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.

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. 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 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 an 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.
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. 1 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 post-doctoral research with Jon Clardy at Cornell and Chris Ireland at the University of Utah. 1992–93 was spent working in industry as an isolation chemist with Xenova Plc, before returning to New Zealand to take a lectureship at the University of Auckland, where he is currently an Associate Professor.

Murray Munro, Emeritus Professor in Chemistry at the University of Canterbury, has worked on natural products right through his career. This started with diterpenoids (PhD; Peter Grant, University of Otago), followed by alkaloids during a post-doctoral spell with Alan Battersby at Liverpool. A sabbatical with Ken Rinehart at the University of Illinois in 1973 led to an interest in marine natural products with a particular focus on bioactive compounds which has continued to this day. In recent years his research interests have widened to include terrestrial/marine fungi and actinomycetes.
complete genome of Candidatus Endoecteinascidia frumentensis, the ET-743 producer, has now been assembled. Analysis of the phylogenetic markers and protein coding genes suggest that Ca. E. frumentensis belongs to a novel family of the γ-proteobacteria. This better understanding of the biosynthesis of ET-743 will promote efforts to produce the drug directly by in vitro methods or heterologous expression rather than the current semi-synthetic process starting from cyanosafacin.\textsuperscript{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\textsuperscript{T} (Mooreiaceae) the marinazepinones A\textsubscript{1} and B\textsubscript{2}, the marinaziridines A\textsubscript{3} and B\textsubscript{4}, and the marinoquinolines G\textsubscript{1}–I\textsubscript{5}–7 were isolated, while CNU-194\textsubscript{T} (Catalimonadaceae) and CNX-216\textsuperscript{T} both produced the marinopyrazinones A\textsubscript{8} and B\textsubscript{9}.\textsuperscript{26}

This is the first occurrence of azepin-3-one alkaloids in nature and also the first occurrence of aziridine- and pyrazinone-based alkaloids in Gram-negative bacteria. Two new peptaibols 10 and 11 were isolated from Microbacterium sediminis and is the first reported isolation of peptaibols from an actinomycete, not a fungal source.\textsuperscript{27} Following the discovery of an antitrypanosomal series of macrolactams the genome of the producing Micromonaspora sp. was sequenced and the responsible biosynthetic gene cluster (BGC) identified.\textsuperscript{28} By a combination of spectroscopy and sequence data the structures and absolute configurations of the lobosamides A–C\textsubscript{12–14} were established.\textsuperscript{29} 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,\textsuperscript{29} was shown to contain a highly similar BGC. Consequent work led to the isolation and characterisation of the non-MNP mirilactams A\textsubscript{15} and B\textsubscript{16}, confirming the validity and usefulness of this approach to genome-mining.\textsuperscript{28}

The putative BGC for the fluorostatins from Micromonaspora rosaria\textsuperscript{30} was expressed heterologously in Streptomyces coelicolor and led to the isolation of fluorostatin L\textsubscript{17} and a fluorostatin heterodimer 18,\textsuperscript{31} while investigation of another Micromonaspora sp. resulted in isolation of a pimarane derivative 19.\textsuperscript{32} Based on Micromonasporaceae 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.\textsuperscript{33} Aminoimidazoles 20 and 21,\textsuperscript{34} diketopiperazines 22 (ref. 35) and 23 (ref. 36) (new to marine)\textsuperscript{37} and dimeric indoles 24 and 25 (ref. 38) were reported from Norcadipsis and Rubrobacter spp. Work on the actinomycete Saccharothrix sp. led to the isolation of further aromatic polyketides saccharothrixones A–D\textsubscript{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.\textsuperscript{39}

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

Michèle Prinsep received her BSc (Hons) and PhD degrees from the University of Canterbury, where she studied the isolation and structural elucidation of biologically active secondary metabolites from sponges and bryozoans under the supervision of Professors Blunt and Munro. She undertook postdoctoral research on cyanobacteria with Richard Moore at the University of Hawaii before returning to New Zealand to take up a lectureship at the University of Waikato, where she is currently an Associate Professor.
components and new derivatives of known compounds (methylation, hydroxylation, etc.). Molecular networking coupled with genome sequence data allowed for the rapid correlation between a BGC and the resultant secondary metabolite (pattern-generation). In this example it was found that the cluster NPRS40 was unique to one strain. Peptidogenomics was used to correlate this BGC with the 1171.42 Da parent ion node which in turn led to the characterisation of retimycin A\textsuperscript{30}, a new quinomycin-like depsipeptide.\textsuperscript{40} Sioxanthin\textsuperscript{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 \textit{Salinospora} spp. during vegetative growth. The biosynthesis of sioxanthin is also unusual as the carotenoid biosynthesis genes are non-clustered in the \textit{Salinospora} genomes.\textsuperscript{41}

The first successful heterologous expression of a gene cluster from the \textit{Salinospora} genome has been made. An 18kb type II PKS gene cluster from \textit{S. pacifica} with high homology to the enterocin locus in \textit{Streptomyces maritimus} was transferred to \textit{S. coelicolor} M1146 and \textit{S. lividans} TK23. Both clones produced enterocin. This opens the way to further explore the cryptic pathways of the \textit{Salinospora}'s secondary metabolome.\textsuperscript{42} From the screening of a pre-fractionated library of marine bacterial-derived extracts against \textit{Plasmodium falciparum} (\textit{P. falciparum}) a new class of antimalarials was discovered from a \textit{Salinospora} sp. The salinipostins A–K \textsuperscript{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 \{\textit{S\textsubscript{p}}, \textit{S\textsubscript{c}}\}. The potency against \textit{P. falciparum} ranged over three orders of magnitude (0.05 \textmu M to 46 \textmu M) varying with the length of \textit{R\textsubscript{i}} and \textit{R\textsubscript{j}}: salinipostin A \textsuperscript{32} was the most potent. In contrast, the salinipostins were relatively non-toxic to mammalian cells (>50 \textmu M). Encouragingly, initial attempts to select for resistance in \textit{P. falciparum} were not successful.\textsuperscript{43}

Also in the antimalarial area was the quantitative high throughput screening of another large natural products library (16 503 extracts) across four orders of magnitude in concentration against six geographically different strains of \textit{P. falciparum} which identified two \textit{Streptomyces} spp. for further investigation. Each contained a similar suite of compounds so only \textit{S. bangulaensis} was explored further. The recently identified actinoramide A/pandanamide A\textsuperscript{44,45} was the major metabolite along with three new analogues actinoramide D–F\textsuperscript{43–45}. 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 congers 46, 47 and 48 from a *Streptomyces* sp. and, subject to supply, further studies will examine the mechanism by which active lobophorins activate UPR.

New ansamycin analogues 53–55 were obtained from a mutant strain of *S. seoulensis*, and further ikarugamycin derivatives (tetramic acid macrolactams) 56–58 were isolated from a *S. zhaozhouensis*. 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.

A new analogue of the dilactone echinomycin was characterized from a *Streptomyces* sp. along with an ewd dike topiperazine. Another macrolide in the balomycin family, was produced by a *Streptomyces* sp. isolated from litter at a river mouth. 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.

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. A further depsipeptide in the salinamide series, F 50, was isolated from re-cultivation of *Streptomyces* sp. CNB-091. To address the bottleneck that often impedes progress in research, 3D-NMR techniques have been applied to the structure determination of peptidic natural products of interest. To balance costs, yield and relative 13C/15N abundance the growth media used peptone and yeast extract and [U-13C]-glucose. The *Streptomyces* sp., isolated from *Eudistoma olivaceum* was fermented in this media and the two peptides under study, eudistamides A 51 and B 52, were isolated. Seven of the typical protein triple resonance experiments were evaluated. Of these 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.

