Marine natural products††

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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 2014.1 As in previous reviews, the structures are shown only for new compounds, or for previously reported compounds where there has been a structural revision or a newly established stereochemistry. Previously reported compounds for which first syntheses or new bioactivities are described are referenced, but separate structures are generally not shown. Where the absolute configuration has been determined for all stereocentres in a compound, the identifying diagram number is distinguished by addition of the † symbol. The new format for this review introduced for the previous review† has been retained, with only a selection of highlighted structures (197) now shown in the review. Compound numbers for structures not highlighted in the review are italicised, and all structures are available for viewing, along with their names, taxonomic origins, locations for collections, and biological activities, in a ESI†† document associated with this review.

The Reviews section (2††) contains selected highlighted reviews, with all other reviews referenced in a section of the ESI.†† It is with great regret that we note the passing of Professor Tatsuo Higa, University of the Ryukyus and the Open University of Japan, on May 24 2016. Since 1965 Professor Higa has made many publications of his work, principally on MNPs. Most notable was his discovery of the manzamines. He was a regular participant at MNP conferences, and his quiet and friendly manner will be remembered and missed.

†† Electronic supplementary information (ESI) available. See DOI: 10.1039/c6np00124f
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. A statistical analysis of bioactive MNPs discovered from 1985 to 2012 has been made. The potential for MNPs as antiviral agents has been extensively reviewed. Marine fungi as the source of anticancer agents, antimicrobial compounds and antiviral agents have been described. There have been surveys of anticancer compounds from marine sponges and microalgae, while the bioactivities of specific classes of MNPs such as peptides, polyacetylenes, indole alkaloids, and halogenated compounds have been reviewed. More specific types of bioactivity have been examined in reviews of MNPs for management of diabetes from seaweeds, and compounds with neuroprotective activity and antifouling properties. MNPs from marine cyanobacteria and actinomycetes of the genus Salinispora have been discussed. The role of metagenomics in biodiscovery continues to develop as described in two new reviews. Other emerging concepts for enhancing the biodiscovery effort, and recent advances in other experimental technologies, have been described. The online database MarinLit 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 relationship of biologically active MNPs from marine cyanobacteria and actinomycetes continues to be updated and has been the principal source of information for this review.

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.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-216T (*Catalimonadaceae*) and BNG-16T both produced the marinopyrazinones A 8 and B 9.26

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

![Structure of marinopyrazinones](image1.png)

The putative BGC for the fluostatins from *Micromonospora rosaria*30 was expressed heterologously in *Streptomyces coelicolor* and led to the isolation of fluostatin L 17 and a fluostatin heterodimer 18,31 while investigation of another *Micromonospora* sp. resulted in isolation of a pimarane derivative 19.32 Based on *Micromonosporaceae* spp. the parameters for induced biosynthesis by interspecies interaction in co-culture were explored using a micro-scale approach and LC/MS-PCA methods to assess secondary metabolite production.33 Aminoimidazoles 20 and 21,34 diketopiperazines 22 (ref. 35) and 23 (ref. 36) (new to marine)37 and dimeric indoles 24 and 25 (ref. 38) were reported from *Norcardiopsis* and *Rubrobacter* spp. Work on the actinomycete *Saccharothrix* sp. led to the isolation of further aromatic polyketides saccharothrixones A–D 26–29, new members of the tetracenomycin (Tcm) family. Saccharothrixone D is unusual in that it has the opposite chirality to Tcm C at each stereocentre.39

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

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-generati...
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\textsuperscript{46–50} congeners \textsuperscript{46, 47} and \textsuperscript{48} from a \textit{Streptomyces} sp. and, subject to supply, further studies will examine the mechanism by which active lobophorins activate UPR.\textsuperscript{51} The gene cluster for the anti-infective desotamides from \textit{S. scopuliridis} has been identified and a heterologous expression in \textit{S. lividans} and \textit{S. coelicolor} the desotamide congener \textsuperscript{G 49} was characterized.\textsuperscript{52} A further depsipeptide in the salinamide series, \textsuperscript{F 50}, was isolated from re-cultivation of \textit{Streptomyces} sp. CNB-091.\textsuperscript{53} To address the bottleneck that often impedes progress in research, 3D-NMR techniques have been applied to the structure determination of peptidic natural products of interest. To balance costs, yield and relative \textsuperscript{13}C/\textsuperscript{15}N abundance the growth media used peptone and yeast extract and \textsuperscript{15}NH\textsubscript{4}Cl and [\textsuperscript{U-\textsuperscript{13}C}]glucose. The \textit{Streptomyces} sp., isolated from \textit{Eudistoma olivaceum} was fermented in this media and the two peptides under study, eudistamides A \textsuperscript{51} and B \textsuperscript{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.\textsuperscript{54} New ansamycin analogues \textsuperscript{53–55} were obtained from a mutant strain of \textit{S. seoulensis},\textsuperscript{55} and further ikarugamycin\textsuperscript{56} derivatives (tetramic acid macrolactams) \textsuperscript{56–58} were isolated from a \textit{S. zhaozhouensis}.\textsuperscript{57} A combination of gene inactivation and complementation, synthetic substrates and extensive phylogenetic tree analyses revealed that tetramic acid and pyridone biosynthesis proceeds via a series of Dieckmann cyclases.\textsuperscript{58} A new analogue of the dilactone echinomycin \textsuperscript{59} was characterized from a \textit{Streptomyces} sp. along with a new diketopiperazine \textsuperscript{60}. Another macrolide in the bafilomycin family \textsuperscript{61}, was produced by a \textit{Streptomyces} sp. isolated from litter at a river mouth.\textsuperscript{60} Following genetic manipulation of a marine \textit{Streptomyces olivaceus} by disruption of \textit{orf-1741}, a putative transcriptional gene, three halogenated dibenzoxazapinone derivatives, the mycemycins C–E \textsuperscript{62–64}, were isolated from the mutant strain and are the first dibenzoxazapinones produced from a microbial source.\textsuperscript{61} Marine Actinobacteria continue to surprise with the versatility of their biosynthetic machinery. Phylogenetic studies have
led to the identification of 13 distinct marine actinomycete groups. The chemical investigation from one of these groups, a member of the family Streptomycetaceae, led to the isolation of two new classes of marine alkaloid, represented by actinobenzoquinoline 65, and the actinophenantrolines 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 70,64 two epimeric benzofurans 71 and 72,64 ten angucyclinone derivatives 73 and 74,65 75–82,66 anthracyclines 83 and 84 (ref. 67) a naphthacene glycoside 85 (ref. 68) (new to marine) and a further aureolic acid 86 (ref. 69) were isolated from sedimentary or endophytic Streptomyces spp. A strategy for containing HIV is reactivation of the latent virus in combination with HAART. In the search for reactivators a 5000 strong microbially-derived pre-fractionated natural product library was screened against a model of in vitro HIV latency in human CD4+ T cells. Selected pre-fractions were subjected to LC/MS fractionation and re-assayed. This identified a series of abyssomicin™ 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 93,72 four cycloheximide derivatives 94–97,73 a furanone 98,73 an x-pyrene 99,74 four benzothioate glycosides 100–103,77 an alkylamide 104,73 an aniline derivative 105 with algicidal properties79 and an incompletely characterized cylaslabdan-like compound 106.80 Anti-dormant mycobacterial properties were reported for the known terrestrial antibiotic nybomycin84 isolated, in this instance, from a marine Streptomyces. This is the first report of nybomycin from a marine source.85 The biodiversity of the Yellow Sea was explored with sediment samples collected from five locations between 50–100 m. Culturing led to the isolation of 613 actinomycete samples of which 89 species were shown to produce extracts with good antimicrobial properties against an array of microorganisms. Of these 76 were Streptomyces spp. while the remaining 12 split across four genera (Kocaria, Micromonospora, Nocardiopsis, Saccharomonospora). After 16S rRNA gene analysis the Streptomyces spp. could be split into 17 clades. This survey indicated that this previously under-explored ocean contains a wealth of microbial potential. One of the Streptomyces species further explored produced three diketopiperazine dimers, including the new dimer isonaseseazine B 107, a stereoisomer of naseseazine B.81,84

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

A series of known depsipeptides, kailuin B–F **124**–**128**, and two new analogues kailuin G **129** and H **130** were isolated from *Photobacterium halotolerans*. During this study the double bond configuration of kailuin D **126** was corrected and the previously unreported configuration at C-3 of the β-acyloxy grouping of all of the kailuins **124**–**126** and **129**–**131** assigned using a combination of Mosher’s chemistry and 1H, 13C-NMR shifts. It was suggested that as the kailuins had previously been isolated from *Vibrio* spp., which predated the description of the type strain for *Photobacterium halotolerans*, revisiting the taxonomy might be in order.

