Marine natural products‡

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This review covers the literature published in 2014 for marine natural products (MNPs), with 1116 citations (753 for the period January to December 2014) 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 (1378 in 456 papers for 2014), 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

These annual reviews of marine natural products were initiated by the late Professor D. John Faulkner in 19841,2 and continued by the New Zealand group since 2003. A feature of the reviews has been the inclusion of the structures for all new MNPs, and any subsequently revised structures. The number of new MNPs reported each year has steadily grown from 332 in 1984 to 1378 in this present review of the 2014 literature. This has inevitably resulted in an increased size for each review. With the ever-increasing size creating difficulties for preparation of the annual review, the NPR Editorial Board suggested changing the format to focus on a selection of highlighted structures. To maintain the usual comprehensive coverage of all new and revised MNPs, we have prepared a ESI‡ document with links associated with this review, showing all structures, along with their names, taxonomic origins, locations for collections, and biological activities. The numbers for all highlighted structures in this review (169) are shown in non-italicised bold font, while italicised numbers refer to the remaining structures in the ESI document.‡ For structures that have their absolute configurations fully described, the compound number in the diagrams is preceded with †. In addition to the highlighted compounds in this review, we have retained the inclusion of reference to first syntheses of MNPs, and comments on new information on ecological aspects, bioactivities or other relevant data for previously reported MNPs, all as non-highlighted material. The Reviews section (Section 2) has also been reformatted to show selected highlights, with all other reviews referenced in a section of the ESI document.‡

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2 Reviews

There continues to be a steady increase in the number of reviews of various aspects of MNP studies. Some of the more significant reviews (16) are given here while a listing of the remainder (71) is given in the ESI section. A comprehensive review of MNPs reported in 2012 has appeared. Marine-sourced anticancer and cancer pain control agents in clinical and late preclinical development have been reviewed, and New horizons for old drugs and drug leads were described. The implications of the Convention on Biological Diversity (1999) and its Nagoya Protocol (2010) on the collection of marine genetic resources has been discussed and should be noted by all who collect marine organisms for MNP studies. The putative microbial origin of sponge metabolites has been the subject of several reviews and articles. Developments in chemical ecology for fish and benthic algae and invertebrates for 2010–2012 have been reviewed, with comment on the biosynthesis of bioactive MNPs by symbiotic microorganisms. Polyketide biosynthesis in dinoflagellates has been reviewed. There have been comprehensive reviews for marine nucleosides, saxitoxin, and tetrodotoxin. A review of Emerging strategies and integrated systems microbiology technologies for biodiscovery of marine bioactive compounds provides a very useful oversight of a number of developing techniques. AlgaeBase: an on-line review of MNPs reported in 2012 has appeared.

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

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.

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.

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.
resource for algae is an article describing a very comprehensive algal database. As in previous years, the MarinLit database has been updated and used as the literature source for the preparation of this present review.

3 Marine microorganisms and phytoplankton

Even considering the trend of recent years that many marine natural products research efforts are directed towards microorganisms, there has been a sharp upward swing in the number of new metabolites reported from marine microorganisms [677 vs. 493 in 2013]. Unless otherwise stated, compounds described in this section were obtained from cultures of the named microorganisms.

3.1 Marine-sourced bacteria (excluding from mangroves)

The number of new compounds reported from marine bacteria (164) is similar to the 158 reported in 2013. A metagenomic approach has identified the gene cassette responsible for the biosynthesis of calyculin A, originally isolated from the sponge Discodermia calyx, as microbial in origin, arising from Candidatus Entotheonella sp. Functional analysis of the biosynthetic pathway has shown that the end product is actually a diphasate protoxin, phosphocalyculin A 1 rather than calyculin A, suggesting a phosphorylation/dephosphorylation mechanism for the active chemical defence of the host sponge. A further diphosphate, protoxin phosphocalyculin C 2, has been isolated from D. calyx but can be assumed to have arisen from the same microbial source. Phosphocalyculin C, although potent (IC_{50} = 36 nM vs. P388), is 5000 times less toxic than calyculin C itself.

A Chinese sediment-derived strain of Actinalloteichus cyanogriseus was the source of cyanogramide 3, an unprecedented spirocyclic alkaloid with multidrug-resistance (MDR) reversing activity. An interesting dereplication strategy was utilised in the study of marine microorganisms. Phosphocalyculin C, although potent (IC_{50} = 36 nM vs. P388), is 5000 times less toxic than calyculin C itself.

A Korean sediment-derived strain of Bacillus subtilis (B. subtilis) has yielded a variety of linear lipopeptides with differing biological properties, the gageopeptides A–D 6–9 gageostatins A–C 10–12 and gageotetrins A–C 13–15. Most are non-cytotoxic with good antibacterial activity, but better antifungal activity especially against the late blight pathogen Phytophthora capsici in the case of gageotetrins A–C. A trans-formation-associated recombination (TAR) cloning approach was used to capture, activate and express a 67-kb non-ribosomal peptide synthetase (NRPS) biosynthetic gene cluster from Saccharomonospora sp., resulting in isolation of the dichlorinated lipopeptide antibiotic taromycin A 16.

Solwaraspora sp. (ascidian, Trididemnum orbiculatum, Florida Keys, U.S.A.) produced the trialkyl-substituted aromatic acids, solwaric acids A 17 and B 18. Enrichment with 13C-labelled glucose followed by acquisition of a 13C–13C COSY enabled unambiguous determination of the position of the methyl group on the phenyl ring, an approach which could be very useful for structural determination of molecules with multiple quaternary carbons.

Heronapyrroles A–C are nitropyrrrole metabolites with a partially oxidised farnesyl chain appended that were obtained from a Streptomyces sp. Biosynthetic considerations prompted the hypothesis that a mono-tetrahydrofuran-diol, heronapyrrole D might be an as yet unidentified metabolite of the bacterium. The gageotetrahydropyran-diol, heronapyrrole A was partially oxidised farnesyl chain appended that were obtained from a Streptomyces sp. Biosynthetic considerations prompted the hypothesis that a mono-tetrahydrofuran-diol, heronapyrrole D might be an as yet unidentified metabolite of the bacterium. Following a putative biomimetic synthesis of heronapyrrole D the metabolite was then detected in cultures of the bacterium, thus validating this approach. Total synthesis of heronapyrrole C has also been reported. Mollemycin A 20 is a first-in-class glycol-hexadepsipeptide-polyketide from a Streptomyces sp. (sediment, South Molle Is., Queensland, Australia) and active against certain Gram-positive and Gram negative bacteria, in addition to extremely potent antimalarial activity.
against drug sensitive and MDR Plasmodium falciparum (P. falciparum) clones.\textsuperscript{34}

A deep-sea strain of Streptomyces, previously a source of spiroindimicins A–D,\textsuperscript{35} lynamycins A and D\textsuperscript{35} and piericidins\textsuperscript{36} has now led to isolation of a number of bisindole alkaloids; indimicins A–E 21–25, lynamycins F 26 and G 27\textsuperscript{37} and piericidin E1 28\textsuperscript{38} using the same modified A1BFe + C medium. Piericidin E1 28 was shown to be an intermediate in the biosynthesis of piericidin A1\textsuperscript{38} during identification of the biosynthetic gene cluster.

