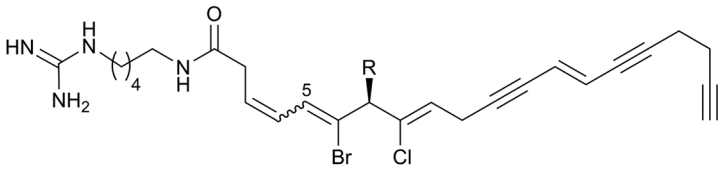


881

An unidentified sponge yielded two aromatic bases ***882*** and ***883***,[607] while a mixture of Thorectid 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 *Dragmacidon* 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_oG_1 phase.[611]



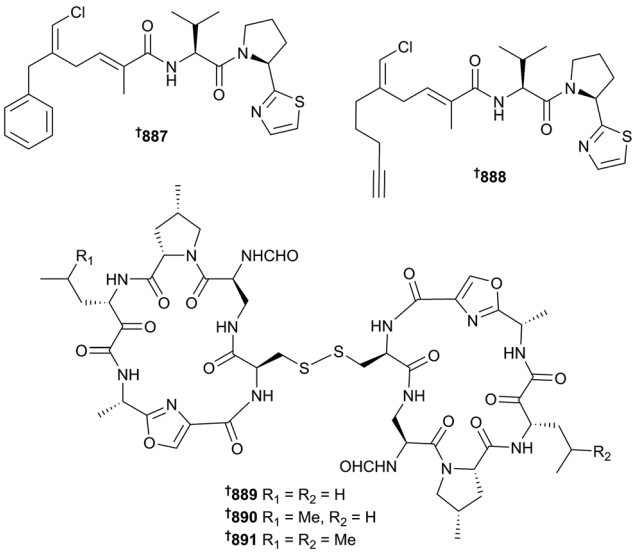
864 (3*Z*,5*Z*), R = OH
865 (3*Z*,5*E*), R = H



866 (3*Z*,5*Z*), R = OH
867 (3*Z*,5*E*), R = H

The known fungal metabolites gibepyrones 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 (IC_{50} 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 reisolation 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]

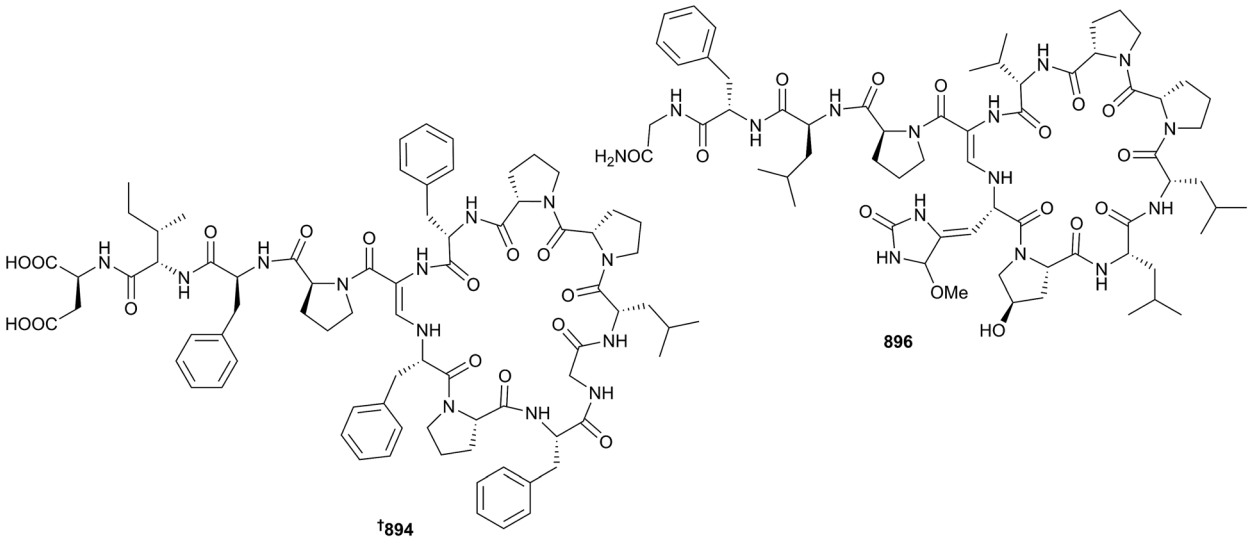
Stellettapeptins A **900** and B ***901*** are hybrid NRPS/PKS depsipeptides isolated from *Stelletta* sp. Structures were established using a combination of degradation studies and comprehensive NMR experiments. Both exhibited anti-HIV activity in HIV_{RF}-infected human T-lymphoblastoid cells with EC_{50}'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] *Hemimycale arabica* and *Acanthella cavernosa* were sources of hemimycalins ***904*** and ***905*** (ref. 619) and diketopiperazines ***906*** and ***907***.[620]