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 actinobenzoquinolone 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.82

Further bohemamine derivatives 69 and 70,83 two epimeric benzofurans 71 and 72,84 ten angucyclinone derivatives 73 and 74,85 75–82,86 anthracyclics 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-like 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 1,71 but further examination revealed that abyssomicin 2 88 was enantiomeric with the synthetic derivative as the absolute configuration of abyssomicin 1 had been incorrectly assigned. In this process the structure of abyssomicin 1 was also reassigned as abyssomicin 1 87. The mechanism of reactivation by the abyssomicins remains to be elucidated.72

A number of other compounds of lower molecular weight were also isolated from actinomycetes or Streptomyces spp. These included two butenolides 92 and 93,78 four cycloheximide derivatives 94–97,79 a furanone 98,80 an x-pyrone 99,80 four benzothioate glycosides 100–103,80 an alkylamide 104,80 an aniline derivative 105 with algidic properties79 and an incompletely characterized cysslabdan-like compound 106.82 Anti-dormant mycobacterial properties were reported for the known terrestrial antibiotic nybomycin86 isolated, in this instance, from a marine Streptomyces. This is the first report of nybomycin from a marine source.82 The biodiversity of the Yellow Sea was explored with sediment samples collected from five locations between 50–100 m. Culturing led to the isolation of 613 actinomycete samples of which 89 species were shown to produce extracts with good antimicrobial properties against an array of microorganisms. Of these 76 were Streptomyces spp. while the remaining 12 split across four genera (Kocuria, Micromonospora, Nocardiosis, Saccharomonomospora). 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 diketopiperazin dimers, including the new dimer isonaseseazine B 107, a stereoisomer of naseseazine B.82,84

A modified diketopiperazine 108 with antimalarial properties was isolated from a Streptomyces sp. isolate from the Florida Keys as part of the outcome of screening a large collection of microorganisms for antiproliferative and antiplasmodial properties.85 There were three reports of new compounds from the phylum Firmicutes. These covered the isolation of new glycolipids 109 and
A new siderophore 133 and pre-pseudomonine 132 (new to marine) were isolated from a sponge-associated Pseudomonas fluorescens. 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.

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 xiamycins and other indolesesquiterpenes from mangrove Streptomyces sp. endophytes the xiamycin biosynthetic gene cluster was successfully transferred to S. griseus. From the recombinant strain three minor, sulfonyl-bridged dimeric congeners sulfadixiamycin A–C 135–137 were isolated. From a biosynthetic perspective a sulfonyl-linkage is unusual and it was postulated that a direct flavin-mediated SO₂ incorporation was involved. Other aspects of the biosynthesis of the xiamycins and the cyclisation cascades were elucidated by the biomimetic synthesis of key intermediates.

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

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

A further mud-flat Streptomyces produced the dilactone-tethered, pseudo-dimeric peptides mohangamide A 157 and B 158. Apart from the dilactone-tethering, another interesting feature of these metabolites was the acyl chain-bearing dihydroxyridine. A four-step derivatisation approach was used to determine the absolute configuration at C-62 of mohangamide A 157. Also isolated from a tidal mud-flat or saltern Streptomyces...
sp. were 159, 160 (ref. 109) and 161–165,180,181 while the salinazinones A 166 and B 167 are first examples of a natural alkaloid with an oxazinone-pyrrolidine core.122

A number of successful synthetic and biosynthetic studies have been realised. These included peptide-based targets such as marthiapetide,113,114 the disulfide-containing peptide thiocombine C9,157,158 bogorol A and the more thermodynamically-favoured (Z) isomer,117,118 the siderophores amphibactin-T119 and moanachelin ala-B.120,121 The first synthesis of fradcarbazole120 was by semi-synthesis123 from staurosporine.124 Also successfully synthesised were the nitrosporeusines,125,126 fijilide A,127,128 marinsporolide129,130 and splenocin B.131,132 A new route to isoquinolines was developed for the synthesis of mansouramyacin133,134 and a total synthesis and full stereochemical assignments have been completed for heronapyrroles A 168 and B 169.135,136 A further synthesis of bacillamide B137 has confirmed the absolute configuration as (S) and that the specific optical rotation is negative.138 The unusual anthracycline marmoycin139 has been successfully synthesised and fluorescent microscopy studies indicated that it accumulates in the lysosomes and not the cell nucleus.140 The synthesis of immunoaffinity fluorescent probes of chlorizidine A141 established that two cysteine proteins, part of the glycolytic cycle, were the targets for chlorizidine,142 while studies on the mechanism of action of thalassospiramides143 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 akaoelide145 and lorneic acid146 identified type 1 PKS clusters and the PKS origins were supported by 13C-labeling studies.147 The biosynthetic gene cluster for the production of the marformyins,148 mfn, has been identified from Streptomyces drozdowiczii and encodes six NRPSs’s and related proteins for the assembly of the depsipeptide core structure.149 Two papers addressed heronamide150 biosynthesis. Firstly, the gene cluster for heronamide F was identified from a deep-sea Streptomyces sp. and the presence of a β,γ-migrated diene system in the side-chain confirmed by 13C-labeling studies.151 The second paper was a theoretical examination of the proposed transannular [6 + 4] cycloaddition proposed as a step in the biosynthesis of heronamide A. The DFT computational results support that proposal and suggest that the cycloaddition is highly stereoselective giving one product, but proceeds via an 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.133,134 and Sorangium cellulosum,155 a myxobacterium, respectively. Chlorotonil differs from anthracimycin in that all sp³ stereocenters are inverted, there is an additional methyl group and a gem-dichloro entity. The two biosynthetic gene clusters have been compared in two papers published side-by-side. Both compounds are formed by trans-AT PKS pathways and clusters in the chlorotonil genome readily explain the chlorination and methylation pattern. In each case the decalin ring system is formed by a spontaneous [4 + 2] cycloadition and it is proposed that the alternative stereochemistries are
in part a consequence of the orientation of the C16 methyl group
pre-organising the PKS-bound intermediate prior to the [4 + 2]
cycloaddition.\textsuperscript{156,157} The biosynthesis of two similar \textit{Salinispora pacifica} metabolites, salinipyrone and pacifcanone,\textsuperscript{158} was unexpectedly correlated with the large PKS cluster from \textit{Micromonospora carbonaceae}\textsuperscript{159} that produces the macrolide rosamicin\textsuperscript{160} and illustrates how domain and module skipping can give rise to polyketide product diversity.\textsuperscript{161} From a study of splenocin\textsuperscript{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.\textsuperscript{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\textsuperscript{163} required bioinformatics analysis, bioinspired syntheses and MS metabolomics profiling.\textsuperscript{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 \textit{Salinispora} bacterial genomes. The strategy operates by querying the genomes for duplicated housekeeping genes that are co-localised with biosynthetic gene clusters.\textsuperscript{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\textsuperscript{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.\textsuperscript{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 \textit{Acremonium} (benzophenones \textbf{170–172} (ref. 168)), \textit{Alternaria}
usual, the genus *Aspergillus* has been well studied. Of particular note was a continuing study into the biosynthesis of the prenylated indole alkaloids *notoamides*, as 183 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 stephaclins 176 and versicolamide B. 177 Feeding of [13C]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, 191 phenyl ether derivatives 198–202, of which dehydrocyclopeptine 201 and viridicatin 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 pyrilmepine derivative 215, 188 peptides 216 and 217, 189 218, 190 hydroxyphenylacetic acid derivative 219, 193 alkaloids 220 (also synthesised) 193 and 221–225, the steroids 226, 2-O-methylbutyro lactone I 227 (asper bolide C) 194 and 2-O-methylbutyro lactone 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. 200 The stereochemistry of 5’-hydroxyasperentin 203 was established as (3R,10R,13S,14S) 255 by X-ray crystallography. 201 New metabolites were isolated from the genera *Auxarthron* (triterpene glycoside 256 (ref. 203)) and *Beavera* (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. 260 Additionally, the absolute configuration of the co-isolated tetramic acid F-14329, previously obtained from terrestrial *Chaunopycnis* 260 and *Tolypocladium* species, was established as 263 and is a first time MNP. *Chaunolidone* 262 possessed selective and potent cytotoxicity to the NCI-H460 cell line. 263 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*. 206