A new siderophore **132** and pre-pseudomonine **133** (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 sulfaaxiamycin 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 bacacrylone 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 chlora*. 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. 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 161–165,110,111 while the salinazines A 166 and B 167 are first examples of a natural alkyld with an oxazino-pyrophildione core.112

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 thiochloro-drilline C,115,116 bogorol A and the more thermodynamically-favoured (Z) isomer,117,118 the siderophores amphibactin-T119 and moanachelin aia-B.120,121 The first synthesis of fradcarbazole120 was by semi-synthesis123 from staurosporin.124 Also successfully synthesised were the nitrosporeusines,125,126 fijilode A,127,128 marinisorpolide129,130 and splenicin 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 reconfirmed the absolute configuration as (S) and that the specific optical rotation is negative.138 The unusual anthracycline marmoycin139 has been successfully synthesised and fluorescent microscopy studies indicated that it accumulates in the lysosomes and not the cell nucleus.140 The synthesis of immunofluorescence 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 thalassospi-rarnides143 confirmed that the homonanar 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 akaneo-lide145 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 marformy-cins,148 mfn, has been identified from Streptomyces drozdowiczii and encodes six NRPS’s and related proteins for the assembly of the depsipeptide core structure.149 Two papers addressed heronamide150 biosynthesis. Firstly, the gene cluster for heronamide F was identified from a deep-sea Streptomyces sp. and the presence of a β,γ-migrated diene system in the side-chain confirmed by 13C-labeling studies.151 The second paper was a theoretical examination of the proposed transannular [6 + 4] cycloadition as a step in the biosynthesis of heronamide A. The DFT computational results support that proposal and suggest that the cycloaddition is highly stereoselective giving one product, but proceeds via a ambimodal transition state that can lead to both the observed [6 + 4] and unobserved [4 + 2] products with the [4 + 2] product being less stable (3.2 kcal mol⁻¹).152 Structurally, anthracimycins and chlorotonil are virtually identical but were isolated from a Streptomyces sp.153,154 and Sorangium cellulosum,155 a myxobacterium, respectively. Chlorotonil differs from anthracimycin in that all sp³ stereocenters are inverted, there is an additional methyl group and a gem-dichloro entity. The two biosynthetic gene clusters have been compared in two papers published side-by-side. Both compounds are formed by trans-AT PKS pathways and clusters in the chlorotonil genome readily explain the chlorination and methylation pattern. In each case the decalin ring system is formed by a spontaneous [4 + 2] cycloadition and it is proposed that the alternative stereochemistries are
The biosynthesis of two similar *Salinispora pacifica* metabolites, salinipyrone and pacicanone,\(^{158}\) was unexpectedly correlated with the large PKS cluster from *Micro- monospora carbonacea*\(^{159}\) that produces the macrolide rosamicin\(^{160}\) and illustrates how domain and module skipping can give rise to polyketide product diversity.\(^{161}\) From a study of splenocin\(^{162}\) 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.\(^{163}\) To reach the conclusion that indole-C-3 methylation of \(\text{cyclo-L-Trp-L-Trp}\) precedes indole-C-3' prenylation and transfer of a second methyl to the \(N\)' position in the biosynthesis of the nocardioazine alkaloids\(^{164}\) required bioinformatics analysis, bioinspired syntheses and MS metabolomics profiling.\(^{164}\) Target-directed genome mining is a new strategy for the discovery of new biosynthetic pathways and the concept was developed around an analysis of the pan-genome of \(86\) *Salinospora* bacterial genomes. The strategy operates by querying the genomes for duplicated housekeeping genes that are co-localised with biosynthetic gene clusters.\(^{165}\) The initial development of cytological screening of natural product extracts using a high content imaging approach to generate phenotype fingerprints has been extended from the original \(312\) extracts\(^{166}\) to over \(5000\) pre-fractionated extracts from marine Actinobacteria and demonstrated the role that untargeted cytological screening can play in ascertaining the pathways and the mechanisms disrupted and so leading to a targeted selection of extracts based on a potential mode of action.\(^{167}\)

### 3.2 Marine-sourced fungi (excluding from mangroves)

Studies of fungi continue to be on the rise with \(371\) new compounds reported in 2015 compared to \(318\) in 2014 and \(223\) in 2013. A number of new metabolites have been obtained from the genera *Acremonium* (benzophenones 170–172 (ref. 168)), *Alternaria*...
(tricycloaternarenes 173 and 174, and a spiro decalin derivative 175 [ref. 170]), Arthrinium (alkaloids 176–178 [ref. 171] and cytocalasins 179–183). Of these, arthrinium A 179 was claimed as new but is a known natural product derivative 173 and ketocytochalasin 183 (ref. 173) is a first time MNP. 174 Citromycetin analogue 184 was obtained from an Ascomyta sp. 175 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, 176 184 analogue 185 into versicolamide B and also into seven new metabolites 177 186 (ref. 170), tricycloalternarenes 178 (tricycloaternarenes 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 spiculisorpic acid analogues 196 and 197, 181 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 pyrrolepeptide 215, 188 216 and 217, 189 218, 190 hydroxyphenylacetic acid derivative 219, 193 alkaloids 220 (also synthesised) 190 and 221–225, 195 the steroids 226, 2-O-methylbutyrolactone I 227 (aspernolide C) 194 and 2-O-methylbutyrolactone II 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. 190 The stereochemistry of 5’-hydroxyasperentin 200 was established as (3R,10R,13S,14S) 255 by X-ray crystallography. 200 New metabolites were isolated from the genera Auxarthron (triterpene glycoside 256 [ref. 203]) and Beauveria (co-culture with Penicillium) (citrinin derivatives 257 and 258 [ref. 204]). Several new tetracyclic 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 tetracyclic acid F-14329, previously obtained from terrestrial Chaunopycnis 260 and Tolypocladium 261 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. 208

An OSMAC approach was utilised in the isolation of polyketides 264 and 265 from Cladosporium sphaerospermum 209 and other metabolites obtained from Cladosporium species included...
diketopiperazines 266 and 267,218 bicyclic lactam 268 (ref. 211) and polyketides 269 and 270.212 New metabolites isolated from the genera Corynebora included chromone derivatives 271–282 (ref. 213) while Dichotomomyces spp. produced the thio-diketopiperazines 283–285, 284 (ref. 214) and 285 (ref. 215) as first time MNPs,216 and steroids 286–288.217 From Emericella spp. the polyketides 289–296 (ref. 218) and lactones 297–300 (ref. 219) were characterised while the isopimaranes 301 (ref. 220) came from an Epicoccum sp. and a Eurotium sp. gave the prenylated indole diketopiperazines 302–316.221 The co-isolated alkaloid neoehcunin 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.222 Further new metabolites were obtained from the genera Glomastix (macrolides 317–321 (ref. 224)), Graphium (thiodiketopiperazines 322–329,235 330 and 331 (ref. 226)) and Hypocrea (furans 332, 333 and cyclopentenone derivatives 334–338).227 Two of these compounds, N-2-methylbutyl-2-phenylacetamide237 and N-(2-methylbutyl)-2-phenylacetamide239 338 were first time MNPs.227 New natural products were isolated from the genera Lophiostoma (merosesquiterpenoids craterellin D 339 and craterellin A340; first marine isolation for the latter),231 and Nectria (monoterpenoid α-pyriones 341 and 342).232 Of these, nectriapyrone D342 was simultaneously isolated from a terrestrial fungus as gypynone B.233 The genera Neosartorya and Paecilomyces also yielded new metabolites (alkaloids 343 and 344,234 meroterpenes 345 and alkaloids 346 and 347 (ref. 235) and butenolide derivatives 348 and 349,236 alkaloids 350 and 351,237 352 and 353 (ref. 238) and octaketide spiroketals 354–357 (ref. 239)). The genus Penicillium was, as always, a prolific source of new metabolites, including bisthioketopiperazines 358 and 359, sesquiterpenes 360 and 361,239 phenolic bisbolanes 362–364 and nor-bisbolane 365,241 benzoic acid derivative 366,242 citrinin derivatives 367–370 and tetratic acid analogues 371 and 372.243 A culture of P. admetzioides was the source of the dithiodiketopiperazine derivatives penicidametazime A 373, with the unique spiro[furan-2,7-pyrazino[1,2-b][1,2]oxazine] skeleton, along with an analogue, penicidametazime B 374, both inhibitors of the plant pathogenic fungus Alternaria brassicae.244 Penicitrinine A, 375 also with a unique spiro skeleton, was obtained from P. citrinum and was cytotoxic to a wide range of tumour cell lines. It also induced apoptosis and suppressed metastasis.245

Phthalide derivatives 376 (ref. 246) (first time MNP) and 377, isopatulin247 378 (first time MNP),248 and oxindole alkaloids 379–386 were also isolated from the Penicillium genus.249 Another oxindole alkaloid 387 was claimed as new and named cyclopamide 1149 but had already been reported in 2014 as aspergillicine D.250 The current report does however represent the first marine isolation.249 The gene cluster from Penicillium expansum responsible for biosynthesis of the indole alkaloids communesins251 has been identified. In the process, three new metabolites, communesin 1–K 388–390 were isolated. The investigation confirmed that communesins originate from L-tryptophan via coupling of tryptamine and aurantiocline.252

Further metabolites isolated from the genus Penicillium include meroterpenes 391 and 392,253 alkaloids 393,254 394–396,255 diphenylmethane derivative 397,256 phenolic enamide 398 and meroterpenoid 399,257 azaphilone derivatives 400–402 and diphenyl ether derivatives 403 and 404.258 The planar structure of 404 appears in a screening library259 but no source is given for the compound. Chromones 405–409,260 sesquiterpenes 410–413,261 merosesquiterpenes 414 and 415,262 1,4-diazepane 416,263 tanazawa acids 417–420,264 diketopiperazine 421,265 polyketides 422–426,266 spiroindoline alkaloids 427 and
isolated along with pestarhamnoses A and B when grown axenically but coculture of this strain with another Penicillium strain obtained from the same sponge elicited production of the known compounds norlichexanthone and monocerin (first time MNP), neither of which was detected in the individual axenic cultures of the two strains.