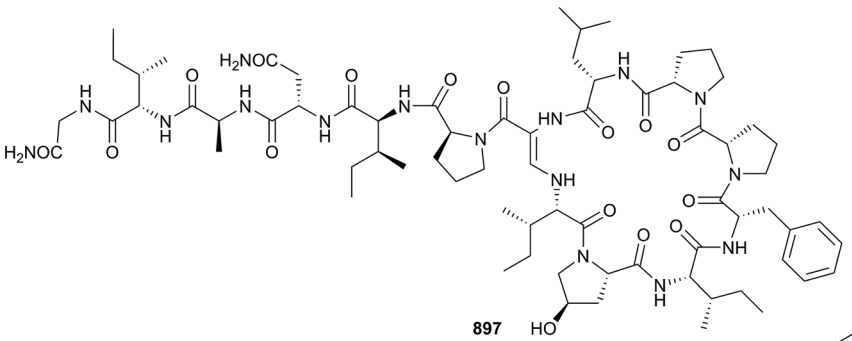
Both enantiomers **908** and **909** of spirocyclic spiroreticulatine were isolated from *Fascaplysinopsis.* X-ray studies suggested the presence of a racemate, prompting the researchers to separate the compounds *via* chiral chromatography. The absolute configuration of each stereoisomer was determined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

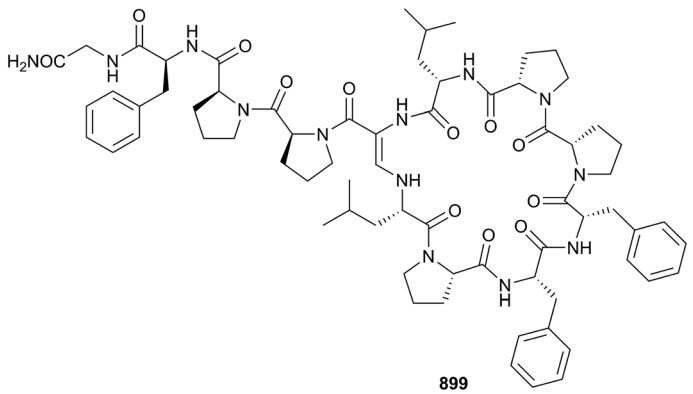
Three diamine-type alkaloids ***910–912*** were isolated from Indonesian *Neopetrosia*[622] and *Acanthostrongylophora*[623] sponges, while a *Neopetrosia* sp. also yielded two nucleosides ***913*** and ***914***, one of which was also synthesised.[624] Indole alkaloids were isolated from *Ircinia* ***915*** 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]

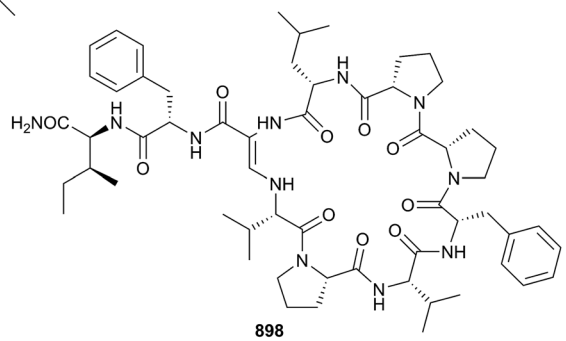
Guanidine-type alkaloids have been isolated from *Biemna laboutei* ***926–930***,[632] *Pseudoaxinella reticulata* ***931–934***,[633] *Monanchora arbuscula* ***935–940*** (the synthesis of ***935*** was also achieved),[634] and *M. pulchra* ***941–943***,[635] while oroidin-type pyrrolo-alkaloids were 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 puupehenone[651] was also isolated. Exposing **996** to mild acid ($CDCl_3$) 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*,