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 267,218 bicyclic lactam 268 (ref. 211) and polyketides 269 and 270.217 New metabolites isolated from the genera Corynebora 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,218 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 B222,223 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.224 Further new metabolites were obtained from the genera Glomastix (macrolides 317–321 (ref. 224)), Graphium (thiodiketopiperazines 322–329,325 330 and 331 (ref. 226)) and Hypocrea (furan derivatives 332, 333 and cyclopentenone derivatives 334–338).227 Two of these compounds, N-isobutyl-2-phenylacetamide228 337 and N-(2-methylbutyl)-2-phenylacetamide229 338 were first time MNPs.227 New natural products were isolated from the genera Lophiostoma (merosesquiterpenoids craterellin D 329 and craterellin A230 340; first marine isolation for the latter),231 and Nectria (mono-terpenoid α-pyrones 341 and 342,232 Of these, nectriapyrone D233 342 was simultaneously isolated from a terrestrial fungus as gulpyrone B.234 The genera Neosartorya and Paecilomyces also yielded new metabolites (alkaloïds 343 and 344,234 meroditerpenes 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 spiroketalts 354–357 (ref. 239)). The genus Penicillus was, as always, a prolific source of new metabolites, including bisthiodiketopiperazines 358 and 359, sesquiterpenes 360 and 361,238 phenolic bisbolanes 362–364 and nor-bisbolane 365,241 benzoic acid derivative 366,242 citrin derivatives 367–370 and tetrac acid analogues 371 and 372,434 A culture of P. ademetzioides was the source of the dithiodiketopiperazine derivatives penicidalactone B A 373, with the unique spiro[furan-2,7-pyrazino[1,2-b][1,2]oxazine] skeleton, along with an analogue, penicidalactone 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, isopotulin44 378 (first time MNP),246 and oxindole alkaloids 379–386 were also isolated from the Penicillus genus.249 Another oxindole alkaloid 387 was claimed as new and named cyclopamide 149 but had already been reported in 2014 as aspergilline D.250 The current report does however represent the first marine isolation.250 The gene cluster from Penicillinum expansum responsible for biosynthesis of the indole alkaloids communesins251 has been identified. In the process, three new metabolites, communesin I–K 388–390 were isolated. The investigation confirmed that communesins originate from L-tryptophan via coupling of tryptamine and aurantioclavine.252

Further metabolites isolated from the genus Penicillus include meroterpenes 391 and 392,253 alkaloids 393,254 394–396,255 diphenylmethane derivative 397,256 phenolic enamide 398 and meroterpenoid 399,225 azahilene derivatives 400–402 and diphenyl ether derivatives 403 and 404.258 The planar structure of 404 appears in a screening library259 but no source is given for the compound. Chromones 405–409,260 sesquiterpenes 410–413,261 merosesquiterpenes 414 and 415,262 1,4-diazepane 416,263 tanzawaic acids 417–420,264 diketopiperazine 421,265 polyketides 422–426,266 spiroindoline alkaloids 427 and
isolated along with pestarhamnoses A and cultivated on a modified medium which contained equal concentrations of sodium chloride and potassium bromide in an expectation of producing brominated analogues of the previously isolated pestalochlorides.\(^\text{278,279}\) Interestingly, no brominated analogues were detected but pestalochlorides C and D were isolated along with pestarhamnoses A–C.\(^\text{442–444}\)\(^\text{277}\)

Other fungal genera to yield new metabolites included *Phaeosphaeria* (polyketides 445 and 446),\(^\text{280}\) *Phoma* (cytochalasin derivatives 447–449, cytochalasin B6 [ref. 281] 450 [first NP isolation]),\(^\text{282}\) *Pleosporales* (pleosporalins A–G 451–457),\(^\text{283}\) *Pseudoallescheria* (chlorinated benzofurans 458 and 459),\(^\text{284}\) pseudelliones A–C 460–462 [ref. 285]) and *Pseudogymnoascus* (nitratred asteric acid derivatives 463–466).\(^\text{286}\) The ascidian-derived *Roussoella* sp. produced roussoellatide 467, a dichlorinated polyketide with an unprecedented skeleton and experiments with [1–1\(^3\)C], [2–1\(^3\)C] and [1,2–1\(^3\)C]-acetate suggested that biosynthesis proceeds from two pentaketides that each undergo Favorskii rearrangement prior to being joined by an intermolecular Diels–Alder reaction.\(^\text{287}\)

New metabolites were also obtained from the genera *Simplicillium* (diketopiperazine 468 and furanone\(^\text{288}\) 469; the latter a first time MNP\(^\text{289}\)), *Spicaria* (isobenzofurans as acetylated derivatives 470–473),\(^\text{280}\) *Spromastix* (polyphenols 474–484),\(^\text{291}\) *Stachybotrys* (meroterpenoid sulfate 485,\(^\text{292}\) sesquiterpenoid 486 and xanthone derivatives 487 and 488 [ref. 293]), *Talaromyces* (sesquiterpene-conjugated amino acids 489–492,\(^\text{294}\) diphenyl ether derivatives 493–495 and tenellic acid methyl ester (first time MNP)\(^\text{295}\) 496,\(^\text{296}\) oxaphenalonenone dimers 497 and 498 and isopentenyl xanthone 499 [ref. 297]) and *Trichoderma* (tetramic acid derivatives 500–505).\(^\text{298}\) A red algal-derived *Trichoderma* species produced glycovirin,\(^\text{299}\) pretrichodermamide A\(^\text{300}\) and the related trichodermamide A\(^\text{301}\) when grown on a freshwater medium, chlorinated derivatives trichodermamide B\(^\text{302}\) and DC1149B\(^\text{306}\) 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\(^\text{303}\) 508 was obtained with sodium bromide supplementation to the freshwater medium and isolated for the first time as a natural product.\(^\text{303}\) Cultivation of the strain in seawater supplemented with dimethylsulfosiloxane (DMSO) yielded the trithio-derivative, chlorotrithiobrevamide 509.\(^\text{304}\) Decalin derivatives 510–512,\(^\text{305}\)

A soft coral-related *Pestalotiopsis* sp. was the source of enantiomeric alkaloid dimers (+) and (−)-pestaloxazine A 434 and 435.\(^\text{277}\) 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.\(^\text{273}\)

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

428,\(^\text{287}\) 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 antimigratory activity against the highly metastatic breast cancer cell line MDA-MB-231.\(^\text{280}\) A sponge-derived *Penicillium* sp. yielded the fusarielin analogue 432 when grown axenically but coculture of this strain with another *Penicillium* strain obtained from the same sponge elicited production of the known compounds norlithoxanthone\(^\text{279}\) and monocrin\(^\text{271}\) 433 (first time MNP), neither of which was detected in the individual axenic cultures of the two strains.\(^\text{272}\)
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 \(339\) \(538\) 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\(^+\)-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.,\(^{318}\) 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-(6E,8E)-hexadecadienoic acid \(542\), previously known only from methanalysis 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).\(^{321}\) Acetylglutetoxin \(543\) was obtained for the first time as a MNP as was the known synthetic open-chain hemisuccinimide \(544,523\) (Penicillium cookica) which was named penicillimide.\(^{322}\) Alternariol-9-methyl ether 3-O-sulfate \(545\), previously obtained from *Alternaria* sp., an endophyte of the Egyptian medicinal plant *Polygonum senegalense*,\(^{323}\) was obtained for the first time from the marine environment from endophytic *Alternaria alternata*.\(^{324}\) The nortriterpenes asperwentin A-C (Aspergillus wentii)\(^{237}\) have been synthesised\(^{328}\) as have the prenylated indole alkaloids, (+)-nootamide I (Aspergillus sp.)\(^{329}\) and (−)-17-hydroxy-citralinalin B (Penicillium citrinum)\(^{330}\) via a unified strategy.\(^{331}\) Herbarins A and B originally obtained from *Cladosporium herbarum*\(^{232}\) have been synthesised via a multi-step procedure and both displayed antioxidant properties.\(^{332}\) Starting from the sugar \(\alpha\)-lyxose, total synthesis of cochlomycin \(534,333\) has been achieved.\(^{334}\) Total synthesis of the macrolide dendrodolide \(K\)\(^{335}\) (Dendrodochium sp.) has been accomplished from a commercially available substrate by a convergent strategy\(^{336}\) and other dendrolides (\(F, G, I, J\) and \(L\))\(^{337}\) have also been synthesised via a unified strategy employing ring-closing metathesis.\(^{338}\) A unified strategy was also employed in the total synthesis of lutealbusins A and B,\(^{339}\) indole diketopiperazines isolated from sediment-derived *Acrnostagamus luteoalbus*.\(^{340}\) In addition to the new compound talaromycin \(C\),\(^{336}\) purpactins \(A,341\) \(C^{342}\) and penicillide\(^{343}\) exhibited potent antifouling activity against settlement of *Balanus amphitrite* larvae\(^{296}\) as did alteltorin I, a metabolite of both terrestrial\(^{344}\) and marine* Alternaria alternata*.\(^{346}\) A number of known cyclic dipeptides, \(\text{cyclo}(\text{Gly}-\text{L-Pro}),\text{cyclo}(\text{L-Ala}-\text{L-Pro}),\text{cyclo}(\text{L-Ala}-\text{L-Pro}),\text{cyclo}(\text{L-4-Hyp-L-Pro})\)\(^{347}\) and \(\text{cyclo}(\text{L-Hyp-\text{L-Phe}})\)\(^{348}\) were reisolated from *Eupenicillium brefeldianum* and extracellular alkalinisation and hydrogen peroxide production in plant cell suspensions, indicating their potential as induced systemic resistance (ISR) elicitors.\(^{349}\) Viridicatol, a metabolite of *Aspergillus versicolor*,\(^{155}\) 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.\(^{350}\) Spiromistaxones 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 fibronolytic 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*.\(^{364}\)