Growth of the strain in modified ISP3 medium yielded heronamides D–F 29–31.\textsuperscript{39} Violapyrones H 32, I 33, B 34 and C 35\textsuperscript{40} were obtained from Streptomyces sp. (starfish, Acanthaster planci, Chuuk, Federated States of Micronesia).\textsuperscript{41} Violapyrone C 35 has since been synthesised and the absolute configuration determined.\textsuperscript{42}

A study of the biosynthetic pathway for marineosins\textsuperscript{43} in Streptomyces sp. led to isolation of 23-hydroxyundecylprodiginine 36, 23-ketoundecylprodiginine 37, premarineosin A 38 and 16-ketopremarineosin A 39.\textsuperscript{44} Syntheses of 23-hydroxyundecylprodiginine 36 (both enantiomers and the
perdeuterated version) and of 23-ketoundecyldoprodiginine 37 were reported, as was the feeding of synthetic prodiginine analogues which led to the production of novel premarineosins, although these were not fully characterised. 45

The structure of merochlorin A46,47 has been revised to 4048 and a biomimetic synthesis of (±)-merochlorin B46 has been achieved, 49 while a study of the biosynthesis of the merochlorins revealed that just four enzymes are involved 50 and that a vanadium-dependent chloroperoxidase mediated a complex series of unprecedented transformations in the biosynthesis. Development of a chlorination method paralleling the biocatalytic process led to the identification of previously undiscovered merochlorins 41–43. 51 The known synthetic compound seriniquinone 44 52 has now been obtained as a natural product from Serinicoccus sp. and displayed potent and selective antitumour activity. 53

Investigation of the biosynthesis of sulfur-containing roseobactides54,55 produced by Phaeobacter inhibens indicated that these compounds arise from three subunits – dimethylsulfoxoniopropionate, phenylacetic acid and p-coumaric acid and that roseobactides regulate the symbiosis between P. inhibens and the microalga Emiliania huxleyi. 56 Further new metabolites 45–103 were obtained from the genera Actinoalloteichus, Actinomadura, Actinokineospora, Amycolatopsis, Bacillus, Dermacoccus, Escherichia, Jefua, Micrococcus, Micromonospora, Nocardiosis, Pelomonas, Pseudoalteromonas, Rapidithrix, Salinispora and Shewanella. 57–60 As usual, many new metabolites, and some with revised structures, were also obtained from the genus Streptomyces including 104–172. 81–105 The genera Verrucosporispora and Vibrio also yielded new metabolites 173 and 174. 106,107 Investigation of an octocoral-associated Pseudoalteromonas sp. by MALDI-imaging mass spectrometry (IMS) and molecular network analyses indicated that the strain produces higher levels of the antifungal polyketides, alteramides 106,107 in the dark than in the light and also led to revision of the configuration at C-6 for 175 and 176. 108 In the dark, these compounds were inactivated through a photoinduced intramolecular cyclisation and production of higher levels of these antifungal metabolites in the dark was proposed as a strategy to protect the host corals during night feeding, when they are more exposed. 108 Synthesis of the proposed structure of heronamide C 109 has indicated that the actual structure of the natural product needs to be re-examined 110 and the structure of anthracimycin 111 has also been corrected to 177. 112 Total syntheses of indoxamycins 113 has led to stereochemical revision for the indoxamycins B, 114 D 115 and E 111 to 178–180. 111 A number of other total syntheses of bacterial metabolites have been reported. These include syntheses of the depsipeptides, solanamides A 116 and B 117,118 and arenamides B 119 and C,120,121 and synthesis 122 of the nucoside antibiotic A201A. 121,122 Total synthesis of dixiamycin B 123 was achieved utilising electrochemical oxidation. 124 The alkaloid mansouramycin D125,126 was synthesised, as was 5-deoxytrodotoxin. 127,128 New biological activities have been reported for sporolide B 129 from Salinispora tropica, 130 for some butenolides131,132 and undecyldoprodigiosin 133 from Streptomyces strains. 134,135 Biosynthetic studies have been conducted into various bacterial metabolites including arachidonic acid (in Aureispira marina), 136,137 macroactinamides 138 and bacillaene 139 (in Bacillus marinus), 140 polypyrrolinated aromatics 141 (in Marinomonas mediterranea 142 and Pseudoalteromonas spp.), 143, lomaiviticins (in Salinispora pacifica 144,145,146 (formerly Micromonospora lomaivitienensis), tropodithietic acid 47 (in Pseudonaerobacter inhibens), 148 sulfur volatiles 49 (in the Roseobacter clade) 149 and avaroferrin 150 and putrebacitin 151 (in Shewanella sp.). 151 Biosynthetic studies within the genus Streptomyces include those on thiacoralines 154 (in S. albus), 155 ikarugamycin, 156–158 antimycins 159,160 and polyhydroxylated saturated fatty acids, 161 marinophenazines 162–164 and the isoprenylated phenazines, 165,166 JBIR-46, JBIR-47 and JBIR-48. 167

3.2 Bacteria from mangroves

There has been an increase in the number of new metabolites reported from bacteria associated with mangroves (23 in 2014 vs. 10 in 2013). Lechevalieria aerocolonigenes yielded the cyclopentadecane metabolites, mangromicins A 181, B 182 185 and D–I 183–185,186 with mangromicin A 181 exhibiting potent antitrypanosomal and radical scavenging (DPPH) activities. 168,169 New divergolide congeners 189–192 were obtained from an endophytic Streptomyces strain 170 and the biosynthetic gene cluster for divergolides 171 identified and characterised. 172
Other metabolites 193–203 were isolated from the genera *Jishengella*, *Micromonospora*, *Streptomyces* and *Verrucosispora*, and a bio-inspired total synthesis of the indole sesquiterpenoid sespenine completed.

3.3 Marine-sourced fungi (excluding from mangroves)

Studies of fungi continue to rise with 318 new compounds reported in 2014 compared to 223 in 2013. Sponge-associated *Aspergillus similanensis* yielded two isocoumarin derivatives 204 and 205, and a deacetyl analogue of chevalone C, chevalone E 206, in addition to pyripyropene S 207. While chevalone E 206 itself did not display significant antibacterial activity, it did exhibit synergy with the antibiotics oxacillin and ampicillin against MRSA. Ultrasonication of *Aspergillus versicolor* spores led to the isolation of a mutant with neomycin resistance from which six metabolites not present in the parent strain, including 208 were obtained. Although several patents exist for synthesis of the planar structure of this compound, this is the first natural product (NP) isolation and establishment of stereochemistry.

Cyclo(D-Tyr-D-Pro) was also claimed as a first NP isolation but this has previously been obtained from both terrestrial and marine sources. Lumazine peptides, penilumamide B–D 209–211 and a cyclic pentapeptide, asperpeptide A 212 were obtained from a gorgonian-derived *Aspergillus* sp. The presence of the sulfone penilumamide and the derived sulfoxide penilumamide C 210 led to speculation that these compounds were derived from oxidation of a putative metabolite containing a methionine residue. This led to a feeding experiment with L-methionine resulting in isolation of the sulfide, penilumamide B 209. Yields of penilumamide B 209 and penilumamide increased with increasing concentration of L-methionine and when penilumamide B 209 was exposed to air, penilumamide was detected after a few days whilst penilumamide C 210 was formed several days later.

Of the two prenylated hydroquinone derivatives 213 and 214 obtained from a gorgonian-derived *Aspergillus* sp., 214 exhibited very potent activity against respiratory syncytial virus (RSV). These two metabolites differ only in the configuration of a methyl group on a cyclohexane ring yet given that 214 is an extremely potent anti-RSV agent whilst its epimer 213 is completely inactive, indicating the importance of the configuration of this ring for anti RSV-activity.