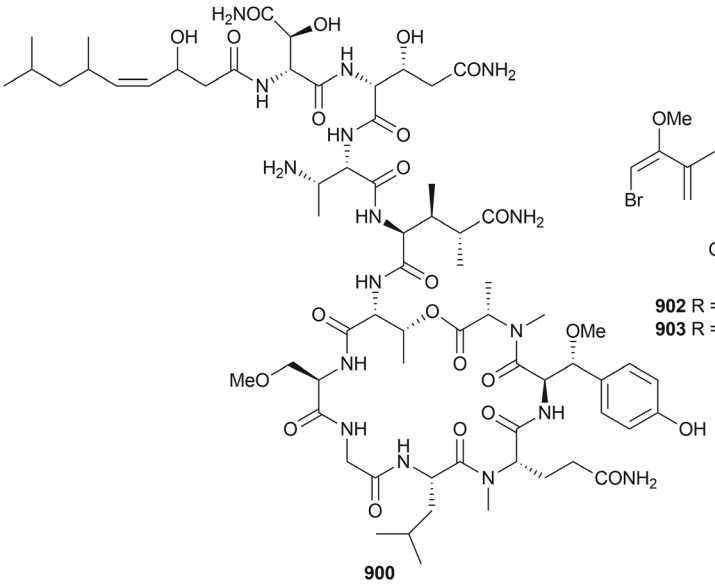


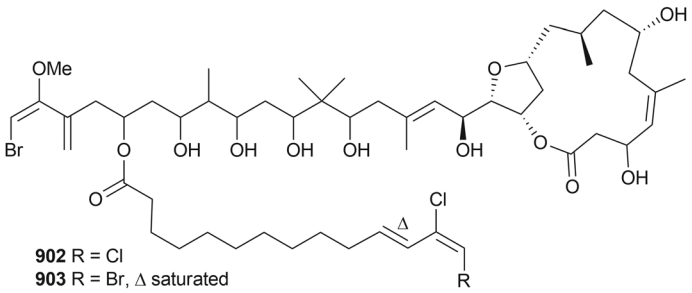


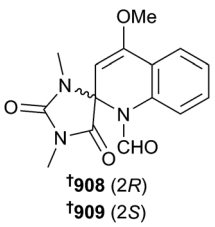


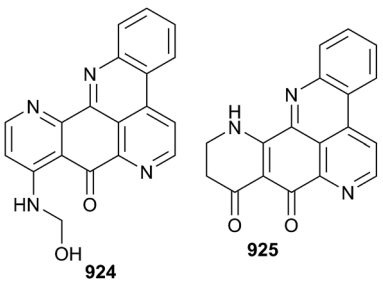
and *Petrosia cortica* respectively. Sesquiterpenoids ***1009*** and ***1010***,[657] and ***1011–1013*** (ref. 658) were isolated from *Dysidea fragilis* and ***1014–1018*** from *Halichondria* sp.,[659] while three farnesylacetone derivatives ***1019–1021*** were reported from *Diacarnus megaspinorhabdosa*.[660] *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 (IC_{50} 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





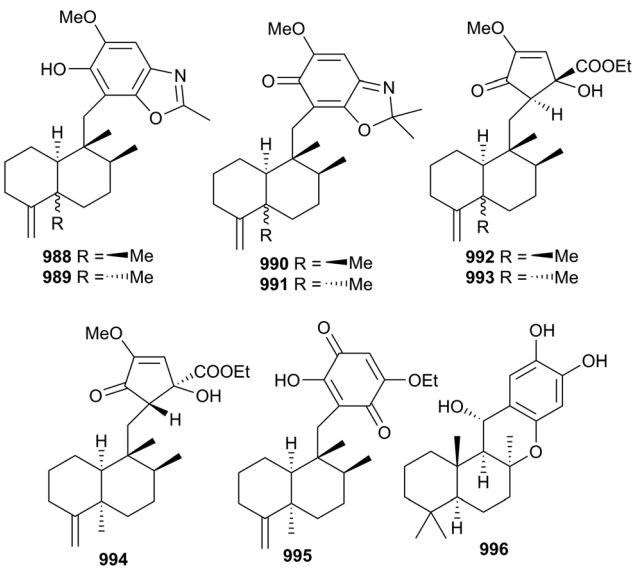


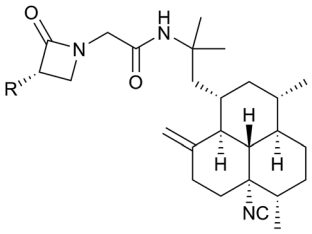


sesterterpenoids were ***1074*** and ***1075*** (*Clathria gombawuiensis*)[675] and ***1076*** (*Haliclona* sp.) sourced from Korean collections.[676]

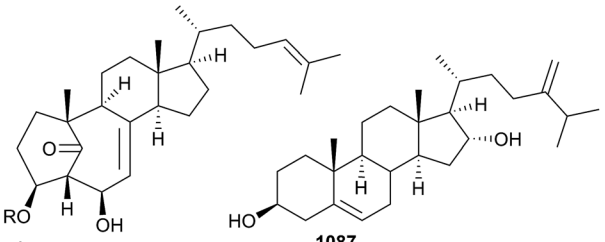
Several new sterols and their degradation products have also been reported from sponges. Epoxide- ***1077*** and peroxide-***1078–1079*** containing sterols were found from *Biemna*[593] and *Monanchora*[677] sponges, respectively, while highly derivatized sterols were isolated from *Dragmacidon australe* ***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 4β,5β-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 (IC_{50} 65 μM), both **1086** and **1087** were not, but instead were immunomodulatory inhibiting mRNA expression of IL-6 by ~70% at 10 μM 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 stellettins 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



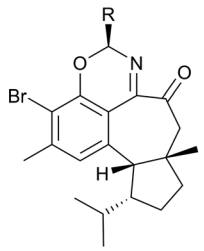


†**1026** R = Me
†**1027** R = OMe

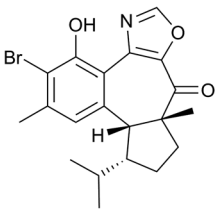


†**1085** R = H
†**1086** R = Ac
1087

absolute configuration of psammaplysin 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 euryspongin A ***1102*** (*Euryspongia* sp.) was also determined using chiroptical techniques.[609] Inconsistencies in NMR data reported for two sponge sterols isolated from *Neofibularia nolitangere*[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 crambescin 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 artherosclerosis.[696] Panicein A hydroquinone[697] (*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 detoxification[699] 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 Ca^{2+}-binding photoprotein aequorin. Ca^{2+} 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