A soft coral-related Pestalotiopsis sp. was the source of enantiohmic alkaloid dimers (+)- and (−)-pestaloxazine A and B. These mixed polyketide-cyclopeptide metabolites (PKS-NRPS hybrids) possessed a unique, symmetric spiro [oxazinane-piperazinedione] skeleton and the racemate and (+)-pestaloxazine A were more selective and more potent.

The genus Pestalotiopsis yielded a number of other new metabolites, including meroterpenoids A and B, iso-coumarin C, phenol D (ref. 274) phthalide derivative E, and pestarhamnoses A–C. The pestarhamnoses were obtained through cultivation on a modified medium which contained equal concentrations of sodium chloride and potassium bromide in an expectation of producing brominated analogues of the previously isolated pestalachlorides. Interestingly, no brominated analogues were detected but pestalachlorides C and D were isolated along with pestarhamnoses A–C.

Other fungal genera to yield new metabolites included Phaeosphaeria (polyketides A and B), Pheoma (cytochalasin derivatives A and B), Pleosporales (pleosporalins A–G), Pestalotiopsis (chlorinated benzofurans A–C), Pseudallescheria (chlorinated benzofurans A–C), and Pseudogymnoascus (nitratred asterric acid derivatives A–C). The ascidian-derived Rousseella sp. produced roussoellatide A, a dichlorinated polyketide with an unprecedented skeleton and unexpected antiproliferative activity against the highly metastatic breast cancer cell line MDA-MB-231. A sponge-derived Penicillium sp. yielded the fusarielin analogue A when grown axenically but coculture of this strain with another Penicillium strain obtained from the same sponge elicited production of the known compounds norlichexanthone and monocerin (first time MNP), neither of which was detected in the individual axenic cultures of the two strains.

New metabolites were also obtained from the genera Simplicillium (diketopiperazine A and B), Stachybotrys (meroterpenoid sulfate A), Pestalotiopsis (diketopiperazine B), and DC1149B (ref. 275) phthalide derivative C, and pestarhamnoses A–C. The pestarhamnoses were obtained through cultivation on a modified medium which contained equal concentrations of sodium chloride and potassium bromide in an expectation of producing brominated analogues of the previously isolated pestalachlorides. Interestingly, no brominated analogues were detected but pestalachlorides C and D were isolated along with pestarhamnoses A–C.

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

The genus Truncateatella was the source of some isoprenylated cyclohexanols 523–536,309 while an antibiotic polyketide 537 and ascoetinin 538 were obtained from a fungus of the Lindgomycetaceae family.310 Synthesis of the octaketide ascospiroketal A, originally obtained from Ascochyla salicorniae,311 via a Ag+-promoted cyclisation cascade, revised the stereochemistry to 539 and indicated that the structure of ascospiroketal B311 should also be revised accordingly.312,313 Remispore A was originally obtained from Remipspora maritima and spontaneously dimerises to form remispore B.314 Comparison of the calculated and measured ECD spectra of remispore B suggested a revision of configuration. By extension the configuration of natural product remispore 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 similannis similannis with the sponge Rhabderma 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 Clostochasys rosea was the source of a new natural product, 4-methyl-(6E,8E)-hexadecadienoic acid 542, previously known only from methanolysis of the mushroom Microporellus subsessilis.320 This fatty acid inhibited growth of MCF-7 cells and down-regulated the lipogenic enzymes acetyl CoA carboxylase (ACC) and fatty acid synthase (FAS).321 Acetylgliotoxin G322,543 was obtained for the first time as a MNP as was the known synthetic open-chain hemisuccinimidine 544,544 (Penicillium copticola) which was named penicillimide.324 Alternariol-9-methyl ether 3-O-sulfate 545, previously obtained from Alternaria sp., an endophyte of the Egyptian medicinal plant Polygonum senegalese,325 was obtained for the first time from the marine environment from endophytic Alternaria alternata.326 The nortiterpenes aspewentin A–C (Aspergillus wentii)327 have been synthesised328 as have the prenylated indole alkaloids, (+)-notoamide I (Aspergillus sp.)329 and (–)-17-hydroxy-citrinalin B (Penicillium citrinum)330 via a unified strategy.331 Herbarins A and B originally obtained from Cladosporium herbarum322 have been synthesised via a multi-step procedure and both displayed antioxidant properties.332 Starting from the sugar D-lyxose, total synthesis of cochliomycine C333,334 has been achieved.335 Total synthesis of the macroclide dendrodolide K337 (Dendrodochium sp.) has been accomplished from a commercially available substrate by a convergent strategy338 and other dendrolides (F, G, I, J and L)377 have also been synthesised via a unified strategy employing ring-closing metathesis.339 A unified strategy was also employed in the total synthesis of luteoalbusins A and B,406 indole diketopiperazines isolated from sediment-derived Acrostalagmus luteoalbus.441 In addition to the new compound talaromycin C,396 purpactins A,442 C442 and penicillide341 exhibited potent antifouling activity against settlement of Balanus amphitrite larvae396 as did altetroxin I, a metabolite of both terrestrial444 and marine445 Alternaria alternata.346 A number of known cyclic dipeptides, cyclo(Gly-L-Pro),147 cyclo(L-Ala-L-Pro),148 cyclo(L-Ala-L-Pro),149 cyclo(L-4-Hyp-L-Pro)549 and cyclo(L-Hyp-L-Phe)549 were resynthesized from Eupenicillium brefeldianum and induced extracellular alkalisation and hydrogen peroxide production in plant cell suspensions, indicating their potential as induced systemic resistance (ISR) elicitors.552 Viridicitol, a metabolite of Aspergillus versicolor,555 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.554 Sporimastixones are chlorodepsidone metabolites of Sporimastix sp.355 which strongly inhibit cholesterol uptake and stimulate cholesterol efflux to apolipoprotein A1 (ApoA1) and high-density lipoprotein (HDL) in RAW264.7 macrophages.556 FGFC1 (fungi fibrinolytic compound 1),557 a metabolite of Stachyhotrys longispore358 has potential as a thrombolytic agent since it induces thrombolysis in a rat model of acute pulmonary thromboembolism without associated bleeding.559 Several studies have explored production of the lipopeptides scopularides A and B446 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 changed by causes in secondary metabolism, but by complex changes in primary metabolism.60 Several other studies362,363 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.263

3.3 Fungi from mangroves

There has been a continued increase in the number of new metabolites reported from mangrove-associated fungi (127 in 2013 vs. 103 in 2014), with the majority coming from endophytic species. An Alternaria sp. yielded cyclohexane, cyclopentane and xanthone derivatives 546–549 (ref. 364) and the genus Aspergillus was the source of many new metabolites including meroterpenoids 550–553,465 polyketides 554–556,466 indole diketopiperazines 557–559,467 isochromane derivatives 560–563 (ref. 368) and the versianthones 564–567 and 568 and 569.469 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 versianthones exhibited cytotoxicity at some level against several HTCLs and versianthone E 568 was an inhibitor of topoisomerase I.469 Further metabolites obtained from the Aspergillus genus include dinaphthalene derivatives 570–573,570 lumazine peptide 574,471 cyclohexanone-furan derivative 575, isocoumarin derivatives 576–578 and 579 (ref. 372) (first marine isolation)377 and polyene 580.274
New metabolites were obtained from the genera *Botryosphaeria* (isocoumarin 581 [ref. 375]), *Cladosporium* (dimeric tetralone 582 [ref. 376]), *Daldinia* (hydranaphthalenone 583 [ref. 377]), *Eurotium* (indole diketopiperazine 584 [ref. 378]), *Euptypella* (cytochalasans 585 and 586 [ref. 379] (new NP) and 587), *Fusarium* (α-pyrone cladobolin V 588 [ref. 381] and 589, cyclic depsipeptides 590 and 591 [ref. 383]), *Lophiostoma* (phenalenone derivatives 592–600 and sesterterpene bipolarenic acid 601 [ref. 384]), *Meyerozyma* (depsidones 602–606 [ref. 385]), *Nigrospora* (acetamidopentane derivative 607 and phenalenone derivative 608 [ref. 386]) and *Paradityctyoarthrinium* (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, α-pyrone 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 cyanogroup 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 *Stemphylium* (aromatic sulfates 660 and 661 [ref. 407]). Stempholin 662 was obtained as a first time MNP. Several studies reported metabolites from species that were unidentified or only partially classified. Sesquiterpenoids 663 and 664 [ref. 409] and coumarin 665 [ref. 410] were obtained from unidentified species (the latter from a mixed culture of two species) and spiridioxynaphthalenes 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. Synthesis of the proposed structures of cephalosporolides H 416 and I 416 has revised the configuration at C-6 of each to (R) (674 and 675) but discrepancies for some 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 419 as has the *Penicillium* metabolite, 420 (−)-penbrugueramine. 421 *Pestalotiopsis* metabolite (6S,1‘S,2‘S)-hydroxypesatalotin 422 has been synthesised 423 and the proposed structure of pestalotioprolide A 424 has been prepared via total synthesis, but a mismatch between the magnitudes of optical rotation data between the reported value for the natural product and the synthetic compound indicate that the stereochemistry of the natural product requires further examination. 425 A number of known natural products were reisolated from *Phakellia fusca* and exhibited a range of activities. Penicillenol A 414, a tetrameric acid derivative, displayed anti-TB activity whilst expansols A 426, 427–429 were potent COX-2 inhibitors and all but expansol D were also potent inhibitors of COX-1.