### 3.3 Fungi from mangroves

There has been a continued increase in the number of new metabolites reported from mangrove-associated fungi (127 in 2015 vs. 103 in 2014), with the majority coming from endophytic species. An *Alternaria* sp. yielded cyclohexanone, cyclopentanone and xanthone derivatives \(546-549\) (ref. 364) and the genus *Aspergillus* was the source of many new metabolites including meroterpenoids \(550-553,365\) polyketides \(554-556,366\) indole diketopiperazines \(557-559,367\) isochromane derivatives \(560-563\) (ref. 368) and the versianthrones \(564-567,368\) and \(568\) and \(569,369\). The absolute configurations of these xanthone-chromane 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 versianthrones exhibited cytotoxicity at some level against several HTCLs and versianthone \(E\) \(568\) was an inhibitor of topoisoasemerase I.\(^{369}\) Further metabolites obtained from the *Aspergillus* genus include dinaphthalene derivatives \(570-573,370\) lumazine peptide \(574,371\) cyclohexanone-furan derivative \(575\), isocoumarin derivatives \(576-578,372\) and \(579\) (ref. 372) (first marine isolation)\(^{373}\) and polyene \(580,374\).
New metabolites were obtained from the genera Botryosphaeria (isoucomarin 581 (ref. 375)), Cladosporium (dimeric tetralone 582 (ref. 376)), Daldinia (hydronaphthalenone 583 (ref. 377)), Eurotiurn (indolediketopiperazine 584 (ref. 378)), Eutypella (cytochalans 585 and 586 (ref. 379) (new NP) and 587), Fusarium (z-pyrones cladobolin V 588 (ref. 381) and 589, cyclic depsipeptides 590 and 591 (ref. 383)), Lophiotoma (phenalenone derivatives 592–600 and sesterterpene bipolarenic acid 601 (ref. 384)), Meieroyzyma (depsideses 602–606 (ref. 385)), Nigrospora (acetamidopentane derivative 607 and phenalenone derivative 608 (ref. 386)) and Paradiicytoarthritis (hydroanthraquinones 609 and 610 (ref. 387)). The genus Penicillium was also the source of a number of new metabolites including polyketide decalins 611–616, sulfide diketopiperazines 617–621, pyrrole-4,5-dione derivative 622, polyketides 623-625 and 626 (ref. 391) (isolated for the first time as a NP) and compound 627, citrinin analogues 628–630, xanthone derivative 631, compounds 632 and 633, 634 and 635, alkaldoids 636 and 637, z-pyrones 638 and 639, dihydroxybenzoic acid derivatives 640 and 641, 642 and 643, (the last two are known compounds) and polyketides 644–647. Pinazaphilone A reported in this paper 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.

Further metabolites were obtained from the genera Pestalotiopsis (prenylated phenols 649 and 650 (ref. 401)), Phomopsis (purine derivative 651 and octadecadiene derivative 652, first isolation as a NP), Setophoma (polyketides 653, 654 and 655, 656, 657 and 658, 659 (ref. 406)), and Steptomyces (aromatic sulfates 660 and 661 (ref. 407)). Stenophol 662 was obtained as a first time MNP. Several studies reported metabolites from species that were unidentifed 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. 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, 417 has revised the configuration at C-6 of each to (R) (674 and 675) but discrepancies for some 13C NMR chemical shifts of the sidechain carbons between those reported for cephalosporolide I and the synthetic compound 675 indicate that the structure of cephalosporolide I may need further investigation. Peniphenones A–D, polyketide metabolites of Penicillium dipodomyicola 418 have been synthesised via a biomimetic method as has the Penicillium metabolite, 419 (−)-penbruguieramine. Pestalotiopsis metabolite (6S,1'S,2'S)-hydroxypestalotin 420 has been synthesised and the proposed structure of pestalotioprolide A 421 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. 422 A number of known natural products were reisolated from Phakellia fusca and exhibited a range of activities. Penicillenol A 414, a tetramic acid derivative, displayed anti-TB activity whilst expansols A–F 416, 417 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. 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*. These acyl amides 684–686 possessed moderate affinity for the CB1 and CB2 cannabinoid receptors. A similar approach was utilised in the isolation of hectoramide 687, hectochlorins B–D 688–690 and jamaicamides D–F 691–693 from *M. producens*. The terpene alkaloid 694 was also obtained from the genus *Moorea*. Bartolosides A–D 695–698 are chlorinated aromatic glycolipids obtained from a *Nodosilinea* species and *Synechocystis salina* respectively. Investigation of the biosynthesis of these molecules prior to completion of the structural assignment provided information that was vital to the structural elucidation of the chlorinated dialkylresorcinol core of these molecules.

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

The genus *Okeania* was the source of the antimalarial polyhydroxy macrolide 701, the macrolactone 702 (ref. 444) and the lipopeptide kurahyne B 703. The related metabolite kurahyne A 695 was also isolated and synthesised. An *Okeania* sp. was also the source of a new macrolide polycavernoside D 704. Polycavernosides 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.

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 Oscillatoriales family, was the source of the polyhydroxylated macrolides 706 and 707. Total synthesis of the cyclodepsipeptide coibamide A 694 was achieved and resulted in the revision of the structure to 708 as a result of reassignment of two stereocentres. Two separate synthetic studies resulted in the structural revision of the lyngbyalosides. Total syntheses of the proposed and correct structures (709) of (−)-lyngbyaloside B were completed and total synthesis of the (18Z) and (18E) isomers of lyngbyaloside C 694 resulted in reassignment of the structures to 710 and 711 respectively. As a result, it was suggested that the structure of lyngbouilloside should likely also be reconsidered. Total syntheses of the
acrylic depsipeptide maedamide\textsuperscript{483} and cyclodepsipeptide largamide B\textsuperscript{482} 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.\textsuperscript{485} Syntheses of (+)-lyngbyabellin M\textsuperscript{466,467} sanctolide A\textsuperscript{466,468} and santacruzamate A\textsuperscript{470,471} were also completed, with the last not exhibiting any inhibition of histone deacetylase (HDAC), unlike the potent inhibition previously reported.\textsuperscript{470} The functions of some enzymes involved in the biosynthesis of the terminal alkyne moiety in the jamaicamides\textsuperscript{487} were elucidated via both in vitro and in vivo analyses.\textsuperscript{473} Dereplication methods based on phylogeny and HPLC-MS were developed which showed that largazole\textsuperscript{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.\textsuperscript{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,\textsuperscript{778} the macrolide 715,\textsuperscript{779} and the linear polyketide 716.\textsuperscript{480} Asparagin acids 717 and 718 were isolated from Azadinium poporum,\textsuperscript{481} whilst the ladder polyether 719 was obtained from Gambierdiscus belizeanus.\textsuperscript{482} Recent studies have shed some light on the biosynthetic pathway to paralytic shellfish toxins (PSTs) such as saxitoxin (STX).\textsuperscript{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.\textsuperscript{484} One of these intermediates has now been converted into cyclic-C 720, a triyclic bigusguanine 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.\textsuperscript{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.\textsuperscript{489} The ciliate Spirostomum teres contains colourless estrus organelles which function as a chemical defence.\textsuperscript{490} The tricyclic quinones spiromistin A 724 and B 725 were isolated from these organelles as a 5 : 1 diastereoisomeric mixture which was lethal to the ciliate Paramesceum caudatum at a relatively low dose. Total synthesis of each confirmed relative configurations.\textsuperscript{491}