1028 R = Me
1030 R = CH_2Ph
1032 R = *i*Pr
1033 R = *i*Bu



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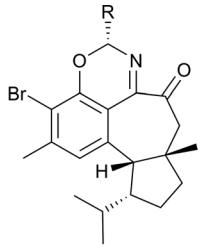
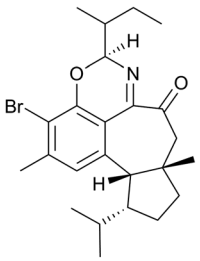


1031 R = CH_2Ph
1034 R = *i*Bu



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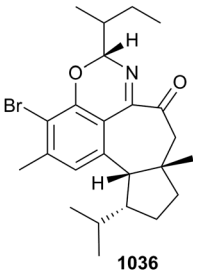
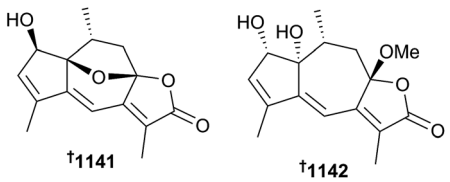


1036

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 callyspongynic acid,[720,721] phosphoiodyn A and placotylene 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_2,[774,775] dictyoceratins A[776] and C,[777–779] and neopetrosiquinones A and B.[780,781] The structure of siphondictyal B[782] has been revised to ***1112***, based upon total synthesis. The biomimetic conversion of siphondictyal B to liphagal[783] *via* a stable *o*-quinone methide supports a novel biogenetic proposal.[784] The sesquiterpenoids aignopsanoic acid A, methyl aignopsanoate and isoaignopsanoic acid A[785] 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.* spongiolactone[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 sesterterpenoids phorbin A,[797,798] luffarins L and I,[799–801] salmahyrtisol A[802] and hippospongide A[803,804] have been finalised.

8 Cnidarians

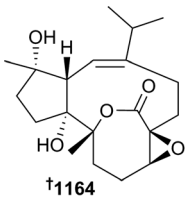
The low number of new compounds reported from cnidarians in 2015 (143) is 40% below the previous decadal average. The chemistry of cnidarians is typically dominated by compounds of terpenoid origin. In 2015 there were a limited number of alkaloids isolated from both soft and hard corals, including the 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 ^{13}C NMR chemical shifts, optical rotation and ECD to determine the structures and absolute configurations of **1141** and **1142.**



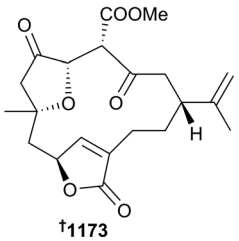
†1141 †1142

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 *Nephthea columnaris*),[821] columnariols A ***1151*** and B **1152** (cultured *N. columnaris*),[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 arboreum*),[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]

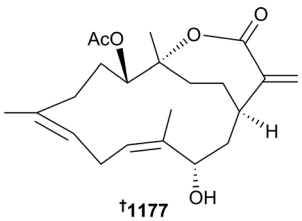
A series of nitrogenous diterpenoids and sesquiterpenoids ***1178–1187*** were reported from *Cespitularia taeniata* – the absolute configuration of cespilamide A ***1178*** was established by a combination of MM2 modeling and Mosher's analysis.[834]



†1164

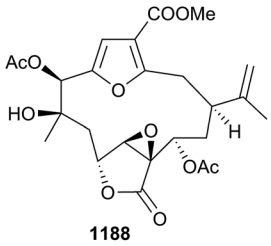


†1173

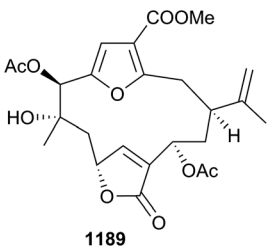


†1177

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.

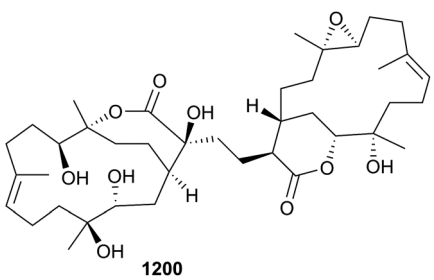


1188



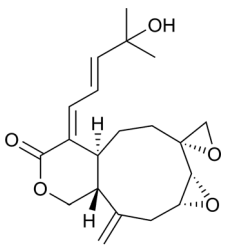
1189

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 sinuflexolide[841] were secured by X-ray studies.



1200

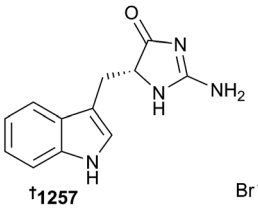
Cytotoxic and anti-inflammatory bis-cembranoids glaucumolide A ***1201*** and B ***1202*** were isolated from cultured specimens of *Sarcophyton glaucum*,[842] while of sarcophytolides M ***1203*** and N ***1204***, only the former exhibited cytotoxicity to a panel of HTCLs.[843] Eight new briarane-skeletoned 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.