### 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, hectorchlorins 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 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 was achieved and resulted in the revision of the structure to 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 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...
acyclic depsipeptide maedamide\(^{461}\) and cyclodepsipeptide larginide B\(^{462}\) also resulted in stereochemical revision of their structures to 712 (ref. 463) and 713 (ref. 464) respectively, the latter consistent with the revised structure previously proposed.\(^{465}\) Syntheses of (+)-lyngbyabellin M\(^{466,467}\) sanctolide A\(^{468,469}\) and santacruzamate A\(^{470,471}\) were also completed, with the last not exhibiting any inhibition of histone deacetylase (HDAC), unlike the potent inhibition previously reported.\(^{470}\) The functions of some enzymes involved in the biosynthesis of the terminal alkyne moiety in the jamaicamides\(^{472}\) were elucidated via both in vitro and in vivo analyses.\(^{473}\) Dereplication methods based on phylogeny and HPLC-MS were developed which showed that largazole\(^{474}\) was always coproduced with either dolastatin 10 (ref. 475) or symplostatin 1 (ref. 476) and that combinations of largazole and dolastatin 10 displayed cooperative activity.\(^{477}\)

### 3.5 Dinoflagellates

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

Nonacosadienes 726 and 727 were obtained as metabolites of the microalga Emiliania huxleyi\(^{492}\) while 12β-deoxydecarbamoylsaxitoxin\(^{493}\) 728 was obtained as a first time MNP.\(^{494}\) Syntheses of the polyketide amphirionin-4 (ref. 495) and ciguatoxin 54-deoxyCTX1B\(^{496}\) have been achieved.\(^{497,498}\) Polyketide synthesis genes unique to two Gambierdiscus species that produce maitotoxin\(^{499}\) were characterised, perhaps implying them in the biosynthesis of this metabolite.\(^{500}\) Studies with Karenia brevis showed that brevetoxin\(^{501}\) is localised in the chloroplasts and interacts with light harvesting complex II (LHCII) and thioeodosin, so is likely implicated in non-photochemical quenching (NPQ). Differences between toxic and low toxicity K. brevis strains in NPQ and reactive oxygen species (ROS) production supported this.\(^{502}\)

# 4 Green algae

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

The structure and absolute configuration of nigricanose A, isolated in 2007 from Avrainvillea nigricans,\(^{506}\) has been established by enantiomselective total synthesis as 737, correcting aspects of the previously reported configurations.\(^{507}\) Originally isolated as the dimethyl ester, nigricanose A was reported to inhibit the proliferation of several cancer cell lines (IC\(_{50}\) 3 nM), but the synthetic material, identical in all respects to the natural sample, was inactive. The natural material was ∼90% pure and it is now suggested that the potent bioactivity of nigricanose A was associated with a related, co-eluting minor metabolite with sub-nanomolar activity.\(^{508}\) 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.\(^{509}\) 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,\(^{510}\) while astaxanthin and other algal carotenoids have been the focus of many studies and reviews.\(^{511–518}\)

# 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,\(^{519,520}\) Dictyota plectens,\(^{521}\) and Cystoseira trinodis\(^{522}\) respectively. The compounds of mixed biosynthesis was a tranche comprised of a chromene, 746

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Nonacosadienes 726 and 727 were obtained as metabolites of the microalga Emiliania huxleyi\(^{492}\) while 12β-deoxydecarbamoylsaxitoxin\(^{493}\) 728 was obtained as a first time MNP.\(^{494}\) Syntheses of the polyketide amphirionin-4 (ref. 495) and ciguatoxin 54-deoxyCTX1B\(^{496}\) have been achieved.\(^{497,498}\) Polyketide synthesis genes unique to two Gambierdiscus species that produce maitotoxin\(^{499}\) were characterised, perhaps implying them in the biosynthesis of this metabolite.\(^{500}\) Studies with Karenia brevis showed that brevetoxin\(^{501}\) is localised in the chloroplasts and interacts with light harvesting complex II (LHCII) and thioeodosin, so is likely implicated in non-photochemical quenching (NPQ). Differences between toxic and low toxicity K. brevis strains in NPQ and reactive oxygen species (ROS) production supported this.\(^{502}\)
(Homoeostrichus formosana), five acyclic meroderpenoids 747–750, (Sargassum paradoxum)\textsuperscript{531} 751 (Cystophora retroflexa, C. subfarcinata, Sargassum cf. fallax), four cyclic meroderpenoids 752 (Stypopodium flabelliforme),\textsuperscript{536} 753–755 (Stypopodium zonale)\textsuperscript{537} and the cyctophloketals A–E, 756–760, hybrid meroderpenoids from Cystoseira tamariscifolia.\textsuperscript{528} The cyctophloketals, 756–760, each incorporated an O-methyltoluquinol and a phloroglucinol with the cyclic diterpene and are the first examples of meroterpenoids with the rarely found 2,7-dioxabicyclo[3.2.1]octane backbone.\textsuperscript{528} The proposed, unprecedented syn-cis-anti arrangement for the A/B/C ring system in the cyclic meroderpenoid, \( O,(3)\text{-seco-9-ene-6β-taondiol} \) 752 was based on NOESY data and supported the notion that the folding patterns of the presumed biosynthetic precursor, 2-geranylgeranyl-6-methylhydroquinone, are flexible during biosynthesis leading to different classes of metabolites related to the taondiol group.\textsuperscript{528–531} The isolation and characterisation of >20 acyclic meroderpenoids 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].\textsuperscript{524,525}
The non-terpenoid brown algal compounds are represented by the polyketides, 761–770, from Lobophora variegata.\textsuperscript{522} 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.\textsuperscript{533,534} The absolute configuration for the acyclic diterpeneoid elegandiol,\textsuperscript{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.\textsuperscript{537} The first asymmetric synthesis of (−)-dolastatrienol (14-hydroxylolasta-1(15),7,9-triene)\textsuperscript{538} was reported\textsuperscript{539} along with a concise synthesis of dictyodendrins A and F.\textsuperscript{540} Additionally, there were many papers and reviews dealing with the biological properties of brown algal polyphenolics\textsuperscript{541–557} and carotenoids.\textsuperscript{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,\textsuperscript{563} 774,\textsuperscript{544} 775,\textsuperscript{545} oxosqualenoids 776–779,\textsuperscript{546} sesquiterpenoids 780 and 781,\textsuperscript{547} 782,\textsuperscript{548} 783,\textsuperscript{549} 784–785,\textsuperscript{550} diterpenoids 786–788,\textsuperscript{571} 789,\textsuperscript{551} and the mycosporine-like amino acid 790.\textsuperscript{552} The rearranged diterpenoids spirophaerol 786 anthrphaerol 787 and corfusphaeroloxide 788 from Sphaerococcus coronopifolius have unprecedented tricyclic skeletons.\textsuperscript{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 benzoglycetraphene ligands have never been seen in any fossil compounds, and only recently a study\textsuperscript{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.\textsuperscript{575} Syntheses of plomcanone and isoplocamenone have confirmed their structures\textsuperscript{576} and established their absolute configurations.\textsuperscript{577} Total syntheses of the proposed structures of microladallenes A, B and C\textsuperscript{578} confirmed the structures of A and B but indicated that microladallene C could not be correct.\textsuperscript{579} Additional studies on bis(2,3-dibromo-4,5-dihydroxyphenyl)-methane (Rhodomela larix)\textsuperscript{580} and bis(2,3-dibromo-4,5-dihydroxybenzyl) ether (Odonthalia corymbifera)\textsuperscript{581} have revealed significant activities in a range of assays, all indicating the potential of these compounds for development as anticancer agents.\textsuperscript{582–584} Studies on eight brominated inochoes from Laurencia bronniatnii\textsuperscript{585} have revealed that some of them constitute a new class of relatively potent naturally occurring aryl hydrocarbon receptor (AhR) agonists.\textsuperscript{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,\textsuperscript{591} cerebrosides 807–815 (ref. 588) and 816–833,\textsuperscript{589} and lysosphingolipids 834 and 835 (ref. 590) were reported from Spheciospongia vagabunda, Aulosaccus sp. and Spirastrella purpurea, respectively, while the genera Biemma, Callyspongia, Haliclona and Xestospongia yielded taurinates 836,591 polysaturated 837–839,592 840 (ref. 593) and brominated 841 (ref. 594) fatty acids. Stelletta sp. provided six new glycosidated fatty acids stelletaside A1–B1 842–847. The structures of these N,N-dimethylptrescine-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\textsubscript{50} 9 μM).\textsuperscript{595}

Polycyclicenes were found in extracts of Callyspongia implexa 848,596 Petrosia sp. 849–851,597 Halichondria sp. 852–854,597 Pleroma sp. 855–861,598 and Xestospongia sp. 862 and 863.599 The nanomolar-scale isolation of mollenynes B–E 864–867 from
Spirastrella mollis posed several challenges. First, the extremely low yields of isolated compound imposed limitations on acquiring usable NMR spectra, and second, unequivocal placement of the chlorine and bromine atoms upon the carbon backbone was difficult due to the similarity in $^{13}$C chemical shifts. The former issue was resolved by use of a cryogenically-cooled NMR microprobe while the latter exploited a new band-selective HSQC experiment for enhanced resolution by only detecting a small region of the $^{13}$C dimension. This facilitated the observation of the $^{35}$Cl/$^{37}$Cl isotopic effect that causes a splitting of a chlorinated $^{13}$C resonance of around 1 Hz. The biosynthesis of these compounds could involve an unusual “dyotropic shift” of Cl and Br atoms, which would also account for the observed inversion of configurations within the series.600