Nonacosadienes 726 and 727 were obtained as metabolites of the microalga Emiliania huxleyi\textsuperscript{492} while 12β-deoxydecarbomoylsaxitoxin\textsuperscript{493} 728 was obtained as a first time MNP.\textsuperscript{494} Syntheses of the polyketide amphirionin-4 (ref. 495) and ciguatoxin 54-deoxyCTX1B\textsuperscript{496} have been achieved.\textsuperscript{497,498} Polyketide synthesis genes unique to two Gambierdiscus species that produce maitotoxin\textsuperscript{499} were characterised, perhaps implicating them in the biosynthesis of this metabolite.\textsuperscript{500} Studies with Karenia brevis showed that brevetoxin\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{504} and a triterpene acid 736 from Codium dwarkense.\textsuperscript{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,\textsuperscript{506} has been established by enantioselective total synthesis as 737, correcting aspects of the previously reported configurations.\textsuperscript{507} Originally isolated as the dimethyl ester, nigricanoside A was reported to inhibit the proliferation of several cancer cell lines (IC\textsubscript{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.\textsuperscript{508} 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.\textsuperscript{509} 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,\textsuperscript{509} while astaxanthin and other algal carotenoids have been the focus of many studies and reviews.\textsuperscript{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 xenocanes, 740–743 and two cytotoxic sterols 744 and 745 isolated from Canistrocarpus cervicornis,\textsuperscript{519,520} Dictyota plectens,\textsuperscript{521} and Cystoseira trinodis\textsuperscript{522} respectively. The compounds of mixed biosynthesis was a tranche comprised of a chromene, 746

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Structure of compound 720.}
\end{figure}
(Homoeostrichus formosana), five acyclic meroditerpenoids 747–750, (Sargassum paradoxum)\(^\text{524}\) 751 (Cystophora retroflexa, C. subfarcinata, Sargassum cf. fallax), four cyclic meroditerpenoids 752 (Stypopodium flabelliforme),\(^\text{726}\) 753–755 (Stypopodium zonale)\(^\text{527}\) and the cyclophloketals A–E, 756–760, hybrid meroditerpenoids from Cystoseira tamariscifolia.\(^\text{528}\) The cyclophloketals, 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.\(^\text{528}\) The proposed, unprecedented syn-cis-anti arrangement for the A/B/C ring system in the cyclic meroditerpenoid, \(\text{O},\text{C}(3)\text{-seco}-9\text{-ene}-6\beta\)-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.\(^\text{528–531}\) 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].\(^\text{524,525}\)
The non-terpenoid brown algal compounds are represented by the polyketides, 761–770, from Lobophora variegata.\[^{532}\] When considered as a group their biosynthetic origins can be rationalised by involvement of a non-acetate starter acyl-CoA, most likely a dodecanoic acid unit, and type III polyketide synthases.\[^{533,534}\] The absolute configuration for the acyclic diterpenoid elegandiol,\[^{535,536}\] 771, was unequivocally re-established as (S) using VCD. This insightful paper outlines the approaches necessary for using VCD in the determination of absolute configuration.\[^{537}\] The first asymmetric synthesis of (−)-dolastatrienol (14-hydroxydolasta-1(15),7,9-triene)\[^{538}\] was reported\[^{539}\] along with a concise synthesis of dictyodendrins A and E.\[^{540}\] Additionally, there were many papers and reviews dealing with the biological properties of brown algal polyphenolics\[^{541–557}\] and carotenoids.\[^{15,558–561}\]

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[ghi]tetrathene 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 plonomacene and isoploacene 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-dihydroxybenzyl)ether (Rhodomela laris)\[^{580}\] 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 inodes from Laurencia bronniati\[^{585}\] 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\[^{804–806}\] 807–815 (ref. 588) and 816–833,\[^{809}\] and lysosphingolipids 834 and 835 (ref. 590) were reported from Sphoecospongia vagabunda, Aulosaccus sp. and Spirastrella purporea, respectively, while the genera Biema, Callyspongia, Haliclona and Xestospongia yielded taurinated\[^{836}\] polyunsaturated\[^{837–839}\] 840 (ref. 593) and brominated 841 (ref. 594) fatty acids. Stelletta sp. provided six new glycosidated fatty acids stelletoside A1–B1 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).\[^{845}\]

Polyacetelenes were found in extracts of Callyspongia impexa\[^{848,849}\] Petrosia sp. 849–851,\[^{857}\] Halichondria sp. 852–854,\[^{857}\] Pleroma sp. 855–861,\[^{858}\] and Xestospongia sp. 862 and 863.\[^{859}\] The nanomolar-scale isolation of mollenynes B–E 864–867 from
**Spirastrella mollis** posed several challenges. First, the extremely low yields of isolated compound imposed limitations on acquiring usable NMR spectra, and second, unequivocal placement of the chlorine and bromine atoms upon the carbon backbone was difficult due to the similarity in $^{13}$C chemical shifts. The former issue was resolved by use of a cryogenically-cooled NMR microprobe while the latter exploited a new band-selective HSQC experiment for enhanced resolution by only detecting a small region of the $^{13}$C dimension. This facilitated the observation of the $^{35}$Cl/$^{37}$Cl isotopic effect that causes a splitting of a chlorinated $^{13}$C resonance of around 1 Hz. The biosynthesis of these compounds could involve an unusual “dyotropic shift” of Cl and Br atoms, which would also account for the observed inversion of configurations within the series.  

An unidentified sponge yielded two aromatic bases 882 and 883, 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.  

A surprisingly small number of peptides and depsipeptides were reported in 2015, given sponges are normally prolific reservoirs of such compounds. The $\alpha$-ketoleucine or $\alpha$-ketovaline-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 contained spirolakortone 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.  

The known fungal metabolites gibepyrones C 868 and F 869 (ref. 601) were isolated from the marine environment for the first time.  

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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<sub>50</sub> 0.86 μM).<sup>412</sup> Four collections of <i>Callyspongia aerizusa</i> 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 <i>M. tuberculosis</i> 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,<sup>613,614</sup> previously isolated in vanishingly small quantities, allowed for complete structural elucidation which necessitated structural revisions as shown.<sup>615</sup>

Stelletapeptins A 900 and B 901 are hybrid NRPS/PKS depsipeptides isolated from <i>Stelleta</i> sp. Structures were established using a combination of degradation studies and comprehensive NMR experiments. Both exhibited anti-HIV activity in HIV<sub>PR</sub>-infected human T-lymphoblastoid cells with EC<sub>50</sub>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.<sup>616,617</sup> 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.<sup>618</sup> Hemimycale arabisca and <i>Acanthella cavernosa</i> were sources of hemimycals 904 and 905 (ref. 619) and diketopiperazines 906 and 907.<sup>620</sup>

Both enantiomers 908 and 909 of spirocyclic spiroetheructatuline were isolated from <i>Fascaplysinopsis</i>. 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 biogenesisc from tryptophan, glyxol and dimethyl urea was proposed.<sup>621</sup>

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

Guanidine-type alkaloids have been isolated from <i>Bienna laboutei</i> 926–930,<sup>412</sup> <i>Pseudoaxinella reticulata</i> 931–934,<sup>633</sup> <i>Monanchora arbusca</i> 935–940 (the synthesis of 935 was also achieved),<sup>634</sup> and <i>M. pulchra</i> 941–943,<sup>635</sup> while oroidin-type pyrrolo-alkaloids were sourced from the genera <i>Styliissa</i> 944 and 945 (ref. 636) and <i>Agelas</i> 946 (synthesis also completed).<sup>637</sup> 947 and 948,<sup>438</sup> 949–951,<sup>439</sup> 952–956.<sup>440</sup> A series of bromotyrosine-derived compounds were reported from a member of the Verongida 957 and 958,<sup>641</sup> <i>Pseudoaxineta arbatisa</i> 959–961,<sup>442</sup> P. <i>purpurea</i> 962 and 963,<sup>443</sup> <i>Acanthendrilla</i> sp. 964,<sup>444</sup> <i>Suberea</i> sp. 965–967 (ref. 645) and <i>Aplysina lacunosa</i> 968–970.<sup>446</sup> As always, prenylated metabolites dominate the compounds reported from sponges. Isolated meroterpenoids include 971–976,<sup>447</sup> 977–984,<sup>448</sup> and 985–987 (ref. 649) from <i>Dysidea</i> sponges. A novel approach was taken to promote the production of several “natural products”. Homogenised <i>Verongula rigidula</i>, a sponge with known potent oxidative potential, was added to homogenised <i>Smenospongia aurea</i> and <i>S. cerebriformis</i> and incubated in ethanol for one week. LC-MS guided isolation of the <i>Smenospongia</i> 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.<sup>656</sup> Pupehenol 996 (Dactylospogon sp.) exhibited pronounced anti-inflammatory activity. The known compound pupehenone was also isolated. Exposing 996 to mild acid (CDCl<sub>3</sub>) at slightly elevated temperatures (30 °C) resulted in quantitative conversion of pupehenol to pupehenone, suggesting the latter is actually an artefact of isolation.<sup>657</sup>