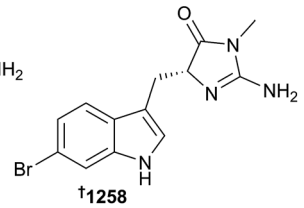
1213

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]

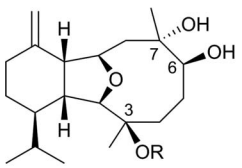


†1257

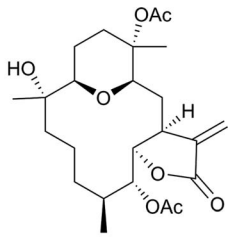


†1258

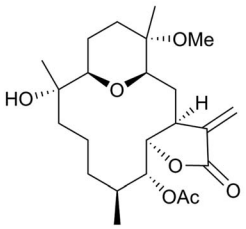
As noted in last year's review,[1] clarification of the structures of cladiellin diterpenes including the sclerophytins (*Sclerophytum capitalis*)[862] is an ongoing issue. Based upon re-analysis of NMR data Friedrich and Paquette in 2002 proposed a number of structural revisions.[863] Synthesis of the 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 litophynin 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]



†1259 R = Ac
†1260 R = CO*n*Pr

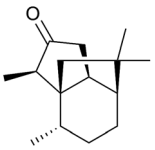


†1261



†1262

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 III[874] (*Clavularia viridis*),[875] tubastrine[876] (*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.



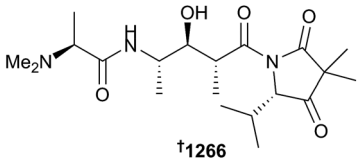
†1264

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] Excavatolide 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 artifactual 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 A[893] and convolutamines I[894] 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 stereoselective 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 monoheneicosanoin[902] ***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]

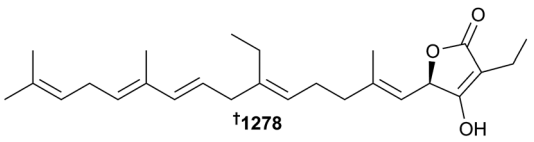


†1266

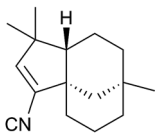
10 Molluscs

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 competiton 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 isocyano 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-isocyanoclovene **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 aplysiasecosterol A

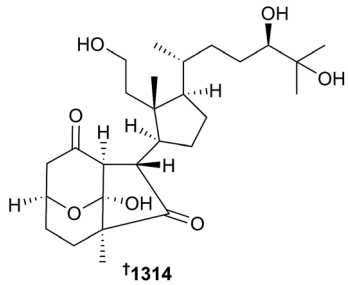


†1278



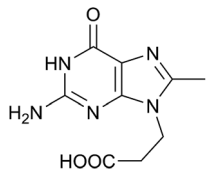
†1279

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.



†1314

Re-examination of extracts of *Elysia crispata* (Venezuela) has led to the characterisation of (−)-phototridachiahydropyrone ***1315***,[918] a molecule previously speculated to be a MNP based upon its biomimetic photochemical formation from the related metabolite tridachiahydropyrone.[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 *Dicanthais orbita*.[920] 6-Bromohypaphorine (*Hermissenda crassicornis*), previously known as a sponge[921,922] and tunicate metabolite,[923] is a mild agonist of human α7 nAChR but shows no effect on muscle-type nAChR from *Torpedo californica*.[924] Dolastatin 16 obtained by total synthesis[925] 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, genuanine **1316** was isolated from *C. genuanus* and the structure confirmed by synthesis.[932] Compound **1316** exhibited potent paralytic activity in mice, mimicking the activity of the crude venom extract.

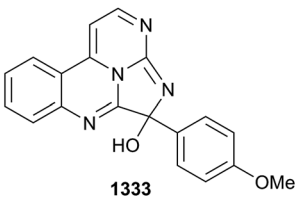


1316

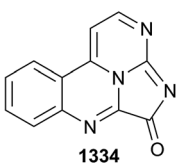
A small library of analogues representing desmethyl and/or propionate sidechain positional isomers were all devoid of activity. At the other molecular weight extreme, a specialised insulin Con-Ins G1, bearing post-translational modifications characteristic of conotoxins, *e.g.* hydroxyproline and γ-carboxyglutamate, 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-1α) required for HIF-1α (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.



1333



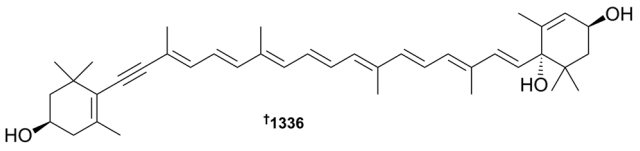
1334

An expeditious total synthesis of shishijimicin A[941] has been reported,[942] confirming the structure and opening the door for further biological evaluation of this potently cytotoxic enediyne. The structure of tunichrome Sp-1 (ref. 943) has been confirmed by total synthesis[944] and a new catalytic asymmetric synthetic route to (−)-perophoramidine[945] has been disclosed.[946] Cell-cycle arrest at the G_2/M phase and induction of apoptosis in HeLa cells[947] was observed for the ascidian alkaloid eudistomin H,[948] while eusynstyelamide B[949] also induces G_2/M phase arrest, causes double strand breaks in DNA and is a topisomerase II poison.[950] Further investigation of clavanin 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 polyandrocarpamines[955] were found to be inhibitors of H_2S production by cystathionine beta-synthase,[956] and SAR studies have been reported for thiaplidiaquinones A and B[957] (various biological targets),[958] cadiolides A–C[959,960] (antibacterial),[961,962] rubrolides[963] (photosynthesis inhibitors),[964] meridianins[965] (antimalarial and antituberculosis),[966] isogranulatimide[967] (cytotoxicity),[968] and lamellarins[969] (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 (lessoniosides A–G) were reported from *Holothuria lessoni*.[982] As the structures were proposed based solely upon MS^n data, there are few data to define the associated aglycones and so the structures