An unidentified sponge yielded two aromatic bases 882 and 883,607 while a mixture of Thorectid and Verongid sponges was the source of a new isoscorbic acid derivative 884, although this was speculated to be of fungal origin.605 Euphrosinia sp. from Okinawa yielded eurydiene 885 (ref. 609) while an Australian Dragmacidon sponge contained triphenyl 886. Smenothiazoles A 887 and B 888 are two chlorinated thiazoles isolated from Smenospongia aurea (Little Inagua, Bahamas). These metabolites are of mixed PKS/NRPS origin that bears significant resemblance to the cyanobacterial compound jamaicamide B.472 Both compounds showed in vitro inhibition of four solid HTCLs in the 1–100 nM range, and could selectively induce apoptosis in some cell lines via cell cycle blockage in the G2M phase.611

The known fungal metabolites gibeyporones C 868 and F 869 (ref. 601) were isolated from the marine environment for the first time.602 Sponges of the Plakortis genus are well known producers of methyl and ethyl branched polyketide peroxides. Studies of P. angulosipculatus 870–872,604 Plakortis sp. 873–875 (ref. 604) and P. bergquistae 876–880 (ref. 605) were reported in 2015. Of note was the investigation of P. simplex which contained spiroplakortone 881. This modestly cytotoxic compound (IC$_{50}$ 37.5 μM against L5178Y mouse lymphoma) has an unprecedented spirocyclic core ring system and it suggested that it is formed via a hybrid polyketide/amin acid biosynthetic pathway. The structure of 881 was solved by a comprehensive combination of spectroscopic and computational studies to establish the configuration of the spiro-center.606

A surprisingly small number of peptides and depsipeptides were reported in 2015, given sponges are normally prolific reservoirs of such compounds. The α-ketoleucine or α-ketonorvaline-containing dimeric cyclopentapeptides nazumazoles A–C 889–891 (Theonella swinhoei) were detected as an exceedingly broad peak using ODS-HPLC and were isolated as an inseparable mixture. A significant number of degradative
Three diamine-type alkaloids 910–912 were isolated from Indonesian Neopetrosia223 and Acanthostrongyluspora223 sponges, while a Neopetrosia sp. also yielded two nucleosides 913 and 914, one of which was also synthesised.624 Indole alkaloids were isolated from Ircinia 915 and 916,625 Plakortis 917 and 918 (ref. 626) and Spongia 919 and 920 (ref. 627) sponges. An Aaptos sponge yielded three aaptamine alkaloids 921–923.628 A Bienna sp. was the source of two pyridoacridines N-hydroxy-methylisoxyctadamine 924 and neolabuanine 925. The structure assigned to 925 had previously been incorrectly attributed to labuanine A.629 The current study determined that this isolate was in fact ecionine A.629 Both compounds induced similar levels of cellular differentiation of human leukaemia tumour cells to normal erythrocytes at similar levels (ng mL−1) to doxorubicin.631

Guanidine-type alkaloids have been isolated from Bienna labou诶i 926–930,632 Pseudoaxinella reticulata 931–934,633 Monanchora arbuscula 935–940 (the synthesis of 935 was also achieved),634 and M. pulchra 941–943,635 while oridon-type pyrrolo-alkaloids were sourced from the genera Styllisa 944 and 945 (ref. 636) and Agelas 946 (synthesis also completed).637 947 and 948,638 949–951,639 952–956,640 A series of bromotyrosine-derived compounds were reported from a member of the Verongida 957 and 958,641 Pseudoceratina arctica 959–961,642 P. purpurea 962 and 963,643 Acanthodrilla sp. 964,644 Suberea sp. 965–967 (ref. 645) and Aplysina lacunosa 968–970.646 As always, prenylated metabolites dominate the compounds reported from sponges. Isolated meroterpenoids include 971–976,647 977–984,648 and 985–987 (ref. 649) from Dysidea sponges. A novel approach was taken to promote the production of several “natural products”. Homogenised Verongula rigidà, a sponge with known potent oxidative potential, was added to homogenised Smenospongia aurea and S. cerebriformis and incubated in ethanol for one week. LC-MS guided isolation of the Smenospongia extracts yielded several new 4,9-friedodrimane meroterpenoids 988–995. Whilst 992–995 are likely artefacts of the ethanol incubation, the other new compounds are all likely true biochemically-produced metabolites. The fused iminoquinone moiety of 990 and 991 is unprecedented in known natural products. Compounds 989–991 and 995 were moderately cytotoxic to two HTCLs.650 Pupehenone 996 (Dactylospogia sp.) exhibited pronounced anti-inflammatory activity. The known compound pupehenone651 was also isolated. Exposing 996 to mild acid (CDCl3) at slightly elevated temperatures (30 °C) resulted in quantitative conversion of pupehenone to pupehenone, suggesting the latter is actually an artefact of isolation.652

A series of adociaquinone compounds 997–1002 was reported from an Indonesian Xestospongia sp.,653 while meroterpenoids 1003–1005,654 1006,655 1007 and 1008 (ref. 656) were isolated from Agelas nakamurai, Strongylophorastrongylata,
and *Petrosia cortica* respectively. Sesquiterpenoids 1009 and 1010,657 and 1011–1013 (ref. 658) were isolated from *Dysidea fragilis* and 1014–1018 from *Halichondria* sp.,659 while three farnesylacetone derivatives 1019–1021 were reported from *Diacarnus megaspinorhabdosa*.660 *Niphates* and an unidentified Dictyoceratid sponge were the sources of 1022 (ref. 661) and 1023–1025,662 respectively. Monampilines B 1026 and C 1027 are potent antimalarial β-lactams (IC₅₀ 44.5 and 43.3 nM vs. *P. falciparum*, respectively) isolated from *Svenzea flava* and were both synthesised from a known diisocyanide.663

Investigation of *Hamigera tarangaensis* revealed a series of brominated nitrogenous hamigeran diterpenoids 1028–1036. All incorporated an amino acid as part of the nitrogen heterocycle although stereochemical arguments required the inclusion of allo-isoleucine in 1035 and 1036 implying the intriguing possibility of a joint sponge/prokaryotic biogenesis.664 Sponges remain prolific producers of sesterterpenoids. Sarcothragin C 1037 was isolated from *Sarcothragus* sp.665 while a manoalide congener 1038 and several luffalides 1039–1044 came from *Luffariella variabilis*666 and *Luffariella* sp.,667 respectively. Two suvanine sesterterpenoid salts 1045 and 1046 were found from *Coscinoderma* sp.668 A large number of scalaranes 1047–1051,669 1052 and 1053,670 1054–1058,671 1059 and 1060,672 1061–1071,673 1072 and 1073 (ref. 674) were reported from five different sponge genera, *Carteriospongia*, *Hyattella*, *Ircinia*, *Phyllospongia* and *Spongia* respectively. Other new
sesterterpenoids were 1074 and 1075 (Clathria gombawuensis)\textsuperscript{675} and 1076 (Haliclona sp.) sourced from Korean collections.\textsuperscript{676}

Several new sterols and their degradation products have also been reported from sponges. Epoxide-1077 and peroxide-1078–1079 containing sterols were found from Biemma\textsuperscript{677} and Monanchora\textsuperscript{677} sponges, respectively, while highly derivatized sterols were isolated from Dografacidon australis 1081 (ref. 610) and Polyblastiformis 1082 and 1083.\textsuperscript{678} A new 9,11-secosterol 1084 came from a Korean Ircinia sp. The first naturally occurring bicyclo[4,3,1]-A/B ring system steroids, monanchosterols A and B 1085 and B 1086, were isolated along with a third sterol 1087 from Monanchora sp. (Gageo Is., Korea). The biogenesis of the ring-contracted compounds was suggested to begin from a common 4β,5β-epoxysterol. The only other report of such a ring system is from a synthetic study published by Barton in the 1980s.\textsuperscript{680} While 1085 was toxic to RAW264.7 cells (IC\textsubscript{50} 65 μM), both 1086 and 1087 were not, but instead were immunomodulatory inhibiting mRNA expression of IL-6 by ~70% at 10 μM even though monanchosterols A and B only differ by a single acetylation.\textsuperscript{681}