A series of adociaquinone compounds 997–1002 was reported from an Indonesian <i>Xestospongia</i> sp.,<sup>651</sup> while meroterpenoids 1003–1005,<sup>652</sup> 1006,<sup>653</sup> 1007 and 1008 (ref. 656) were isolated from <i>Agelas nakamura</i>, <i>Strongylocyphora strongylata</i>, <i>Natural Product Reports</i>
and *Petrosia cortica* respectively. Sesquiterpenoids 1009 and 1010,677 and 1011–1013 (ref. 658) were isolated from *Dysidea fragilis* and 1014–1018 from *Halichondria* sp.,679 while three farnesylacetone derivatives 1019–1021 were reported from *Diacarbus megaspinorhabdosa*.680 Niphates and an unidentified Dictyoceratid sponge were the sources of 1022 (ref. 661) and 1023–1025,682 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. Sarcothragin C 1037 was isolated from *Sarcothragus* sp.665 while a manaoalide 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) and 1076 (Haliclona sp.) sourced from Korean collections.

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 and Monanchora sponges, respectively, while highly derivatized sterols were isolated from Dragmacidon australis 1081 (ref. 610) and Polymastia boletiformis 1082 and 1083. A new 9,11-secosterol was isolated from a Korean Ircinia sp. 1084. 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 Monanchoora 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 (IC50 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 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 although the name stellettin N had been used previously for a different structure.684 The
Obtained the absolute configuration of psammamycin A \textbf{1101} (ref. 685) (isolated in the current study from \textit{Aplysinella stronglylanata}) was established from detailed comparison of calculated and experimental ECD data in conjunction with NMR studies including Mosher’s analysis,\textsuperscript{686} while the absolute configuration of euryospongion A \textbf{1102} (\textit{Eurypogia sp.}) was also determined using chiroptical techniques.\textsuperscript{687} Inconsistencies in NMR data reported for two sponge steroid isolated from \textit{Neofibularia nolitangere}\textsuperscript{688} with those isolated from Japanese edible mushrooms necessitated structural revision to \textbf{1103} and \textbf{1104}.\textsuperscript{689} Hepatitis B infection poses a major human health risk. Two sponge-derived polybrominated biphenyls\textsuperscript{690,691} isolated from Indonesian \textit{Dysidea} species were found to possess hepatitis antiviral activity with selectivity indices of 12.8–18.2.\textsuperscript{692} Transcriptic analysis of HepG2 hepatocarcinoma cells treated with both \textit{Crambe crambe} metabolites crambscinc 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.\textsuperscript{693} The bastadin-class of bromotyrosine compounds, in particular bastadin-6,\textsuperscript{694} suppress foam formation in macrophages via inhibition of cholesterol-ester formation, and may have application in the treatment of atherosclerosis.\textsuperscript{695} Panicein A hydroquinone\textsuperscript{696} (\textit{Haliclona mucosa}) inhibits the efflux of doxorubicin by the Hedgehog receptor Patched and enhances the anticancer efficacy of the drug.\textsuperscript{697} A hypothesis put forward over a decade ago that marine isonitriles and isothiocyanates may exert an antihelminth activity via interference of heme detoxification\textsuperscript{698} has been corroborated. The mode of action of these compounds was assessed using a scaled-down version of Egan’s \beta-hematin assay demonstrating that marine isonitriles inhibit \beta-hematin crystallisation and supported by \textit{ab initio} calculations of the stability of the isonitrile complexes bound to iron in heme.\textsuperscript{700} Gracilins A, H and L\textsuperscript{701,702} along with tetrahydroaplysulphurin-1,\textsuperscript{703} all isolated from \textit{Spongiomella sp.}, were found to modulate mitochondria function in neuroblastoma cells by regulating storage of calcium entry in a similar manner to cyclosporine \textit{A via} binding to cyclophilin D.\textsuperscript{704} Okadaic acid (OA), a potent marine cytotoxin that inhibits protein phosphatases, was originally isolated from \textit{Halichondria okadai} but later identified as being produced by the dinoflagellate \textit{Prorocentrum lima} and actively bioaccumulated by the sponge.\textsuperscript{705} The role and mechanism of OA accumulation by \textit{Halichondria} has not yet been established. Exposure of an extract of \textit{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 \textit{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 \textit{Ca}\textsuperscript{2+}-binding photoprotein aequorin. \textit{Ca}\textsuperscript{2+} does not displace OA from its binding site, suggesting a different mechanism for OA release by the sponge.\textsuperscript{706} A comprehensive LCMS analysis of 253 \textit{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.\textsuperscript{707} The ability of 26 sponges to inhibit bacterial quorum-sensing without cytotoxic activity was investigated. The extract of \textit{Ircinia felix} was found to be the most potent inhibitor of H. okadai.
quorum-sensing with the activity linked to the felixinin furanoesquiterpenoid class, 786–788 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. 771 First total syntheses were reported for many compounds including the lipids motulacetic acid F, (E)- and (Z)-antazirine, 712–714 mycalol (revised to 1105) 725–727 and myrmekioside A 724,729 and polyacetylenes callyspongyloceric acid, 728,729 phospho-oxid A and placto-ylene A 723–725. The structure of plakin-dione 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 hemicadial 1107 was also solved by synthesis. 728,729 Total syntheses of polyketides gracilioether B and C 731–732 and hippocal-phinin A 732,733 mycothiazole, 746–748 aromatic renieramycin I, 730,734 and peptides cyclcinamidine A, 739 corticamidine B, 740–742 stylissamide X'43,744 and stylissatin A 750,754 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 749,752 mycalolid B, 751,752 and muironilde A 1110 being completed, the latter requiring a structural revision. 753,754 Pyridines nakinadine D–F, 755,756 indoles scalaridin A 757,758 dragmacinid D 1111,759–761 dandradi A 762,763 and guanidine batzelladine B 764,765 are alkaloid compounds that have all been synthesised. Although the stereo-selective 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 marine metabolite. 782 Clavatadine A 768,769 aplysinellamides A and B, 770,771 and 11-deoxyfistularinin-3 (ref. 772 and 773) were syn-thesised for the first time. Meroterpenoids that had initial total syntheses are panicein A, 774,775 dictyoceratin A 776 and C, 777–779 and neopetrosiquinones A and B. 780,781 The structure of siphondicytal B 781 has been revised to 1112, based upon total synthesis. The biomimetic conversion of siphondicytal B to liphalgal 782 via a stable 8-quinone methide supports a novel biogenetic proposal. 784 The sesquiterpenoids aignopsoinoic acid A, methyl aignopsanolide and isoaignopsainic acid A 785 have been syn-thesised, with absolute configurations and that of the related compound microcinon-1 1113 (ref. 786) established. 787 Several diterpenoids have succumbed to total synthesis: viz. spino-lactone, 787,789 debronomhamigeran E, 790,791 and kalihinol B, 790,792 While the racemic synthesis of ambilbol A had earlier been achieved, 794,795 the first enantioreactive synthesis has established the absolute configuration as 1114. 797 The total syntheses of the ses-querpenoids phlorin A, 797,798 luffarins L and I, 799–801 salmehyrtisol A 802 and hippo-spongoid 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 ehenbergi 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 (Litophytton arboreatum), 809 cyclopentenones 1126 (Sinariedia sandensis) 810 and 1127 and 1128 (Sinariedia acuta), 811 eudesmane-type 1129 (Sinariedia gaweli), 812 subergane-type 1130 (Subergorgia suberosa), 813 monocyclic and bicyclic germacrenes 1131 (Sarcophyton glaucum) 814 and 1132 and 1133 (Cappella sp.), 815 caryophyllanes 1134 and 1135 (Rumpheia antipathies), 816 and guaiane lactones 1136–1140 (Menella kanasa) 817 and 1141 and 1142 (Menella woodin). 818 Of note was the use of a diverse array of computational techniques, including calculated 13C NMR chemical shifts, optical rotation and ECD to determine the structures and absolute configurations of 1141 and 1142.