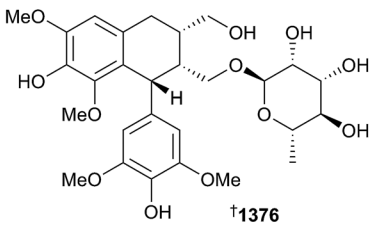


†1336

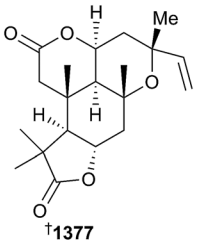
are not shown in this review. Using cladoloside C as a model (*Cladolabes schmeltzii*),[983] chemical transformations combined with Moshers analysis has determined C-22 as having (*R*)-configuration.[984] The authors speculated that all C-22 functionalised sea cucumber glycosides may have the same (22*R*) 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-2A[987] (starfish *Protoreaster nodosus*)[988] and steroidal glycosides astrosterioside A[989] (starfish *Astropecten monacanthus*)[990] and linkosides A and B[991] (starfish *Linckia laevigata*)[992] have been confirmed by total synthesis. Further studies using purified pentahydroxynaphthoquinone echinochrome A[993,994] have identified suppression of SERCA2A Ca^{2+} reuptake[995] 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 pathway[999] 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 (*Thelenota anax*) 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

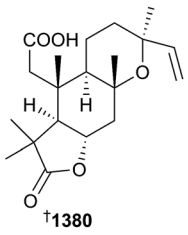
Mangroves or their associates were the sources of antiviral cyclohexylideneacetonitriles ***1363–1366*** (*Bruguiera gymnorrhiza*),[1003] a phenolic ***1367*** and a diol ***1368*** from the fruits of *Avicennia marina*,[1004] phenolics and a cerebroside ***1369–1372*** (*Sonneratia ovata*),[1005] glycosides **1373** (*Kandelia candel*)[1006] and ***1374–1376*** (*Bruguiera gymnorrhiza*),[1007] *seco*-labdanoids ***1377–1380*** (*Excoecaria agallocha*),[1008] dolabrane-diterpenes ***1381–1386*** (*Ceriops 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.



†1376

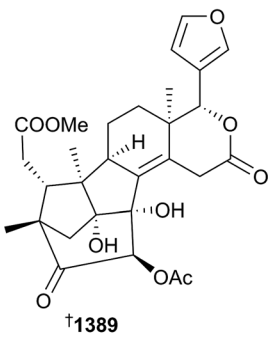


†1377

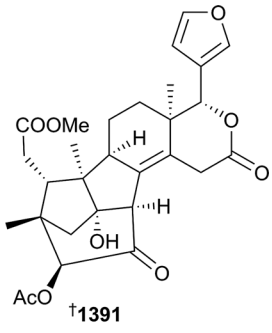


†1380

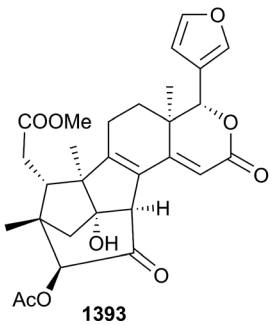
The absolute configurations of new limonoids, including thaixylomolins I **1389**, K **1391** and M **1393**, were determined by TD-DFT calculations of ECD data.[1010] NMR data observed for **1391** were identical to those reported for the known phragmalin-skeletoned limonoid moluccensin J[1014] – close 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 (*Ceriops tagal*)[1015] to exhibit cytotoxicity *in vitro* towards a panel of haematologic cell lines, and *in vivo* towards



†1389



†1391

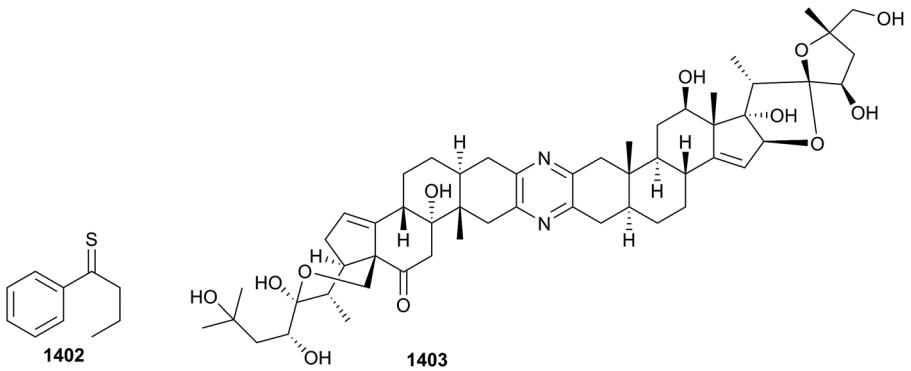


1393

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 xyloccensin E[1019] and I[1020] (*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