A nortriterpenoid-saponin 1088,\textsuperscript{685} 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\textsuperscript{682} although the name stellettin N had been used previously for a different structure.\textsuperscript{684} The
absolute configuration of psammaplysin A (ref. 685) (isolated in the current study from Aplysinella strongylata) was established from detailed comparison of calculated and experimental ECD data in conjunction with NMR studies including Mosher’s analysis,⁶⁶⁶ while the absolute configuration of eurypongin A (Euryponga sp.) was also determined using chiroptical techniques.⁶⁶⁷ Inconsistencies in NMR data reported for two sponge steroids isolated from Neofibularia nolitangere⁶⁶⁸ with those isolated from Japanese edible mushrooms necessitated structural revision to 1103 and 1104.⁶⁶⁹ Hepatitis B infection poses a major human health risk. Two sponge-derived polybrominated biphenyls isolated from Indonesian Dysidea species were found to possess hepatitis antiviral activity with selectivity indices of 12.8–18.2.⁶⁷⁰ Transcriptomic analysis of HepG2 hepatocarcinoma cells treated with both Crambe crambe metabolites crambescin C1 (ref. 692) and A1 (ref. 693) showed that the former protects against cytotoxic oxidative damage by induction of metallothionein, while the latter is ineffective.⁶⁷¹ The bastadin-class of bromotyrosine compounds, in particular bastadin-6,⁶⁷² suppress foam formation in macrophages via inhibition of cholesterol-ester formation, and may have application in the treatment of atherosclerosis.⁶⁷³ Panicein A, a hydroquinone (Haliclona mucosa) inhibits the efflux of doxorubicin by the Hedgehog receptor Patched and enhances the anticancer efficacy of the drug.⁶⁷⁴ A hypothesis put forward over a decade ago that marine isonitriles and isothiocyanates may exert antioxidant activity via interference of heme detoxification⁶⁷⁵ has been corroborated. The mode of action of these compounds was assessed using a scaled-down version of Egan’s β-hematin assay demonstrating that marine isonitriles inhibit β-hematin crystallisation and supported by ab initio calculations of the stability of the isonitrile complexes bound to iron in heme.⁶⁷⁶ Gracilins A, H and L along with tetrahydroaplysulphurin-1,⁶⁷⁷ all isolated from Spongiella sp., were found to modulate mitochondrial function in neuroblastoma cells by regulating storage of calcium entry in a similar manner to cyclosporine A via binding to cyclophilin D.⁶⁷⁸,⁶⁷⁹ Okadaic acid (OA), a potent marine cytotoxin that inhibits protein phosphatases, was originally isolated from Halichondria okadai but later identified as being produced by the dinoflagellate Prorocentrum lima and actively bioaccumulated by the sponge.⁷⁰⁰ The role and mechanism of OA accumulation by Halichondria has not yet been established. Exposure of an extract of H. okadai to OA indicated strong binding to two proteins, OA Binding Proteins (OABP) 1 and 2. While unsurprisingly OABP1 is a protein phosphatase, OABP2 is not. The X-ray crystal structure of OABP2.1 obtained from H. Okadai bound to OA showed that it has significant binding affinity for OA and has a limited homology to known protein scaffolds. Surprisingly, the global fold of OABP2.1 was most similar to the jellyfish Ca²⁺-binding photoprotein aequorin. Ca²⁺ does not displace OA from its binding site, suggesting a different mechanism for OA release by the sponge.⁷⁰¹ A comprehensive LCMS analysis of 253 Aplysina sponges comprising ten different morphologies showed that the sponge secondary metabolome correlates better with the sponge phenotype, described by invertebrate morphology, rather than the microbiome.⁷⁰² The ability of 26 sponges to inhibit bacterial quorum-sensing without cytotoxic activity was investigated. The extract of Ircinia felix was found to be the most potent inhibitor of
quorum-sensing with the activity linked to the felixinin furanosesquiterpenoid class.\textsuperscript{7,68–70} Chemical examination of adult and bud larvae of the chemically-defended sponge \textit{Tethya maza} indicated that the sterol composition of both were largely similar, suggesting that the larvae are also defended during reproduction.\textsuperscript{71} First total syntheses were reported for many compounds including the lipids motulevalic acid \textit{F}, \textit{E} and \textit{Z}-antazirine,\textsuperscript{72–74} mycolal (revised to \textit{1005})\textsuperscript{75–77} and myrmekioside \textit{A},\textsuperscript{78,79} and polyacetylenes callyspongynic acid,\textsuperscript{78,79} phosphoicydyn \textit{A} and plactylene \textit{A}.\textsuperscript{73,75} The structure of plakinidone has been corrected to \textit{1006}; the compound is highly sensitive to air oxidation. The compound’s relative configuration was also determined,\textsuperscript{76,77} while the relative configuration of the C-36 to C-42 portion of hemicalide \textit{1107} was also solved by synthesis.\textsuperscript{78,79} Total syntheses of polyketides gracilhoeter B and \textit{C}\textsuperscript{70}–\textit{71} and hippoclaxin,\textsuperscript{73,75} mycothiazole,\textsuperscript{74–76} aromatic renieramycin \textit{I},\textsuperscript{77,78} and peptides cyclocinamide \textit{A},\textsuperscript{79} corticamide \textit{B},\textsuperscript{78–74} styllasamide \textit{X}\textsuperscript{75–74} and styllasitin \textit{A}\textsuperscript{74–76} have all been realised. The total synthesis of yaku’amine \textit{A} \textit{1108}, requiring a structural revision of its core region, required revision of structure, and also that of congener \textit{B} \textit{1109}.\textsuperscript{74–76} Macrolides are attractive targets for synthesis with the construction of tulearin \textit{A},\textsuperscript{76–78} the core region, required revision of structure, and also that of \textit{Z}-[\textit{1109}] and \textit{1107}–\textit{1109}.\textsuperscript{74–76} The total syntheses of the sesquiterpenoid \textit{phorbin} \textit{A},\textsuperscript{75,76} and \textit{11-deoxy}–\textit{debromohamigeran} \textit{E},\textsuperscript{78,79} were also solved by synthesis.\textsuperscript{79}–\textit{81} The total syntheses of \textit{the} chemicalide \textit{1107} is 40% below the previous decadal average. The total syntheses of \textit{the} sesquiterpenoid \textit{aptalid} \textit{A}\textsuperscript{82} and \textit{haploperoxide} \textit{1125} (\textit{Sarcophyton auritum})\textsuperscript{83} the dianminopropyl analogue \textit{1116} (\textit{Paraplexaura} sp.)\textsuperscript{84} and new examples of zoanthenamines \textit{1117}–\textit{1123} from the hard coral \textit{Zoanthus kuroshio}. The simple cinnamate ester \textit{1124} was isolated from \textit{Sarcophyton ehrenbergii} and the structure confirmed and absolute configuration assigned by stereoselective synthesis.\textsuperscript{85} A series of seventeen sesquiterpenes were reported, comprised of a himachalene-type peroxide \textit{1125} (\textit{Litophyton arboretum})\textsuperscript{86} cyclopentenones \textit{1126} (\textit{Sinarria sandensis})\textsuperscript{87} and \textit{1127} and \textit{1128} (\textit{Sinarria acuta})\textsuperscript{88} eudesmane-type \textit{1129} (\textit{Sinarria gowleri})\textsuperscript{89} subergabene-type \textit{1130} (\textit{Subergorgia suberosa})\textsuperscript{90} monocyclic and bicyclic germacrenes \textit{1131} (\textit{Sarcophyton glaucum})\textsuperscript{91} and \textit{1132} and \textit{1133} (\textit{Cappella sp.})\textsuperscript{92} carophyllanes \textit{1134} and \textit{1135} (\textit{Rumphella antipathies})\textsuperscript{93} and guaiane lactones \textit{1136–1140} (\textit{Menella kanasa})\textsuperscript{94} and \textit{1141} and \textit{1142} (\textit{Menella woodin}).\textsuperscript{95} Of note was the use of a diverse array of computational techniques, including calculated \textsuperscript{13}C NMR chemical shifts, optical rotation and ECD to determine the structures and absolute configurations of \textit{1141} and \textit{1142}.

Of four tocopherol-derived metabolites \textit{1143} and \textit{1144} (ref. 819) and \textit{1145} and \textit{1146},\textsuperscript{820} hirsutocospio \textit{A} \textit{1143} exhibited strong anti-inflammatory activity and cladophenol glycosides \textit{A} \textit{1145} and \textit{B} \textit{1146} exhibited mild cytotoxicity towards three HTCLs. Thirty-one cembrane-related metabolites reported from cnidarians in 2015 included \textit{1147} (\textit{Sarcophyton glaucum}),\textsuperscript{814} epoxynaphthenol \textit{1148–1150} (field-collected \textit{Nepthia columbaria}),\textsuperscript{821} columnariol \textit{A} \textit{1151} and \textit{B} \textit{1152} (cultured \textit{N. columbaria}),\textsuperscript{822} sarcophine and ehrenbergol congeners \textit{1153–1157} (\textit{Sarcophyton ehrenbergii}),\textsuperscript{823} cis-cyclopentylated cashanes \textit{1158–1163} (\textit{Sinarria sp.}),\textsuperscript{824} sarcophegelans \textit{A–D} \textit{1164–1167} (\textit{Sarcophyton elegans}),\textsuperscript{825} tricyclic \textit{1168} (\textit{Sarcophyton solidum}),\textsuperscript{826} pyrans \textit{1169} and \textit{1170} (\textit{Sarcophyton trocheliophorum})\textsuperscript{827} and \textit{1171} (\textit{Litophyton arboretum}),\textsuperscript{809} hydroperoxycembranoid \textit{1172} (\textit{Sarcophyton trocheliophorum}),\textsuperscript{828} and \textit{1173–1177} (\textit{Sinarria sandensis} and \textit{S. flexibilis}),\textsuperscript{829} X-ray studies were used to determine the complete structural and stereoregional characterization of sarcophegen \textit{A} \textit{1164},\textsuperscript{825} cmbranoid 1173 and isosinulaflexiolide \textit{K} \textit{1177}.\textsuperscript{829} X-ray studies were also used to confirm the structures and configuration of previously reported cmbranoids sarsoxide \textit{B} (\textit{Sarcophyton trocheliophorum})\textsuperscript{820,826} pukalide (\textit{Leptogorgia alba})\textsuperscript{831} and dendrophoide \textit{F} (\textit{Dendronephthya sp.})\textsuperscript{832,833} The trivial name epoxynaphthenol assigned to \textit{1150} (ref. 821) has been used previously.\textsuperscript{831}

A series of nitrogenous diterpenoids and sesquisqualenoids \textit{1178–1187} were reported from \textit{Cespitularia taeiata} – the absolute configuration of cespilamide \textit{A} \textit{1178} was established by a combination of MM2 modeling and Mosher’s analysis.\textsuperscript{834}

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 anxioytic ceramide \textit{1115} (\textit{Sarcophyton auritum}),\textsuperscript{803} the dianminopropyl analogue \textit{1116} (\textit{Paraplexaura} sp.),\textsuperscript{806} and new examples of zoanthenamines \textit{1117}–\textit{1123} from the hard coral \textit{Zoanthus kuroshio}.\textsuperscript{807}
Rare examples of cembranoid 7,8-diols 1188 and 1189 were isolated from Sinularia gaweli.\(^{82}\) The structure assigned 1188 is the (−)-enantiomer of the known cembranoid leptomold acetate (Leptogoria sp.),\(^{83}\) 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)\(^{86}\) were unfortunately given the trivial names sinumerolide A and (7E)-sinumerolide A, names previously attributed to cembranoids reported from the same organism.\(^{87}\) 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.\(^{88}\) A mildly cytotoxic norcembranoid 1192 was isolated from cultured specimens of S. numerosa.\(^{89}\) Six β-methylene-γ-lactone cembranoids 1193–1198, epoxide 1199 and bis-cembranoid sinulaflexolide L 1200 were reported from Sinularia flexibilis.\(^{90}\) The structure and relative configuration of 1200 and absolute configuration of known co-metabolite sinulflexolide\(^{91}\) were secured by X-ray studies.