Of four tocopherol-derived metabolites 1143 and 1144 (ref. 819) and 1145 and 1146, 820 hirsutocospio A 1143 exhibited strong anti-inflammatory activity and cladophenal glycosides A 1145 and B 1146 exhibited mild cytotoxicity towards three HTCLs. Thirty-one cnidarene-related metabolites reported from cnidarians in 2015 included 1147 (Sarcophyton glaucum), 814 epoxynephenolon 1148–1150 (field-collected Nepthia columna-ris), 821 columnarians A 1151 and B 1152 (cultured N. columna-ris), 822 sarcophine and ehrenbergol congeners 1153–1157 (Sarcophyton ehenbergi), 823 cis-cyclopropylated casbanes sinularcasbane G-L 1158–1163 (Sinariedia sp.), 824 sarcophelagans A–D 1164–1167 (Sarcophyton elegans), 825 tricyclic 1168 (Sarcophyton solidum), 826 pyrans 1169 and 1170 (Sarcophyton trochothelorum) 827 and 1171 (Litophytton arboreum), 809 hydroperoxycembranoid 1172 (Sarcophyton trochothelorum), 828 and 1173–1177 (Sinularia sandensis and S. flexibilis), 829 X-ray studies were used to determine the complete structural and stereochemical characterization of sarcophelaguan A 1164, 825 cembranoid 1173 and isoisinulaflexiolide K 1177,829 X-ray studies were also used to confirm the structures and configuration of previously reported cembranoids sarsololid B (Sarcophyton trochothelorum) 830,831 pukalide (Leptogorgia alba) 831 and dendropholin F (Dendrophycya sp.) 832,833 The trivial name epoxynephenolon assigned to 1150 (ref. 821) has been used previously. 831

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. 814
Rare examples of cembranoid 7,8-diols 1188 and 1189 were isolated from *Sinularia gaweli*. The structure assigned 1188 is the (−)-enantiomer of the known cembranoid leptomodi acetate (*Leptogorgia* sp.), while 1189 was found to be a potent inhibitor of pro-inflammatory iNOS production in LPS-stimulated murine macrophages.

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

Cytotoxic and anti-inflammatory bis-cembranoids glaucumolide A 1201 and B 1202 were isolated from cultured specimens of *Sarcophyton glaucaum*, while of sarcophytolides M 1203 and N 1204, only the former exhibited cytotoxicity to a panel of HTCLs. Eight new briarane-skeletoned diterpenes were reported in 2015 (*briarenolides K 1205, L 1206* [ref. 844]) and U–Y 1207–1211. *Briareum* sp.; dichotellide V 1212. *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.), and six were eunicellins (1216 and 1217, *Muricella sibogae*; 1218–1221, *Cladiella hirsuta*). Of note was that the structure of 1213 was secured by X-ray studies.

From the cnidarians a variety of steroids were isolated that included pregnane glycosides (1222 and 1223, *Cladiella hirsuta*), *seco*-sterols (1224–1229, *Subergorgia suberosa*); a *seco*-ketosterol hydroperoxide 1230 (Litophyton arboreum); *keto*-steroids (1231–1233, *Subergorgia rubra*); 1234 hydroxylated/ polyhydroxylated sterols (1234–1237, *Sinularia acuta*); 1238–1243, *Palystoa tuberculosa*; 1244–1249 and known 1250, *Klyxum fliccum*; 1251–1254, *Menella woodin*; 1255, *Dichotella gemmacea* and a steroidal glycoside (*Sinularia nanolobata*). 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*. 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*. The toxicity of the α-pore-forming toxin equinatoxin II depends upon its ability to assemble into oligomers on the cell surface, 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. A comprehensive sequence

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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.863

As noted in last year’s review,1 clarification of the structures of cladidiolin diterpenes including the sclerophytins (Sclerothymum capitale)864 is an ongoing issue. Based upon re-analysis of NMR data Friedrich and Paquette in 2002 proposed a number of structural revisions.865 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. 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 manmosa)866 have been revised (again)867 and confirmed by total synthesis.868,869

Further biological studies of lipids and sterols from Eunicea fusca and Eunicea sp. have identified some to exhibit antibiofilm action in the absence of antimicrobial effects,863 alyconolidine-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 Cambranoids exhibit peroxisome proliferator-activated receptor transactivational effects,885 antiprotozoal activities,885 antosteoporotic 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 diterpene originally isolated from Briareum excavatum, exhibits anti-inflammatory and analgesic effects in vitro and in vivo models.890 Two sesquiterpenes, (Z,E) and (E,E)-germacrones, constituents of the gorgonian Phyllogorgia dilatata, are odorous volatiles with fragrant, marine and slightly woody odours with citrus aspects.891 Finally, amphidinolide P, originally reported from the marine dinoflagellate Amphidinium sp., was isolated from the octocoral Stragulum bicolor and also in its predator, the nudibranch Marionia limceana.892 A likely artificial methyl acetate 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 Anathia tortuosa, along with kororamide A and convolulamines I and J. 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.904 The tripeptide janolusimide B 1266 is the first peptide to be isolated from a bryozoan and was obtained from Bugulina flabellata.905 Janolusimide B is an N-methyl analogue of janolusimide,906 which was isolated from a Mediterranean nudibranch, Janolus cristatus, a known predator of bryozoans. Hydrolysis, derivatisation and stereo-selective synthesis of fragments were utilised to establish the stereochemistry.900 Four new bryostatins,900 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.\textsuperscript{999} The known synthetic compound \textit{p}-methylsulfonylmethyl-phenol\textsuperscript{998,999,1271} was obtained as a first time NP and monoheneicosanoin\textsuperscript{998} 1272 was obtained as a new MNP from \textit{Cryptosula pallasiata}.\textsuperscript{993} Synthesis of amathamide F originally obtained from \textit{Amathia wilsoni}\textsuperscript{994} has confirmed the revision of the structure proposed in 2011 (ref. 905) (1273).\textsuperscript{906}

10 Molluscs

The number of new metabolites reported from molluscs (43) is a substantial increase in the average number reported per year over the past decade. Azaspiracids 7–10 1274–1277 were isolated from extracts of the mussel \textit{Mytilus edulis} and the structures characterised by NMR and mass spectrometry.\textsuperscript{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.\textsuperscript{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.\textsuperscript{909} Electrophysiological and competition binding experiments have identified that 13-desmethyl spiroilide C is a potent but relatively non-selective ligand of nACHRs while 13,19-didesmethyl spiroilide C is more selective of the muscular-type receptor.\textsuperscript{910} Both MNPs interacted weakly with muscarinic AChRs. Further investigation of the unusual occurrence of tetrodotoxin in New Zealand collections of the nudibranch \textit{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.\textsuperscript{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 (\textit{Charcotia granulosa}),\textsuperscript{912} a series of antimalarial isocyano and isothiocynato sesquiterpenes 1279–1283 (\textit{Phyllidia ocellata}),\textsuperscript{913} scalarane sesterpenes 1284 and 1285 (\textit{Glossodoris hikuensis}) and diterpene 1286 (\textit{Goniobranchus albonares}),\textsuperscript{914} norscalaranes 1287–1296 and spongian diterpenes 1297–1305 (\textit{Dorispismatica} (= \textit{Glossodoris} atromarginata)).\textsuperscript{915} Granuloside 1278 is the first example of a linear homosesterterpene.\textsuperscript{916} 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.\textsuperscript{911}

Two studies of sea hares identified eight new dactyloclene diterpenes 1306–1313 from a Greek collection of \textit{Aplysia depilans},\textsuperscript{916} while a Japanese collection of \textit{A. kurodai} was the source of modestly cytotoxic 9,11-secosteroid aplysiasecosterol A 1314.\textsuperscript{917} The absolute configuration of 1314 was established by comparison of calculated and experimental ECD data using a simplified model of the tricyclic \(\gamma\)-diketone core of the MNP and by modified Mosher’s analysis.