1402 **1403**

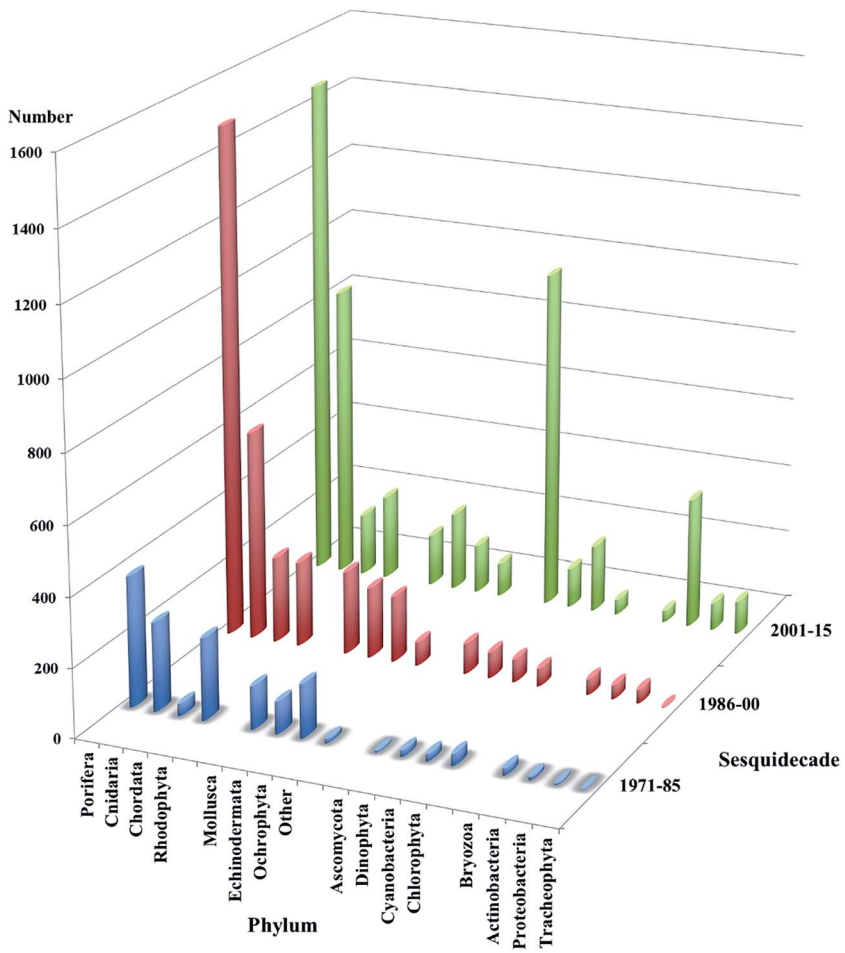


Fig. 1 The most abundantly collected phyla by sesquidecade.

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) hilgendorfii* 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

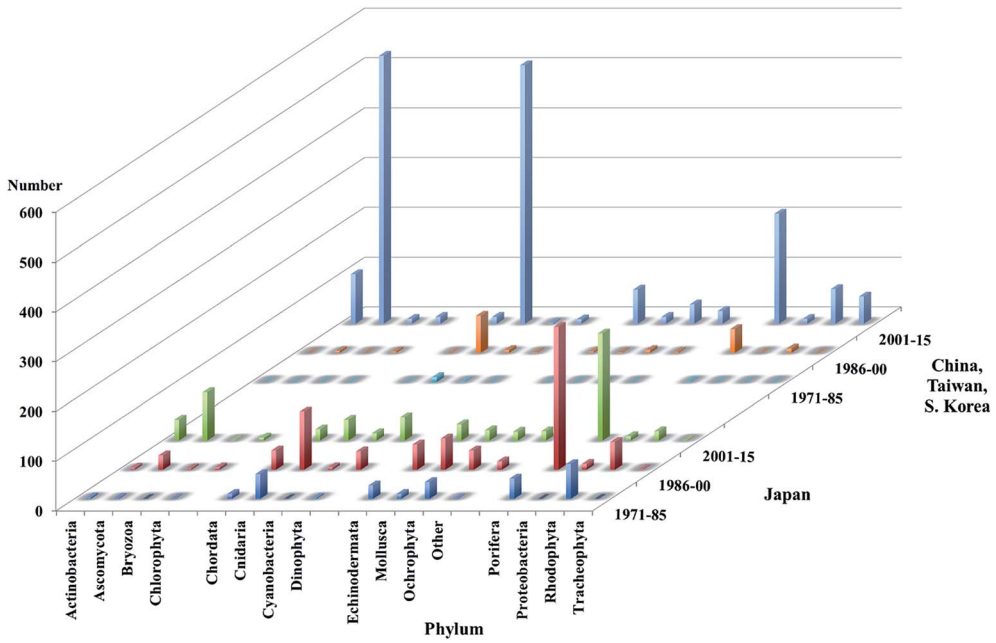


Fig. 2 Collections in Japanese waters by sesquidecade contrasted with the collections in Chinese, Taiwanese and S. Korean waters.