Cytotoxic and anti-inflammatory bis-cembranoids glaucumolide A 1201 and B 1202 were isolated from cultured specimens of Sarcophyton glaucum,\(^{92}\) while of sarcophytolides M 1203 and N 1204, only the former exhibited cytotoxicity to a panel of HTCLs.\(^{93}\) Eight new briarenane-skeletoned diterpenes were reported in 2015 (briarenolides K 1205, L 1206 (ref. 844) and U–Y 1207–1211.\(^{84-85}\) Briareum sp.; dichtotelide V 1212.\(^{86}\) Dichtotelia 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.),\(^{94}\) and six were eunicellins (1216 and 1217,\(^{88}\) Muricella sibogae; 1218–1221,\(^{89}\) 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),\(^{95}\) seco-sterols (1224–1229, Subergorgia suberosa)\(^{96}\) a seco-ketosterol hydroperoxide 1230 (Litophyton arboreum),\(^{97}\) ketosterols (1231–1233, Subergorgia rubra),\(^{98}\) hydroxylated/polyhydroxylated sterols (1234–1237, Sinularia acuta);\(^{99}\) 1238–1243, Palythoa tuberculosa);\(^{82}\) 1244–1249 and known 1250, Klyxum flaccidum;\(^{101}\) 1251–1254, Menella woodin;\(^{102}\) 1255, Dichtotelia gemmacea)\(^{103}\) and a steroidal glycoside (1256, Sinularia nanolobata).\(^{104}\) The C-24 configuration of 1250 was corrected by comparison with related MNPs. Investigation of MNP chemistry of sea anemones has identified two new imidazo-porocycles 1257 and 1258 from the sea anemone Heteractis aurora.\(^{105}\) 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.\(^{87}\) The toxicity of the β-pore-forming toxin equinatoxin II depends upon its ability to assemble into oligomers on the cell surface,\(^{88}\) 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.\(^{95-96}\) A comprehensive sequence
alignment study of cnidarian toxins suggests a common origin of sodium channel and a subtype of potassium channel toxins in sea anemones and that pore-forming toxins have evolved under strong evolutionary constraints.\textsuperscript{861}

As noted in last year’s review,\textsuperscript{1} clarification of the structures of cladiellin diterpenes including the sclerophytins (\textit{Sclerophytmum capitatis})\textsuperscript{862} is an ongoing issue. Based upon re-analysis of NMR data Friedrich and Paquette in 2002 proposed a number of structural revisions.\textsuperscript{863} Synthesis of the purported structure of sclerophytin F as well as three diastereomers, combined with re-examination of published NMR data, has led to the conclusion that sclerophytins E and F are in fact the same compound 1259.\textsuperscript{864} The study concluded that all sclerophytins share the sclerophytin A skeleton with variation of acylation at the C-3 and C-6 positions and that the C-3 configuration inversions proposed by Friedrich and Paquette are incorrect. The structure of litophylin E (\textit{Litophyton sp.})\textsuperscript{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 (\textit{Eunicea manmossa})\textsuperscript{866} have been revised (again)\textsuperscript{867} and confirmed by total synthesis.\textsuperscript{868,869}

A stereodivergent synthesis of four diastereomers has established the structure and absolute configuration of solandelactone I (\textit{Solanderia secunda})\textsuperscript{870} to be 1263,\textsuperscript{871} while total synthesis of the enantiomer has led to correction of absolute configuration of (−)-suberosanone (\textit{Isis hippuris})\textsuperscript{872} to 1264.\textsuperscript{873} The structures of clavulolactones II and III\textsuperscript{874} (\textit{Clavularia viridis}),\textsuperscript{875} tubastrine\textsuperscript{876} (\textit{Tubastrea aurea})\textsuperscript{877} as well as ascidians\textsuperscript{878,879} and breitfussin A and B\textsuperscript{880,881} (\textit{Thulia breitfusst})\textsuperscript{882} have been confirmed by total synthesis.

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

9 Bryozoans

There were five reports (containing 9 compounds) of new metabolites isolated from bryozoans in 2015 compared to three reports (containing 18 compounds) in 2014, so interest in this understudied phylum continues to increase very slowly. The tribrominated alkalioid kororamide B 1265 was isolated from \textit{Anathia tortuosa}, along with kororamide A\textsuperscript{893} and convolutamines I\textsuperscript{894} and J.\textsuperscript{894} All four compounds induced a phenotypic signature in a cell line derived from a Parkinson’s disease patient indicative of effects on vesicular trafficking, a process recently implicated in the disease.\textsuperscript{895} The tripeptide janolusimide B 1266 is the first peptide to be isolated from a bryozoan and was obtained from \textit{Bugulina flavellata}.\textsuperscript{896} Janolusimide B is an N-methyl analogue of janolusimide,\textsuperscript{897} which was isolated from a Mediterranean nudibranch, \textit{Janolus cristas tus}, a known predator of bryozoans. Hydrolysis, derivatisation and stereoselective synthesis of fragments were utilised to establish the stereochemistry.\textsuperscript{898} Four new bryostatins,\textsuperscript{899} bryostatin 21 1267, and 9-O-methylbryostatins 4, 16 and 17 1268–1270 were obtained from \textit{Bugula neritina} although it is probable that 1268–1270 are artefacts since the solvent used for extraction was
methanol. The known synthetic compound \( p \)-methyl-sulfonylmethyl-phenol was obtained as a first time NP and monoheneicosanoin \( 272 \) was obtained as a new MNP from Cryptosula pallasiana. Synthesis of amathamide F originally obtained from Amathia wilsoni has confirmed the revision of the structure proposed in 2011 (ref. 905) \( (1273) \).

10 Molluscs

The number of new metabolites reported from molluscs (43) is a substantial increase in the average number reported per year over the past decade. Azaspiracids \( 7 \)–\( 10 \) \( 1274 \)–\( 1277 \) were isolated from extracts of the mussel Mytilus edulis and the structures characterised by NMR and mass spectrometry. 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. 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. Electrophysiological and competition binding experiments have identified that 13-desmethyl spirolidone C is a potent but relatively non-selective ligand of nAChRs while 13,19-didesmethyl spirolidone C is more selective of the muscular-type receptor. Both MNPs interacted weakly with muscarinic AChRs. Further investigation of the unusual occurrence of tetrodotoxin in New Zealand collections of the nudibranch Pleurobranchaea maculata has led to the metabolite being detected in mucin cells, the mantle, gonad tissue and the digestive gland of the nudibranch as well as in the larvae and eggs but not in the gelatinous egg cases. These findings suggest the toxin is of dietary source and may play a defensive role in the nudibranch. Nudibranchs were the sources of a homosesterterpene \( 1278 \) (Charcotia gravelona), a series of antimalarial isocyanospiroisotriketone and isothiocyanato sesterterpenes \( 1279 \)–\( 1283 \) (Phyllidia ocellata), scalarane sesterterpenes \( 1284 \) and \( 1285 \) (Glossodoris hikuensis) and diterpene \( 1286 \) (Goniobranchus albonares), norscalaranes \( 1287 \)–\( 1296 \) and spongian diterpenes \( 1297 \)–\( 1305 \) (Dorisprismatica \( \equiv \) Glossodoris atomarginata). Granuloside \( 1278 \) is the first example of a linear homosesterterpene. Absolute configuration was assigned by comparison of experimental and calculated ECD data. The structure and absolute configuration of 2-isoycanoclovene \( 1279 \) was secured by X-ray crystallographic analysis of a formamide derivative.