Soft-coral associated *Chondrostereum* sp. has previously been reported to produce hirsutane-framed sesquiterpenes. Cultivation of the fungus in a medium with glycerol as the carbon source led to the isolation of the sesquiterpenes chondrosterin I 215 and J 216 of which chondrosterin J 216 displayed potent activity against HTCLs. Chemical epigenetic modification of *Cochliobolus lunatus* (sea anemone *Palythoa haddoni*) with inhibitors of histone deacetylase (HDAC) resulted in isolation of two brominated 14-membered resorcylic acid lactones 217 and 218, but only in the presence of an HDAC inhibitor.
The chromones engyodontiuone A–H 219–226 and the phenol derivatives 227–229 were derived from deep-sea derived Engyodontium album. Of these, engyodontiuones E–G 223–225 were obtained as racemates.196 The known polyketide aspergillus one B 197 was also isolated and was a potent inhibitor of settlement of Balanus amphitrite (B. amphitrite) larvae.196 Fermentation of a filamentous fungus of the Eurotiomycetes class (ascidian, Lissoclinum patella, Papua New Guinea) produced the pentacyclic oxazinin A 230, derived from a combination of benzoxazine, isoquinoline and pyran rings. Oxazinin A 230 occurred as a racemate and was antimycobacterial.198

Neosartorya pseudoscheri (starfish Acanthaster planci, Hainan, China) produced different suites of metabolites when cultured in different media. When cultured in glycerol–peptone–yeast extract (GlyPy), the diketopiperazines neosartin A 231 and B 232 were produced along with six known diketopiperazines and a precursor alkaloid but when fermented in glucose–peptone–yeast extract (GluPy), a tetracyclic-fused alkaloid neosartin C 233 was produced along with a known meroterpenoid and five known gliotoxin analogues 234–238, obtained here for the first time as NPs.199 Endophytic Paecilomyces variotii (red alga, Grateloupia turuturu, Qingdao, China) yielded varioxepine A 239, an alkaloid with an unprecedented 3,6,8-trioxabicyclo[3.2.1]octane unit.200

Biosynthetic feeding experiments on Penicillium citrinum using 13C labelled glucose, anthranilic acid and ornithine resulted in isolation of two new citrinalins, 17-hydroxycitrinalin B 240 and citrinalin C 241 and supported the proposition that the citrinalins arise from a bicyclo[2.2.2]diazaoctane precursor. Also in this investigation, synthesis of the enantiomer of citrinalin B to 242.201 Penicillipyrones A 243 and B 244 are meroterpenoids obtained from a sediment-derived Penicillium strain and represent a new skeletal class with a unique linkage between the drimane sesquiterpene and pyrone moieties. Penicillipyrone B 244 elicited significant induction of quinone reductase in murine hepatoma cells, indicating a possible cancer preventative role.202 Metabolites 245–254 were also obtained from the genera Acremonium, Arthrinium, Ascotricha and Astrocytis.204–207 As usual, a large number of metabolites were obtained from species of the Aspergillus genus. Two indole diterpenoids 255 and 256, and an isocoumarin 257 were obtained from A. flavius. The known compounds β-aflatrem,208 paspalinine209,210 and leporine B 211 were...
isolated and leporine A\textsuperscript{342} was prepared from the last of these. Configurations were established for each as 258-261 respectively and \(\beta\)-aflatelure and leporine B were isolated for the first time as MNPs.\textsuperscript{210} Other metabolites isolated from the genus \textit{Aspergillus} include 262-327 (the last obtained from co-culture with an unidentified bacterium).\textsuperscript{214-237} New metabolites 328-371 were also obtained from the genera \textit{Beauveria}, \textit{Cladosporium}, \textit{Cochliobolus}, \textit{Curvularia}, \textit{Dendrodochium}, \textit{Diaporthaceae}, \textit{Dichotomomyces}, \textit{Emericella} and \textit{Eurotium}.\textsuperscript{238-250} A pyrrolidinoindoline diketopiperazine dimer, cristatumin E, isolated from \textit{Eurotium herbariorum},\textsuperscript{251} appears to be identical to the previously reported eucristatine.\textsuperscript{252} The genera \textit{Hansfordia}, \textit{Himicola}, \textit{Isaria}, \textit{Neosartorya}, \textit{Nigrospora}, \textit{Paecilomyces} and \textit{Paraconiothyrium} also yielded the new metabolites 372-399,\textsuperscript{179,253-256} The genus \textit{Penicillium} was the source of many other metabolites 400-461.\textsuperscript{279-278} Other genera to yield new metabolites 462-522 were \textit{Pseudallescheria}, \textit{Spicaria}, \textit{Spirormastix}, \textit{Stachybotrys}, \textit{Talaromyces}, \textit{Trichoderma}, \textit{Xylaria} and \textit{Xylariaceae}.\textsuperscript{279-291} while 521 was obtained from a strain of the order Xylariales and also synthesised.\textsuperscript{292} A number of syntheses of fungal metabolites have resulted in structural revisions of the natural products, including syntheses of (-)-protubonine A 522, (-)-protubonine B 523 (\textit{Aspergillus} sp.),\textsuperscript{303,304} and (+)-cristatumin C 524 (\textit{Eurotium cristatum}).\textsuperscript{305,306} Synthesis of the racemate of oxalicumone C (\textit{Penicillium oxalicum})\textsuperscript{307} followed by resolution by chiral HPLC and examination of experimental and calculated EC2 data, resulted in the configuration of the natural product being assigned as (S)-525.\textsuperscript{308} Culture of a strain of \textit{Aspergillus clavatus} isolated from the hydrothermal vent crab \textit{Xenograpsus testudinatus} in the presence of the abiotic stress agent and hydrothermal vent fluid component zinc (as zinc sulfate), elicited production of a known synthetic cyclic peptide\textsuperscript{309} that was isolated for the first time from a natural source and named as clavatustide C 526. The fungus did not produce clavatustide C 526 when cultured in the absence of zinc.\textsuperscript{310} Pericosine E\textsuperscript{309} (\textit{Periconia byssoides}) occurs as an enantiomeric mixture in nature and synthesis of the preferred enantiomer (−)-pericosine E 527 has been reported.\textsuperscript{311} First syntheses of a number of fungal metabolites achieved include those of secalonic acids A\textsuperscript{312} (\textit{Paecilomyces} sp.),\textsuperscript{304} and B\textsuperscript{313} (\textit{Gliocladium} sp.),\textsuperscript{306,307} (±)-sorbiterrin A\textsuperscript{309} (\textit{Penicillium terrestre}),\textsuperscript{309} (−)-auroamide C\textsuperscript{310} (\textit{Penicillium aurantiogriseum}),\textsuperscript{311} calcaripeptides A-C\textsuperscript{312} (\textit{Calcarisporium} sp.),\textsuperscript{311} (−)-aspergilazine A\textsuperscript{114} (\textit{Aspergillus taiwanchengensis}),\textsuperscript{315} aspirin\textsuperscript{316} (\textit{Aspergillus versicolor}),\textsuperscript{317} cochlomycin B\textsuperscript{318} (\textit{Cochliobolus lunatus}),\textsuperscript{319} dendroides\textsuperscript{320} (\textit{Dendrodochium} sp.) A,\textsuperscript{321} B\textsuperscript{322} and E,\textsuperscript{322} paecilocin\textsuperscript{323} (\textit{Paecilomyces variotii}),\textsuperscript{324} penicimonoterpenes\textsuperscript{325} (\textit{Penicillium chrysogenum})\textsuperscript{326} and (−)-penostatin E\textsuperscript{327} (\textit{Penicillium} sp.).\textsuperscript{328} The benzaldehyde derivative isoteretahydraurolgaucin\textsuperscript{329,330} has been shown to exhibit anti-inflammatory activity, inhibiting the NF-κB pathway through suppressing production of both pro-inflammatory mediators and cytokines.\textsuperscript{331} Oxipentyns A\textsuperscript{332,333} and B\textsuperscript{333} exhibited growth stimulatory effects on seedling roots of barley and wheat\textsuperscript{334} while isoechinulin A\textsuperscript{335,336} was a strong inhibitor of settlement of larvae of the barnacle \textit{B. amphitrite}.\textsuperscript{337} Methylpenicinoline\textsuperscript{338} also displayed anti-inflammatory activity, suppressing expression of pro-inflammatory mediators through the NF-κB and MAPK pathways.\textsuperscript{339} Heavy metal stress of two strains of hydrothermal vent fungi (\textit{Aspergillus sclerotiorum} and \textit{A. clavatus}) induced biosynthesis of metabolites that were not produced under normal culture conditions: \textit{A. sclerotiorum} produced asphochrin\textsuperscript{340,341} when stressed with copper and produced stephacidin A\textsuperscript{342} and notoa- mides B\textsuperscript{342} and F\textsuperscript{343} under normal culture conditions whilst \textit{A. clavatus} produced the acetophenone derivative clavatol\textsuperscript{344,345} under stress conditions and deoxytroptoquivaline\textsuperscript{346} and troptoquivaline A\textsuperscript{346} in metal-free culture.\textsuperscript{347}