Re-examination of extracts of \textit{Elysia crispata} (Venezuela) has led to the characterisation of (\textit{\textendash})-phototrichialhydropyrone 1315,\textsuperscript{918} a molecule previously speculated to be a MNP based upon its biomimetic photochemical formation from the related metabolite tridachialhydropyrone.\textsuperscript{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 \textit{Dicanthais orbita}.\textsuperscript{920} 6-Bromohypaphorhine (\textit{Hermisenda crassicornis}), previously known as a sponge\textsuperscript{921,922} and tunicate metabolite,\textsuperscript{923} is a mild agonist of human \(\alpha_7\) nAChR but shows no effect on muscle-type nAChR from \textit{Torpedo californica}.\textsuperscript{924} Dolastatin 16 obtained by total synthesis\textsuperscript{925} was found to be inactive, in contrast to the potent cytotoxicity towards HTCLs originally attributed to the MNP (\textit{Dolabella auricularia}).\textsuperscript{926} New examples of M- and T-supersuperfamily peptides were isolated from Indian collections of \textit{Conus araneous}\textsuperscript{927} and \textit{C. figulinus}\textsuperscript{928} while analysis of venom duct cDNA from \textit{C. litteratus}\textsuperscript{929} and \textit{C. marmoreus}\textsuperscript{930} prompted the cloned expression or chemical synthesis and subsequent biological evaluation of new peptides. Highly detailed transcriptome analysis of \textit{C. episcopatus} identified over 3300 novel full-length conotoxin precursors which represented 9 known and 16 new gene superfamilies.\textsuperscript{931} Six novel cysteine frameworks were identified, providing impetus for further toxin discovery in \textit{Conus} snails. Two studies in particular reported metabolites that expand the chemical repertoire of \textit{Conus} molluscs. In the first of these, a simple guanine derivative, genuanine 1316 was isolated from \textit{C. genuanus} and the structure confirmed by synthesis.\textsuperscript{932} Compound 1316 exhibited potent paralytic activity in mice, mimicking the activity of the crude venom extract.
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 1317,264 an array of halogenated alkaloids 1318–1323 (ref. 935) and 1324,266 taurine amides 1325–1327,267 purines 1328–1331,268 a new pyrroloacridine 1332 (ref. 939) and two unusual tetracyclic-cored alkaloids 1333 and 1334.269 Noteworthy were the isolation, structure elucidation, synthesis and biological evaluation of eudistidines A 1333 and B 1334 (Eudistoma sp., Palau).260 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-1z) required for HIF-1z (hypoxia-inducible factor 1) activation: such inhibitors could find therapeutic use as antitumour agents by acting to down-regulate the expression of hypoxia-selective genes.

An expeditious total synthesis of shishijimicin A491 has been reported,492 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 synthesis494 and a new catalytic asymmetric synthetic route to (+)-perophoramidine495 has been disclosed.496 Cell-cycle arrest at the G2/M phase and induction of apoptosis in HeLa cells497 was observed for the ascidian alkaloid eudistomin H,448 while eusynthylamide B499 also induces G2/M phase arrest, causes double strand breaks in DNA and is a topoisomerase II poison.450 Further investigation of clavanan A, a C-terminal amidated 23 residue antimicrobial peptide,451 has identified it to exhibit no cytotoxicity and to be active in vivo and in a wound healing model of S. aureus infection.452 Preliminary investigation of anti-angiogenic activity in myxoid liposarcomas has identified trabectedin (Yondelis®, E7-743) as an upregulator of inhibitors of matrix metalloproteinases TIMP-1 and TIMP-2, and of TSP-1, a key regulator of angiogenesis-dependent dormancy.453 For several decades, didemnin B and related analogues have been the subject of numerous clinical trials, ultimately resulting in dehydrodidemnin B (Apidrine) 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 (PPTT) and eukaryotic translation elongation factor 1 alpha 1 (EUF1A), the combination of which leads to apoptosis and antineoplastic activity.454 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 polyandrocarpamines495 were found to be inhibitors of H2S production by cystathionine beta-synthase,496 and SAR studies have been reported for thiaplidaiquinones A and B97 (various biological targets),978 cadilolides A–C979 (antibacterial),981 rubrolides982 (photosynthesis inhibitors),984 meridianins985 (anti-malarial and antituberculosis),986 isogranulatimide987 (cytotoxicity),988 and lamellarins989 (cytotoxicity).990

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 (Crowns-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 Astreias rollestoni)974 1338–1341 (starfish Leptasterias ochotensis),975 1342 (sea cucumber Holothuria moebii),977 1343–1347 (starfish Echinaster luzonicus),978 1348–1352 (sea cucumber Cercodemas aniceps),979 1353 (starfish Culcita novaeguineae),980 1354 (sea cucumber Cucumaria japonica),980 and 1355–1362 (sea cucumber Cladolabes schmelzti).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 data, there are few data to define the associated aglycones and so the structures
are not shown in this review. Using cladoloside C as a model (Cladolobes schmelzii), chemical transformations combined with Moshers analysis has determined C-22 as having (R)-configuration. The authors speculated that all C-22 functionalised sea cucumber glycosides may have the same (22R) 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) and PNG-2A (starfish Protoreaster nodosus) and steroidal glycosides astrosteroiside A (starfish Astropecten monacanthus) and linkosides A and B (starfish Linckia laevigata) have been confirmed by total synthesis. Further studies using purified pentahydroxynaphthoquinone echinochrome A and have identified suppression of SERCA2A Ca2+ reuptake and improvement of exercise capacity in rats. A trisaccharide fragment of the starfish ganglioside LLG-3 (Linckia laevigata) promotes neurite extension in human neuroblastoma cells via MAPK/ERK signalling but not via Akt signalling. Polyhydroxylated sterols from the Vietnamese urchin Diadema savignyi induce apoptosis in HTCLs via inactivation of the MAPK/ERK1/2 pathway while sterols from the starfish Protoreaster nodosus were found to inhibit the production of proinflammatory cytokines including IL-12 p40, IL-6 and TNF-α in LPS-stimulated bone marrow-derived dendritic cells. 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. 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.

### 13 Mangroves

Mangroves or their associates were the sources of antiviral cyclohexylideneacetonylitriles 1363–1366 (Bruguiera gymnorrhiza), a phenolic 1367 and a diol 1368 from the fruits of Avicennia marina, phenolics and a cerebroside 1369–1372 (Sonneratia ovata), glycosides 1373 (Kandelia candel) and 1374–1376 (Bruguiera gymnorrhiza), seco-labdanoids 1377–1380 (Excoecaria agallocha), dolabrace-diterpenes 1381–1386 (Ceriops tagal), 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. CD analysis and an X-ray study has led to the revision of the structure of rhizophorin A (Rhizophora mucronata) to that shown for excolide A 1377. The structure of excolide B 1380 was also secured by X-ray analysis.
human T-cell leukemia xenografts, via a mechanism involving ROS-mediated apoptosis and cell cycle arrest.\textsuperscript{1016} In addition the phenethyl cinnamidemicrometam C (\textit{Micromelum falcatum})\textsuperscript{1017} protects against LPS-induced reactive oxygen species in both zebrafish and macrophages\textsuperscript{1018} and limonoids xylocensin E\textsuperscript{1019} and I\textsuperscript{1020} (\textit{Xylocarpus moluccensis} and \textit{X. granatum}) exhibited anti-ulcer gastroprotective activities in rats, likely due to an ability to inhibit H\textsuperscript{+}K\textsuperscript{+}-ATPase activity.\textsuperscript{1021}

\section*{14 Miscellaneous}
A study of the sea grass \textit{Cymodocea serrulata} has afforded an antibacterial constituent, which was attributed to the novel thiocarbonyl \textit{1402}.\textsuperscript{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 \textit{1403}, was isolated as a minor component of extracts of the marine worm \textit{Cephalodiscus gilchristi}.\textsuperscript{1023} Compared to the

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image.png}
\caption{The most abundantly collected phyla by sesquidecade.}
\end{figure}
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.  

Site-directed mutagenesis of the plasmid used for the heterologous expression of arenicin-1, an antimicrobial peptide produced by the polychaete worm Arenicola marina, afforded a number of analogues, one of which, Val8Arg, was equipotent as an antibacterial but with diminished red blood cell haemolytic activity. 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. 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. 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. 

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.

### 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. 

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. 

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. Some years later the structures of the ecteinascidins were independently published and ET-743, a bioactive research find, was transformed over the years to the anticancer drug Yondelis® (trabectedin). In 2015 it was established that the producer of the ecteinascidins was the \(\gamma\)-proteobacterial endosymbiont * Candidatus Endoecteinascidia frumentensis*. 

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. 

Through 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
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 throughout 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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