Two studies of sea hares identified eight new dactylomelane diterpenes \( 1306 \)–\( 1313 \) from a Greek collection of Aplysia depilans, while a Japanese collection of A. kurodai was the source of modestly cytotoxic 9,11-secosteroid aplysiasecosterol A 1314. 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 Elysia crispata (Venezuela) has led to the characterisation of (\( \rightarrow \))-phototridachialhydropryone \( 1315 \), a molecule previously speculated to be a MNP based upon its biomimetic photochemical formation from the related metabolite tridachialhydropryone. Surface-assisted mass spectrometry, whereby on-surface solvent extraction of small molecules onto nanostructured or porous silicon surfaces, has been used to image the distribution of choline esters, brominated indoles and lipids in the tissue of the mollusc Dicanthais orbita. 6-Bromohyppaphorine (Hermisenda crassicornis), previously known as a sponge and tunicate metabolite, is a mild agonist of human \( \alpha 7 \) nAChR but shows no effect on muscle-type nAChR from Torpedo californica. Dolastatin 16 obtained by total synthesis was found to be inactive, in contrast to the potent cytotoxicity towards HTCLs originally attributed to the MNP (Dolabella auricularia). New examples of M- and T-superfamily peptides were isolated from Indian collections of Conus araneosus and C. figulinus while analysis of venom duct cDNA from C. litteratus and C. marmoreus prompted the cloned expression or chemical synthesis and subsequent biological evaluation of new peptides. Highly detailed transcriptome analysis of C. episcopatus identified over 3300 novel full-length conotoxin precursors which represented 9 known and 16 new gene superfamilies. Six novel cysteine frameworks were identified, providing impetus for further toxin discovery in Conus snails. Two studies in particular reported metabolites that expand the chemical repertoire of Conus molluscs. In the first of these, a simple guanine derivative, genuanine 1316 was isolated from C. genuanus and the structure confirmed by synthesis. Compound 1316 exhibited potent paralytic activity in mice, mimicking the activity of the crude venom extract.
A small library of analogues representing desmethyl and/or propionate sidechain positional isomers were all devoid of activity. At the other molecular weight extreme, a specialised insulin Con-Ins G1, bearing post-translation modifications characteristic of conotoxins, e.g. hydroxyproline and γ-carboxyglutamate, was isolated from the venom of the fish-hunting C. geographus. The protein, which has greater sequence similarity to fish insulins than to mollusc versions, elicits hypoglycemic shock in fish, facilitating prey capture by the snails distended false mouth, the so-called ‘net strategy’. Further variants were discovered upon closer examination of the venom extract by MS. A selenocysteine analogue of Con-Ins G1 was synthesised and was found to induce similar effects including being active when added to the water column. Fish-like insulin sequences were also identified in another fish-hunting species, C. tulipa, that also uses the net strategy, whereas sequences were absent in harpoon-method fish hunters.

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 include a meroterpenoid 1317, an array of halogenated alkaloids 1318–1323 (ref. 935) and 1324, taurine amidines 1325–1327,937 purines 1328–1331,938 a new pyridoacridine 1332 (ref. 939) and two unusual tetracyclic-cored alkaloids 1333 and 1334.940 Noteworthy were the isolation, structure elucidation, synthesis and biological evaluation of eudistidines A 1333 and B 1334 (Eudistoma sp., Palau).940 A four-step condensation/cyclisation reaction sequence afforded both natural products, allowing confirmation of their structures. Eudistidine A was found to inhibit an essential protein–protein interaction (p300-HIF-1α) required for HIF-1α (hypoxia-inducible factor 1) activation: such inhibitors could find therapeutic use as antitumour agents by acting to down-regulate the expression of hypoxia-selective genes.

An expeditious total synthesis of shishijimicin A has been reported,941 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 synthesis944 and a new catalytic asymmetric synthetic route to (−)-perophoramide945 has been disclosed.946 Cell-cycle arrest at the G2/M phase and induction of apoptosis in HeLa cells947 was observed for the ascidian alkaloid eudistomin H,948 while eusynstyelamide B949 also induces G2/M phase arrest, causes double strand breaks in DNA and is a topoisomerase II poison.950 Further investigation of clavanin A, a C-terminal amidated 23 residue antimicrobial peptide,951 has identified it to exhibit no cytoxicity and to be active in vivo and in a wound healing model of S. aureus infection.952 Preliminary investigation of anti-angiogenic activity in myxoid liposarcomas has identified trabectedin (Yondelis® , E743) as an upregulator of inhibitors of matrix metalloproteinases TIMP-1 and TIMP-2, and of TSP-1, a key regulator of angiogenesis-dependent dormancy.953 For several decades, didemnin B and related analogues have been the subject of numerous clinical trials, ultimately resulting in dehydrodidemnin B (Aplidine) being granted orphan drug status towards acute lymphoblastic leukemia. Gene-expression mapping has identified didemnin B to be a dual inhibitor of palmitoyl-protein thioesterase (PPT1) and eukaryotic translation elongation factor 1 alpha 1 (EEF1A1), the combination of which leads to apoptosis and antineoplastic activity.954 Gene expression data from cancer cell lines that were either sensitive or resistant to didemnin B identified four gene biomarkers that correlated with sensitivity to the natural product. These biomarkers, associated with epithelial-derived cell lines and also some colorectal, breast and lung cell lines, could be of use in predicting the likelihood of patient response to didemnin B or analogues in a therapeutic setting. Synthetic analogues related to the polyandrocarnamines955 were found to be inhibitors of H3S production by cysstatine beta-synthase,956 and SAR studies have been reported for thiaplidiaquinones A and B957 (various biological targets),958 calodium A-C959–960 (antibacterial),961,962 rubrolides963 (photosynthesis inhibitors),964 meridianins965 (anti-malarial and antituberculous),966 isogranulatimide967 (cytotoxicity),968 and lamellamins969 (cytotoxicity).

12 Echinoderms

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

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

Mangroves or their associates were the sources of antiviral cyclohexylideneacetonitriles 1363–1366 (Bruguiera gymnorrhiza),1004 a phenolic 1367 and a diol 1368 from the fruits of Avicennia marina,2004 phenolics and a cerebroside 1369–1372 (Sonneratia ovata),1005 glycidoses 1373 (Kandelia candel)1006 and 1374–1376 (Bruguiera gymnorrhiza),1007 seco-labdanoids 1377–1380 (Excoecaria agallocha),1008 dolabrane-diterpenes 1381–1386 (Ceriops tagal),1009 and limonoids 1387–1398 (ref. 1010) 1399–1401 (ref. 1011) (Xylocarpus moluccensis and X. granatum). The absolute configurations of the lignin rhamnoside 1376 was secured via analysis of experimental ECD data – the planar structure is identical to that of a previously reported metabolite of Cotoneaster racemiflora though with different magnitude and opposite sign of rotation.1012 CD analysis and an X-ray study has led to the revision of the structure of rhizophorin A (Rhizophora mucronata)1013 to that shown for excolide A 1377.1008 The structure of excolide B 1380 was also secured by X-ray analysis.

The absolute configurations of new limonoids, including thaixylomolins I 1389, K 1391 and M 1393, were determined by TD-DFT calculations of ECD data.1010 NMR data observed for 1391 were identical to those reported for the known phragmaline-skeletoned limonoid moluccensin J1014 – close examination of 2D NMR data requires structural correction of moluccensin J to structure 1391. Limonoids 1389, 1391 and 1393 exhibited mild anti-H1N1 viral activity. Further investigation of previously reported mangrove MNPs has identified the dolabrane-diterpene tagalsin C (Ceriops tagal)1015 to exhibit cytotoxicity in vitro towards a panel of haematologic cell lines, and in vivo towards...
human T-cell leukemia xenografts, via a mechanism involving ROS-mediated apoptosis and cell cycle arrest. In addition the phenethyl cinnamide micrometam C (Micromelum falcatum) protects against LPS-induced reactive oxygen species in both zebrafish and macrophages and limonoids xylocensin E and I (Xylocarpus moluccensis and X. granatum) exhibited anti-ulcer gastroprotective activities in rats, likely due to an ability to inhibit H+K+-ATPase activity.

14 Miscellaneous

A study of the sea grass Cymodocea serrulata has afforded an antibacterial constituent, which was attributed to the novel thiocarbonyl. The spectroscopic data reported for this compound are not however consistent with the proposed structure. A new member of the cephalostatin family, cephalostatin 20, was isolated as a minor component of extracts of the marine worm Cephalodiscus gilchristi. Compared to the...
more potent members of the family (cephalostatins 1–3), cephalostatin 20 was 100–1000 \times \text{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.}^{10,24}

Site-directed mutagenesis of the plasmid used for the heterologous expression of arenicin-1, an antimicrobial peptide produced by the polychaete worm Arenicola marina,\(^{10,25}\) afforded a number of analogues, one of which, Val8Arg, was equipotent as an antibacterial but with diminished red blood cell haemolytic activity.\(^{10,26}\) 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.\(^{10,27}\) 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.\(^{10,28}\) The peroxy 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

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**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. 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\(^{\text{®}}\) [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. Right from the early days of MNPs the phylum Porifera has dominated. In the 1971–1985 sesquidecade the other phyla that were collected most avidly were the Cnidaria, Rhodophyta, Ochrophyta, Mollusca, and Echino-dermata. 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 through the years. The choice of journal in the first sesquidecade was quite different to the latter years with the Journal of Natural Products, Journal of Organic Chemistry, Tetrahedron, Tetrahedron Letters, Australian Journal of Chemistry and Phytochemistry emerging in the second sesquidecade. By the third sesquidecade Organic Letters and Marine Drugs had appeared and have been sought after as the journal of choice in addition to the Journal of Organic Chemistry, Tetrahedron, Tetrahedron Letters and most notably the Journal of Natural Products which has gone from strength to strength. As a proportion, however, more scientists are now publishing in the Other category.

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

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314 CAS Registry Number: 913690-77-4, Koho 587675, Aurora Screening Library, Aurora Fine Chemicals LLC, 7 Apr 2016.


Abstract...