3.4 Fungi from mangroves

There has been a considerable increase in the number of new metabolites reported from mangrove-associated fungi (108 in 2014 vs. 75 in 2013), with the majority coming from endophytic species. Co-culture of \textit{Alternaria} and \textit{Phomopsis} species led to isolation of three cyclic peptides 528-530, all of which exhibited significant activity against a range of plant pathogenic fungi,\textsuperscript{348,349} whilst co-culture of two brown alga (\textit{Sargassum})-derived \textit{Aspergillus} species also produced a cyclic peptide, psychrophilin E 531.\textsuperscript{350}
Aspergillus flavipes was the source of the aromatic butyrolactones, flavipins A 532 and B 533 and the previously synthesised 534,535 and 535,536 of which flavipin A 532 exhibited moderate to good antibacterial activity. Unlike penicillin, it was able to penetrate the biofilm matrix to kill live bacteria inside mature Staphylococcus aureus biofilm.533 An endophytic Diaporthe sp. was the source of diaporine 536, an unprecedented symmetric polyketide which induces conversion of tumour associated macrophages from the M2 to the M1 phenotype in both cellular and animal models.534

The polyketides dothiorelone F 537 and I 538 were obtained from endophytic Dothiorella sp. along with three known analogues.535 Of these analogues, dothiorelone G536 is actually the same as the previously reported cytosporone R,537 also obtained from a mangrove associated species (Leucostoma per- soonii). Peniphenones A–D 539–543 were obtained from Penicillium dipodomyicola. Of these, peniphenone A 539, 540 occurs as a racemate and was separated into its enantiomers by chiral HPLC while peniphenones B 541 and C 542 strongly inhibited Mycobacterium tuberculosis protein tyrosine phosphatase B (MptpB).538

The polyketides 544 and 545 were obtained from co-culture of mangrove soil derived Penicillium sp. with the sediment derived bacterium Streptomyces fradiae and were not produced in discrete bacterial and fungal control cultures, suggesting the activation of silent gene clusters by co-cultivation. These also occurred as a racemate and were separated by chiral chromatography into 544,549 a known terrestrial fungal metabolite (9R,14S)-epoxy-11-deoxyfunicone, but now isolated as a first-time MNP, and the enantiomer (9S,14R)-epoxy-11-deoxyfunicone 545.546 An endophytic Penicillium sp. was the source of a phenyl ether derivative 546 and a spiroax-4-ene-12-one derivative 547 with the spiroax-4-ene-12-one derivative 547 more potent to the MG-63 cell line with in vivo activity and significant inhibition of human osteosarcoma in nude mice upon oral administration.547 The prenylated phenols vaccinol A–G, 548–554 and the naphthalene derivative vaccinal A 555 were isolated from Pestalotiopsis vaccinii. Vaccinal A 555 exhibited potent COX-2 inhibition.556 Other genera or families of fungi associated with mangroves to yield the new metabolites 556–635 were Acremonium, Alternaria, Daldinia, Guignardia, Penicillium, Pestalotiopsis, Phoma, Phomopsis, Pseudolagarobasidium, Rhütidhysteron, Stemphylium and Xylariaceae.557–558

3.5 Cyanobacteria

There has been an increase in the number of new metabolites reported from cyanobacteria since 2013, but the total numbers are still low overall (20 in 2014 vs. 9 in 2013), seemingly continuing an overall downward trend. Typical of the phylum, the vast majority of metabolites reported were peptidic in nature. Although not peptidic, yoshinone A636 and the diastereoisomers yoshinone B1 and B2 637 were isolated from Leptolyngbya sp. Yoshinone A 636 inhibited differentiation of 3T3-L1 cells into adipocytes without accompanying cytotoxicity suggesting potential as an anti-obesity lead.638 A cyanobacterial assemblage, consisting mostly of Lyngbya sp. (now renamed as Moorea sp.) yielded the dolastatin 13 analogue, kurahamide 638, a strong inhibitor of the proteases elastase and chymotrypsin,639 and the acetylenic lipopeptide kurahyne 639 an inhibitor of the HeLa cell line and inducer of apoptosis.640

Mooreamide A 640 is a cannabimimetic lipid obtained from Moorea bouillonii and is the most potent marine-derived inhibitor of the neuroreceptor CB2, reported to date.641 Two new aplysiatoxin analogues, 3-methoxyaplysiatoxin 641 and 3-methoxydebroaplysiatoxin 642 were isolated from Trichodesmium erythraeum and 642, along with the co-isolated known debromo analogues debroaplysiatoxin643 and
for itralamide $\text{B}^{445}$ and coibamide $\text{A}^{446}$ have indicated that the structures of these natural products require revision.$^{447,448}$ Grassypeptolides $\text{A} - \text{C}^{439}$ were shown to selectively inhibit the dipeptidyl peptidase (DPP8) protease and molecular docking studies indicated that grassypeptolide $\text{A}$ binds to the enzyme at two different sites.$^{446}$ Gallinamide $\text{A}^{442}$ was shown to be a potent and selective inhibitor of the human cysteine protease cathepsin $\text{L}$. $^{443}$ A genome mining approach was utilised to identify three proteusin $\text{rSAM}$ epimerases, enzymes which install multiple $\varepsilon$-amino acids in genetically encoded peptide chains, from three strains of cyanobacteria including a marine-derived $\text{Pleurocapsa}$ strain.$^{448}$ A genome mining approach was also used to show that LanA peptides, linear precursor peptides of lanthionine-containing peptides (lanthipeptides),$^{449}$ are highly diverse among different systems and that closely related lanthipeptide synthetases can be associated with quite different substrate sets.$^{450}$

3.6 Dinoflagellates

The number of new metabolites reported from dinoflagellates has remained about the same as for 2013 with 19 compounds reported in 2014. The linear polyketide, amphirionin-4 $\text{658}$, from an $\text{Amphidinium}$ species displayed very potent and selective growth promotion activity on murine bone marrow stromal $\text{ST}-2$ cells. Feeding experiments with $^{13}\text{C}$ single and double labelled acetate indicated that polyk Etide $\text{658}$ comprises a linear $\text{C22}$ chain with two irregular $\text{C1}$ sites (in the terahydrofuran moiety) and four $\text{C1}$ branches.$^{426}$ $\text{Dinophysis acuminata}$ was the source of the macrolide $\text{acuminoline A}$ $\text{659}$ which was non-toxic to human tumour cell lines (HTCLs) but a potent stimulator of actomyosin ATPase activity.$^{427}$ $\text{Belizentrin}$ $\text{660}$, a 25-membered macrolactam obtained from $\text{Prorocentrum belizeanum}$ is the first member of its class of polysaturated and polyhydroxylated macrocycles and displayed potent effects on neuronal network integrity in cerebellar cells, ultimately resulting in cell death.$^{428}$

Other genera of dinoflagellates from which the new metabolites $\text{661-675}$ were isolated include $\text{Amphidinium}$, $\text{Azadinium}$, $\text{Karenia}$ and $\text{Vulcanodinium}$. $^{429-436}$ Tentative structures were assigned to ovatoxin-$\text{g}$ $\text{676}$ and an isomer of palytoxin, the so-called isobaric palytoxin.$^{437}$ The absolute configuration of amphidinin $\text{A}^{438}$ was determined as $\text{677}$. $^{439}$ Synthesis of genetically predicted saxitoxin intermediates with identification and quantification in the dinoflagellate $\text{Alexandrium tamarense}$ and the cyanobacterium $\text{Anabaena cicinalis}$ supports the genetically proposed biosynthetic route$^{440}$ to saxitoxin.$^{441}$

Metabolomic and proteomic analyses indicated that $\text{Karenia brevis}$ exhibited allelopathy against two competitor diatoms $\text{Asterionellopsis glacialis}$ and $\text{Thalassiosira pseudonana}$. The former, which co-occurs with $\text{K. brevis}$, exhibited somewhat more robust metabolism while in the latter, energy metabolism was disrupted and cellular protection mechanisms were impeded.$^{442}$ Other studies examined the biosynthesis of brevetoxin,$^{443,444}$ brevisamide$^{445,446}$ and the genetics of toxin production in $\text{Alexandrium catenula}$. $^{447}$