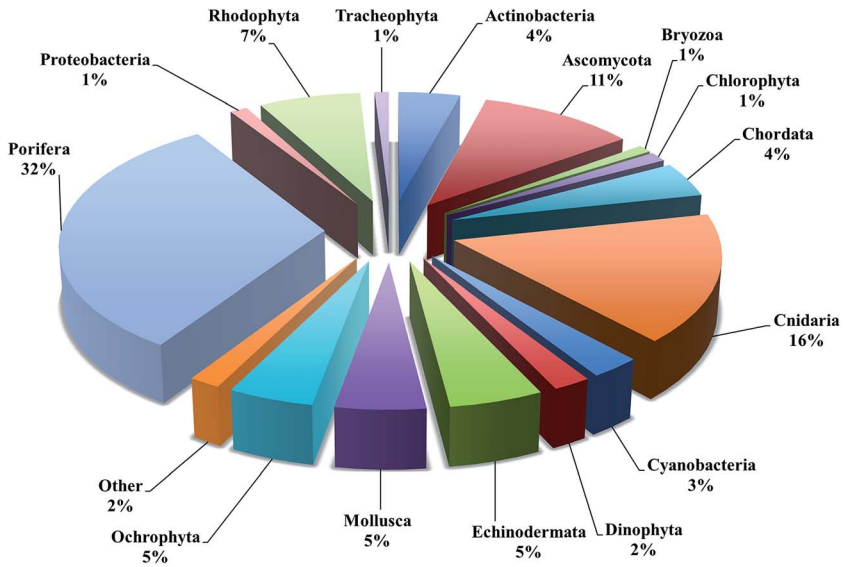


Fig. 3 Distribution of the collection effort over the period 1971–2015 by phylum.

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 ~20 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 antineoplastic 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

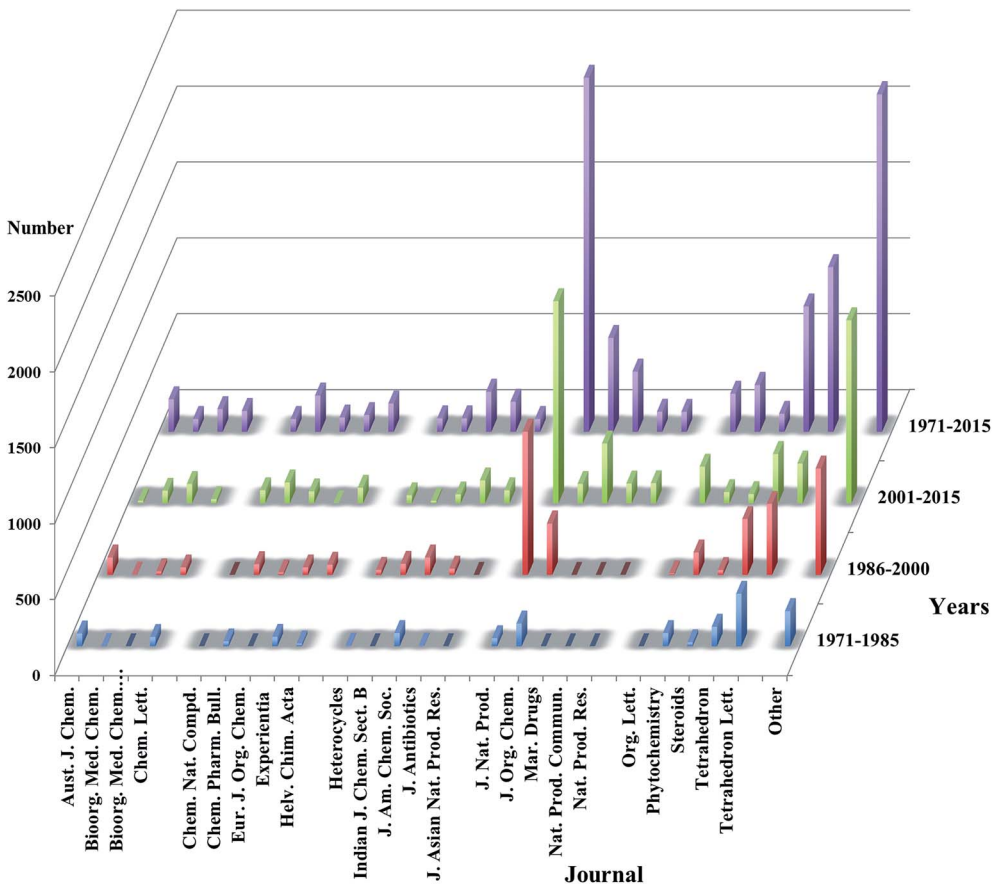


Fig. 4 The 24 most selected journals used overall for publication of new compound data for the period 1971–2015, also shown by sesquidecade.

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.

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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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