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Other new metabolites $\text{643-655}$ were obtained from the genera $\text{Anabaena}$, $\text{Lyngbya}$, $\text{Moorea}$, $\text{Oscillatoria}$ and $\text{Sym-}$

ploca.$^{396-402}$ The absolute configurations of coibacins $\text{A}$ and $\text{B}^{403}$ have been determined as $\text{656}$ and $\text{657}$ respectively by total synthesis.$^{404}$ Syntheses of biselyngbyolide $\text{A}^{405}$ ($\text{Lyngbya (Moorea)}$ sp.),$^{406}$ apratocyn $\text{C}^{407}$ ($\text{Lyngbya (Moorea)}$ sp.),$^{408}$ malevamide $\text{D}^{409}$ ($\text{Symploca hydnoides}$),$^{410}$ micromide$^{411}$ ($\text{Symploca sp}$),$^{412}$ and 12-

epi-hapalindole $\text{Q}$ isonitrile$^{413}$ ($\text{Hapalosiphon laingii}$),$^{414}$ have also been achieved. Total syntheses of the proposed structures

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anhydrodebromoaplysatoxin,$^{394}$ were inhibitors of the Chi-
kungunya virus.$^{395}$

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\[ \text{636} \]

\[ \text{638} \]

\[ \text{639} \]

\[ \text{640} \]

\[ \text{641} \quad \text{R = Br} \quad \text{642} \quad \text{R = H} \]
4 Green algae

Research into green algal chemistry continues at low ebb with just 13 relevant articles published and just three new compounds published for 2014. The new compounds were the racemosines A–C \(^{678–680}\), bisindole alkaloids isolated from *Caulerpa racemosa* which are biosynthetically related to the well-established green algal metabolite caulerpin, also from a *Caulerpa* sp. \(^{450}\)

Caulerpin featured in studies of anti-nociception mechanisms \(^{451}\) and the antituberculosis activities of caulerpin and synthetic analogues. \(^{452}\) Included in the green algal literature for 2014 was a study on the effect of natural lycopene (\(E/Z\) mixture) on a human prostate cancer cell line,\(^ {453}\) while a thought-provoking paper tackled a problem all marine natural product chemists should be alert to – the misuse of taxonomic descriptors and the implications that this has. Misuse of such descriptors appears to be a particular problem with marine algae.\(^ {454}\)

5 Brown algae

The output of new compounds (17) from brown algae in 2014 was again relatively low and although dominated by terpenoid chemistry saw the emergence of a new class of brown algal metabolite. This was the characterisation of a 1-deoxy-sphingoid, 3-epi-xestoaminol C \(^{681}\), from a New Zealand collection of *Xiphophora chondrophylla* following a *M. tuberculosis*-guided fractionation. A genome-wide screening against a library of non-essential gene deletion mutants of *Saccharomyces cerevisiae* established the cellular processes that disrupted.\(^ {455}\)

Some 27 diterpenoids ranging across six classes were isolated from a Chinese collection of *Dictyota plectens*. These included seven new diterpenes, belonging to the dolabellanes \(^{682–684}\), prenylated guaianes \(^{685–687}\), and a xenicane \(^{688}\), known analogues and an ethoxylated artifact as well.\(^ {456}\) Three new diterpenoids, a dolabellane \(^{689}\) a xenicane \(^{690}\), and a prenylated guaiane \(^{691}\) with five previously characterised compounds were characterised from Mediterranean collections of several *Dictyota* spp.\(^ {457}\) Three new, \(^{692–694}\), and three known dolabellane diterpenoids, \(^{458,459}\) were isolated from a Brazilian *D. paffi*, and a single crystal X-ray analysis established the absolute configuration of the known 10,18-diacetoxy-8-hydroxy-2,6-dolabelladiene.\(^ {458,460}\) The meroterpenoids sargachromanol Q \(^{695}\) and R \(^{696}\) along with the known sargachromanol J \(^{461}\) resulted from re-examination of the original extract from *Sargassum silquastrum*,\(^ {462}\) while thunberol, \(^{697}\), is the only new sterol of 6 isolated from the Chinese *Sargassum thunbergii*.\(^ {463}\)

Typical brown algal phlorotannins such as eckol and dieckol have stimulated research into a wide range of topics – heme oxygenase-1 expression,\(^ {464}\) oxidative stress,\(^ {465}\) anti-adipogenic activity,\(^ {466}\) anti-HIV-1\(^ {467}\) and antibacterial activity.\(^ {468}\) Among the studies on the anti-inflammatory properties of phlorotannins\(^ {469,470}\) was the synthesis of a rhodamine-labelled dieckol. Confocal laser microscopy determined that the labeled dieckol was mainly located in the endoplasmic reticulum and studies showed that the anti-inflammatory activity of the conjugate was considerably greater than that of dieckol itself.\(^ {471}\) The potential therapeutic properties of fucoxanthin and derivatives have been studied,\(^ {472,473}\) as have those of polyphenols such as octaphlorethol,\(^ {474–476}\) and mono- and diacylglycerols.\(^ {477}\)
6 Red algae

There continues to be a marked variation in the number of new compounds obtained from red algae and reported each year, with 42 for 2014 compared to 9 for 2013. There was the usual range of structural types with glycolipids, halogenated allenes and alkynes, halogenated monoterpenes, sesquiterpenes, diterpenes, brominated aromatics and the mahorones, unusual 2,3-dibrominated 2-cyclopentenones. The use of rapid dereplication tools (UHPLC–PDA–HRMS, 2D HSQC NMR, software tools and databases) for identification of the allenes and LC-UV-MS-SPE-NMR for the monoterpenes were notable features.

A synthesis of the brominated sesquiterpene aldigenin C showed that the original structure was incorrect, and it was suggested that aldigenin C was probably the known compound caespitol. A synthesis of the proposed structure of prevezol B has shown that the original structure was incorrect. Of the polyhalogenated acyclic monoterpenes isolated from Plocamium spp., surprisingly none had been synthesised until the use of a broadly applicable approach generated four of the naturally occurring compounds and a number of analogues. An asymmetric total synthesis of (-)-bermudynol has been accomplished, while a total synthesis of the snyderane (+)-luzofuran has also been made. The anti-inflammatory potential of 5ß-hydroxyypalisadin B from Laurencia snackeyi has been demonstrated in LPS-stimulated RAW 264.7 macrophages and LPS-induced zebrafish embryo.

7 Sponges

With 283 new structures reported from the phylum Porifera in 2014, sponges have returned again to be a dominant source of new bioactive metabolites, although the growing realisation that microbial symbionts are the real producers of “sponge” specialised metabolites highlights the need for more detailed metagenomic and biosynthetic analyses of sponge matrices.
Sphingoids 740, 741, taurinated fatty acids 742–745, and a large number of polyacetylenes 746–765 and a large number of polyacetylenes 746–765 have been reported from the genera Callyspongia, Coscinoderma, Echinoclathria, Petrosia, Placospongia, Siphonochalina and Xestospongia. The synthesis of a series of miyakosyne A (Petrosia sp.) diastereomers followed by RP-HPLC separation at −56 °C has revealed that the natural product 766 is actually a mixture of two stereoisomers in 96 : 4 (14R) : (14S) ratio. A comprehensive blend of synthesis with NMR, IR and vibrational circular dichroism (VCD) spectroscopy has allowed for the relative configurational assignment of the C-36–C-42 segment of hemicalide 767 (Hemimycale sp.), as well as securing the absolute configuration of C-42. This potent (sub-nM) inhibitor of mitosis was sourced from a deep water sponge collected at the Torres Islands, Vanuatu, but to date has only been reported in a patent. A series of peroxides 768–773, halogenated alkenes 774, 775, and an amide 776 have been reported from Plakortis simplex, Dysidea sp. and Anoxycalyx (Scolymastra) joubini, respectively. Sponges continue to be a prolific source of peptide natural products. Reisolation of cyclolithistide A from a deep sea Discodermia japonica (−200 m, Sagami Bay, Japan), originally reported in 1998, allowed in-depth LC-MS/MS and Marfey’s analyses that necessitated a revision of the amino acid sequence and configurations as shown here. The simple substitution of a side-chain Asp for hydroxy-Asp in pipecolidepsins A 778 and B 779 (Homophymia lamellosa, Saint Marie Is., Madagascar) resulted in a greater than ten-fold increase in activity against three HTCLs. The stellatolides A–G 780–786 are a family of cyclodepsipeptides from a Madagascan Ecionemia acervus. The full stereochiemochemical analyses of several variants were established by Marfey’s analysis, and the solid-phase peptide total synthesis of 780 was also achieved. The unexplained racemisation of ε-Thr during the Marfey’s analysis is a salient warning to all experimentalists using this technique. Several of the stellatolides were cytotoxic in the nM range against three HTCLs. The genera Asteropus, Discodermia, Pipetella, Reniochalina, Stylissa, Suberites and Theonella have also yielded a large number of peptides 787–806. Callyspongolide 807 is an unusual carbamate macrolide with an unprecedented conjugated dienyne side chain isolated from Callyspongia sp. (Ambon, Indonesia). Evaluation of 807 against three HTCLs indicated potent cytotoxicity (IC_{50} = 60–320 nM). Notably, the viability of cell lines treated with callyspongolide was not affected by QVD-OPh, a known caspase-inhibitor, suggesting the test compound induces cellular toxicity in a caspase-independent manner.
The total synthesis of halichondrin A has been accomplished. Halichondrin A is a “phantom” natural product, viz. it is the only member of the norhalichondrin/halichondrin/homohalichondrin family not to have been detected from a natural source, typically Halichondria okadai,535,536 even though concerted efforts have been made to try and detect this compound for more than 20 years. Use of the synthetic material to guide studies searching for the presence of halichondrin A in legacy extracts of H. okadai were unsuccessful.536 A diketopiperazine 808,537 a 3-alkylpyrrolidine 809,538 seven manzamine-type alkaloids 810–816539,540 and seven 3-alkylpyrrolidines 817–823538 have been isolated from the sponge genera Callyspongia, Acanthostreonglyphophora and Top sentia. Axinyssa aculeata (Okinawa) was the source of protoc aculeine B 824 that is a putative novel N-terminal residue for the peptidic toxins aculeines A–C. The structure of this polycyclic compound, including identifying its attachment to the peptide toxins themselves, was determined from detailed synthetic and mass spectrometric studies.542

Other indole 825–829541,544 and β-carboline 830–837544,546 alkaloids were reported from Hyrtios and Luffariella sponges. A biomimetic total synthesis of (+)-dictazole B, isolated from the shallow water sponge Smonosponge cerebriformis,547 has been performed using artificial light to facilitate the [2 + 2] photochemical cycloaddition reaction between alysinopin monomers, under the presumed high local concentration of the parent reactant that would be found in the relevant sponge organelle. This biomimetic route is a viable alternative to the [4 + 2] Diels–Alder cycloaddition that has been presumed to take place in the biosynthesis of the cycloalkynopins.548 Fifteen new aaptamine alkaloids 838–852549–551 have been reported from Aaptos sponges while a new polycyclic aromatic alkaloid 853 came from an Ancorina sp.552 An unbiased screen of a library of 480 sponge extracts identified the surprisingly simple compound girolline553 from Styliissa carteri (Mont Pass, Pohnpei, Micronesia) as a potent inhibitor of signalling of MyD88-dependent and -independent Toll-Like Receptors (TLR) 2, 3, 4, 5 and 7, reducing cytokine production in peripheral blood mononuclear cells and macrophages, therefore imbuing the molecule with potent anti-inflammatory activity. In-depth chemical genetics profiling identified elongation factor 2 as the molecular target of girolline implying inhibition of protein synthesis as its mode of action.554 Guanidine-derived alkaloids 854–863 were reported from Monanchora pulchra,555 Acanthella cavernosa556 and Biemia laboustei,557 while several brominated hymenialdisine-type 864–867 and oroidin/oroidin dimer-type 868–877 came from Callyspongia sp.558 and Agelas sp.,559,560 respectively. A highly scalable, multi gram synthesis of axinellamines A and B (Axinella sp.)561 and analogues has been achieved. Evaluation of the antibacterial properties of racemic synthetic products highlighted their potent inhibition of both Gram positive and negative bacteria (MIC 0.5–8 µg mL−1 vs. eight bacterial cell lines), even though the initial isolation study reported minimal activity. Further detailed investigation could not determine a specific mode of action but did suggest secondary membrane-disruption as the likely route to activity.563 The comprehensive total synthesis of sceptrin, ageliferin and massadine congeners via single electron cycloaddition reactions has several wide-ranging consequences. Firstly, it necessitates the revision of the absolute configuration of sceptrin and its brominated analogues 878–880564–566 and ageliferin and congener 881–883567 as shown here, based upon X-ray crystal structures. Moreover, the massadines had been thought to be rearrangement products from the ageliferins568,569 however the absolute configurations of the two series of compounds are antipodal, hence indicating enantiodivergent biosynthetic pathways in vivo to these bromopyrolyl alkaloids and invalidating the so-called “Scheuer-hypothesis” for their formation.570,571

Bromotyrosine metabolites 884–893 have been isolated from Callyspongia,572 Aplysinella573 and Dendrilla574 sponges, while Haliclona, Petrosia, Phoriospongea and Dragmacidon sponges have yielded substituted purine/pyrimidine compounds 894–898,574–577 As usual, sponges continue to be a valuable reservoir of new terpenoid metabolites. Merosesquiterpenoids 899–930 came from the sponge genera Aka (Siphondictyon), Dysidea, Dactylospongea and Xestospongia.578–584 In particular, xestolactone A 931 and xestosaprol O 932 were isolated from Xestospongia vamsoesti (Palawan Is., Philippines). Xestosaprol O is twenty times more potent as an inhibitor of indoleamine 2,3-oxygenase (IDO; IC50 = 4 µM) than 931 (IC50 = 81 µM), making it a lead towards inhibitors of tumour immune escape. The total syntheses of 932 and two analogues were achieved using the rarely applied silver-catalysed Sato photochemical coupling, leading to a short and efficient synthesis of the natural product. Comparative analysis of 932 and its analogues showed that the 3-OH functional group is highly detrimental for IDO-inhibitory activity.585
A meroterpenoid 933 has been reported from Sarco-
tragus spinulosus.\textsuperscript{289} Similarly, Axinyssa, Dysidea, Ircinia and 
Topsentia sponges were the sources of a number of sesqui-
terpenoids 934–964,\textsuperscript{287–291} some of which had been cleaved, 
while diterpenoids were obtained from Diacarnus mega-
spinorhabdosa 965–970,\textsuperscript{292} Spongia sp. 971–973\textsuperscript{293} and Darwinella 
oxetacea 974–982.\textsuperscript{294} A large number of sesterterpenoids 983–1011 
were reported in 2014 from the sponge genera Clathria, Cosci-
noderma, Hippospongia, Hyrtios, Petrosaspongia, Phorbas and 
Scalarispongia\textsuperscript{294,295–298}. As always, sponges yielded a variety of 
steroids 1012–1019,\textsuperscript{294,295,297,298,299} steroidal amines 1020 and 
1021,\textsuperscript{297} and degraded steroids 1022–1024\textsuperscript{295,296} from species of 
Echinoclathria, Corticium, Haliclona, Ircinia, Petrosia, Plakotis 
and Theonella. T. swinhoei (Xisha Is., S. China Sea) yielded 
swinhoeisterols A 1025 and B 1026 with unprecedented 6/6/5/7 
tetracyclic frameworks. The absolute configurations of the 
compounds were secured by a combination of X-ray diffraction, 
TDDFT ECD calculations and Mosher’s method. Detailed in 
silico analysis of both compounds against 211 potential protein 
targets of relevance for cancer therapy revealed 1025 should 
exhibit activity against the histone acetyltransferase (h)p300. 
This was validated in vitro with IC\textsubscript{50} = 2.9 \mu M while 1026 was 
amost 100 times less potent (IC\textsubscript{50} = 240 \mu M), indicating the 
steric importance of the 9-OH in abrogating activity.\textsuperscript{297} 

![Image](image1.png)

Cinanthenol A 1027 is the first example of a phenanthrene-
containing steroid. It was sourced from Cinachyrella sp. 
collected by dredging at -160 m (Oshima-Shinsone, Japan) 
where the unique phenanthrene-fluorescence signature was 
used to select the sponge from amongst detritus. As well as 
moderate activity against various HTCLs, 1027 was a potent 
estrogen-receptor binder, displacing estradiol in a competitive 
manner with IC\textsubscript{50} = 10 nM, as well as altering estrogen-
responsive gene expression.\textsuperscript{608} 

![Image](image2.png)

A series of triterpenoids 1028–1032 have been reported from 
Jaspis stellifera\textsuperscript{289} and Siphonochalina siphonella.\textsuperscript{610} An artificial 
“sponge” has been developed for the non-destructive 
concentration of marine natural products in sensitive marine 
ecosystems. A pump is used to suction sponge-matrix particles 
that are filtered into a hollow-fibre bioreactor. This is used to 
cultivate microbial symbionts that produce secondary metabolites 
which are, in turn, trapped on reversed-phase cartridges for 
concentration. The artificial sponge system was used in three 
expeditions across 11 locations, two in the Pacific and one in the 
South China Sea, with the deployment at Pulau Lakei (Sarawak, 
Malaysia) yielding jasplakinolide, jasplakinolide B and C in 
a 18 : 1 : 1 ratio, the same proportions as found from Jaspis 
splendens collected near Vanuatu.\textsuperscript{611,612} Metagenomic analyses 
continue to rise in their importance to sponge natural product 
biosyntheses. Detailed metagenomic profiling of the “High 
Microbial Abundance” (38–57\% microbial biomass) sponge Pla-
kortis halichondrioides (Little San Salvador Is., Caribbean Sea) 
found characteristic gene sequences of poribacteria [a bacterial 
phylum found exclusively in sponges] but the known supA and 
sufA biosynthetic clusters observed were absent from the por-
bacteria genomes. Further investigation showed similarity 
between these clusters and protist type I polyketide synthetase 
(PKS) genes hence protists could be a previously overlooked 
reservoir of novel bioactive metabolites.\textsuperscript{613} A comprehensive 
metagenomic survey of the microbial community associated 
with the metabolite-rich sponge Theonella swinhoei has uncovered 
a new bacterial genus, Entothoneilla. This genus is a member of 
the new candidate phylum Tectomicrobia and appears to be a 
widespread sponge endosymbiont across many diverse sponge 
spieces. Moreover, biosynthetic gene cassettes suitable for 
production of many “Theonella swinhoei” NRPS and PKS 
compounds, including the onnamide,\textsuperscript{614} polytheonamide,\textsuperscript{615} ker-
amamide\textsuperscript{616} and cyclotheonamide\textsuperscript{617} classes, have been identified 
in the microbial genome.\textsuperscript{618} A metagenomic approach identified 
the gene cassette for calyculin A (Discodorina calyx)\textsuperscript{618} biosynthesis 
as being microbial in origin, as described in 3.1 Bacteria, and 
resulted in the identification of two diphosphate protoxins (see 1 
and 2).\textsuperscript{21,22} again underscoring the importance of symbiotic 
microbial communities in the production of “sponge” metabolites. 
The microtubule-stabilising mode of action of laulimalide\textsuperscript{621} and 
peloruside A\textsuperscript{622} has been established through the use of high-
resolution crystal structures of the compounds bound to 
tubulin,\textsuperscript{620} while aaptamine\textsuperscript{621} has been shown to have protective 
effects against cisplatin-induced kidney damage,\textsuperscript{621} and also 
prevents photoageing.\textsuperscript{623} A polybrominated diphenylether \textsuperscript{624} (Dysidea granulosa) has been shown to inhibit hepatitis C non-
structural protein NS3 helicase, a validated antiviral target.\textsuperscript{625} The 
four bromotyrosine compounds ianthelliformisamine A–C (Sub-
errea ianthelliformis)\textsuperscript{626} and spermataminine (Pseudoceratina sp.)\textsuperscript{627} 
were selective and potent inhibitors of human carbonic anhydrase 
IX (IC\textsubscript{50} = 0.20–0.36 \mu M), with implications for maintaining 
cellular pH homeostasis and hence application in a variety of 
disease states.\textsuperscript{628} The sesterterpenoid heteronemin (Hyrtios sp.)\textsuperscript{629} 
inhibited trans-activation response DNA-binding protein 43 kDa 
(TDP-43), a key factor of several neurodegenerative states. Heter-
onemin binds to TDP-43 (k\textsubscript{d} = 270 nM) and altered the aggre-
gation state and localisation of this important neurochemical 
target.\textsuperscript{630} The first total syntheses of an all-(Z) octadeca-pentene-
3-one (Callyspongia sp.),\textsuperscript{631,632} strongylodiol G (Strongylophora 
...
sp.), \textit{H. sp.}, \textit{B. (Theonella swinhoei)}, \textit{B. (Plakortis clathrata)}; 0.38 \times 1.18 \text{ epiplatin acid F (Plakinastrella sp.)}, \textit{H. sp.}, and its methyl ester (\textit{Plakortis halichondrioides}); 0.39 \times 1.18 \text{ plakortone L (Plakortis clathrata)}; 0.36 \times 0.64 \text{ gracilooether F (Plakinastrella mamilaris)}; 0.69 \times 0.64 \text{ taumycins A and B (revised \textit{1033} and \textit{1034}, Fascaplysins sp.)}; 0.61 \times 0.66 \text{ polydiscamides B–D (\textit{Ircinia} sp.)}; 0.67 \times 0.67 \text{ callipeltins M (\textit{Latruonula} sp.)}; 0.64 \times 0.69 \text{ topsentolide A2 (revised \textit{1035}, Topsentia sp.)}; 0.67 \times 0.67 \text{ penarolide sulfate A2 (\textit{Penares} sp.)}; 0.62 \times 0.67 \text{ haliclorensin C (Halicyclopsenidrae)}; 0.64 \times 0.65 \text{ nakanidina A (revised \textit{1036}, Amphimedon sp.)}; 0.66 \times 0.67 \text{ thiaplakortone A (\textit{Plakortis lita})}; 0.69 \times 0.67 \text{ (+)-cylindradine A (\textit{Axinella cylindrata})}; 0.66 \times 0.66 \text{ ianthelliformasimines A–C (Suberea ianthelliformis)}; 0.63 \times 0.62 \times 0.63 \text{ tokaradine C (Pseudoceratina purpurea)}; 0.64 \times 0.66 \text{ (+)-hemifusilin 3 (revised \textit{1037}, Verongia sp.)}; 0.65 \times 0.66 \text{ trachycladines A and B (\textit{Trachycladus laevispirulifer})}; 0.67 \times 0.69 \text{ cyclospongiaquinone-1 (\textit{Stelospongia conulata})}; 0.70 \times 0.67 \text{ deoxyspongiaquinol (revised \textit{1038}) and deoxyspongiaquinone (revised \textit{1039}, Euryspongia sp.)}; 0.67 \times 0.67 \text{ plakatin B (\textit{Plakina} sp.)}; 0.65 \times 0.67 \times 0.67 \text{ and clionamine D (\textit{Cliona celata})}; 0.67 \times 0.67 \text{ have all been completed. The total syntheses of the putative structures of 15-oxopuchoenic acid (\textit{Hyrtios} sp.)}; 0.68 \times 0.67 \text{ and astakolactin (\textit{Cacospongia scalaris}) have also been achieved but the spectroscopic data call into question the original identified structures, with no alternative suggestions provided.}

8 Cnidarians

The number of new compounds reported from cnidarians in 2014 (201) is similar to the previous decadal average. The importance of chemical cues in coral reef remediation have been discussed in a study that found that coral and fish juveniles were repelled from reefs that were overfished and seaweed-dominated.82 A method of recovery of such degraded habitats was proposed to involve reduction in fishing harvest of critical species of herbivorous fishes. The chemistry of both hard and soft corals are dominated by terpenes – alkaldoids are only rarely isolated. In 2014 there were seven examples of alkaloids isolated from soft corals, comprised of an unusual diketopiperazine \textit{1040} from \textit{Menella kanisa},83 and six tetracyclederol purines, malonogogenone L–Q \textit{1041–1046}, from \textit{Echinogorgia pseudosasso}.84 In contrast, cnidarians of the order Zoantharia (zoanthids) were the sources of five new parazoanthid congeners \textit{1047–1051} (\textit{Parazoanthus axinellae}).85 These structures were established using a metabolomics model, with LCMS/MS fragment analysis being used to define structures and LC-ECD employed to assign absolute configuration (to \textit{1047, 1048} and \textit{1050}).

Other zoanthamine analogues, \textit{1052–1058}, were isolated from \textit{Zoanthus} sp.86,87,88 and \textit{Zoanthus kuroshio}89 as well as a new 42-hydroxypalytoxin diastereomer \textit{1059} from \textit{Palythoa tuberculosa}.90 Previous studies of an extract of \textit{Palythoa toxica} identified the major toxin to be a 42-hydroxy analogue of palytoxin \textit{1060} however the configuration at positions C-41 and C-42 remained unresolved.91 More recent J-based analysis has defined the configuration at these stereocentres as (41S) and (42S). The same study also established the absolute configuration of a related palytoxin analogue isolated from \textit{P. tuberculosa} as being (42S)-hydroxy(50S)-palytoxin \textit{1059}. The relative affinity of palytoxin, \textit{1059} and \textit{1060} towards a mouse anti-palytoxin monoclonal antibody identified palytoxin to have the most potent \textit{K}_D (nM), while \textit{1059} and \textit{1060} were approximately one and three orders of magnitude less potent respectively. Similar relative levels of cytotoxicity towards keratinocytes were also observed, with palytoxin being the most potent. Palytoxin is known to be capable of disrupting mechanisms of cellular ion homeostasis: NMR studies have defined the C-25–C-33 and C-47–C-53 fragments of palytoxin as being involved with Ca\textsuperscript{2+} coordination.92

A series of butenolide and cyclopentenones \textit{1061–1072} were reported from \textit{Subergorgia suberosa} and \textit{Sinularia} sp. soft corals,93–94 A comprehensive investigation of a Bahamian collection of \textit{Pseudopterogorgia rigida} identified a chамigrame \textit{1073} and seven bisabolans \textit{1074–1079} as new sesquiterpenes.95 The study also reported an extensive number of co-metabolites \textit{1080–1083} that had been previously reported from terrestrial plants or as semi-synthetic derivatives \textit{1084–1090}. Other sesquiterpenes \textit{1091–1110} have been reported from \textit{Rumphella antipathies},96–98 \textit{Lemnalia philippinensis},99 \textit{Menella kanisa},70 \textit{Nephthea erecta},71 an unidentified gorgonian,72 \textit{Dendronephthya sp.},73 \textit{Sinularia kavarattiensis},74 \textit{Echinogorgia sasapo reticulata}95 and \textit{Anthogorgia ochracea}.96 Of these sesquiterpenes, rumpellaic acid \textit{1093} contains a unique skeleton, while shagenes \textit{A1102} and \textit{B1103}102 and ochracenoid \textit{A1109}1096 contain rarely reported skeletons. In the case of the ochracenoid \textit{A}, absolute configuration was assigned by use of TDDFT calculated ECD data.107

A South China Sea collection of \textit{Anthogorgia caerulea} yielded, in addition to two known averymecin macroldides, averymecin B\textit{3a} and 22,23-dihydroaverymecin A\textit{1a}707 two new congeners B\textit{1c} \textit{1111} and B\textit{1c} \textit{1112}.98 All four MNPs exhibited moderate antiouling activities.

Of the thirty-six cnemid related metabolites \textit{1113–1149} reported from cnidarians in 2014,709–712 secoassaramol \textit{1113} (\textit{ Lobophyton crassum})709 is notable as it is derived from the cnemid skeleton via an unusual C-11–C-12 bond cleavage, sinuguysanolide \textit{A1114} (\textit{Sinularia gyrosa}) is an unprecedented C-4 norcembranoid,708 tortuoses \textit{A1146} and \textit{B1147} (\textit{Sarcophyton tortuosum})721 represent the first examples of cembranoids containing a C-2–C-20 ring closure, and sinularols \textit{A1148} and \textit{B1149} (\textit{Sinularia arboroa}) contain a rare C-3–C-9 ring closure.722

Cnidarian chemistry is dominated by metabolites derived from terpene biosynthesis, with particularly large numbers falling into the diterpenoid classification. Thirty-eight new briarane-skeletoned MNPs \textit{1150}, gemmacolides AS–AY \textit{1151–1157}, briareolide \textit{J 1158}, junectelolides M–P \textit{1159–1162}, fragilisinins A–L \textit{1163–1174}, dollfusilins \textit{A1175} and \textit{B1176}, briaviolides A–J \textit{1177–1186} and anthrogonoid \textit{A1187} were reported.
from octocoral species *Pennatula aculeata*, *Dichotella gemmacea*, *Juncella gemmacea*, *J. fragilis*, *Ellisella dolifiusi*, *Briareum violacea*, and *Anthrogorgia caerulea*. As usually happens each year, there is duplication of structure/trivial name amongst a small number of MNPs. In the set of briaranes reported from *Juncella gemmacea* (South China Sea) and *J. fragilis* (also South China Sea), juncellolide O 1161 and fragilisinin G 1169 share the same assigned structure, however spectroscopic and photometric data reported for the two compounds are quite different clearly indicating that one of the structures is in need of revision. The structure and absolute configuration of briaviolide A 1177 was secured by single crystal X-ray analysis.

The second dominant class of diterpenoid metabolites reported from soft corals contain the eunicellin skeleton. Examples of eunicellins were reported from *Anthrogorgia caerulea* (antsimplexin A, 1188), *Muricella sibogae* (sibogins A 1189 and B 1190), *Cladiella* sp. (cladieunicellin J, 1191), *Klyxum molle* (klymollins T–X, 1192–1196), *Cladiella* sp. (cladieunicellin M–Q, 1197–1201), *Cladiella kremphi* (kremphiolins N–R,
Further examples of diterpenoids, 1213 and 1214,739, 1215 and 1216,740 cespitulones A 1217 and B 1218,741 dihydroarsolone 1219, methyldihydroarsoloneate 1220, and sarsolidides B 1221 and C 1222,424 have been isolated from soft corals of the genera Cespitularia, Xenia, and Sarcophyton. Structure elucidation and determination of absolute configuration of 1219 and 1220424 led the authors to propose a revision of the relative configuration at C-2 of the previously reported MNP sarsolenone (to that shown 1223).424 Absolute configuration was assigned to 1219 and 1220 using TDDFT calculations of ECD data.

Sarcophyton ehrenbergii was the source of a number of prostanoids including sarcoehrendins A-J 1224–1233.744 In addition, three prostaglandins previously reported as synthetic compounds 1234–1236 were reported as natural products for the first time. Relatively potent activity was observed towards phosphodiesterase-4, a target for CNS, inflammatory and respiratory diseases. Soft corals also yielded a variety of steroids including pregnanes 1237 and 1238,745 seco-sterols 1239–124446,747 and hydroxylated/polyhydroxylated sterols 1245–126547–53 from species of Schleronephthya, Subergorgia, Sarcophyton, Sinularia, Verrucella, Echinogorgia, and Leptogorgia. Noteworthy amongst these compounds, was the enhanced (synergistic) cytotoxicity observed for paclitaxel in the presence of punicinols A 1257 and B 1258 (Leptogorgia punicea) and that the two sterols were also able to inhibit A549 tumour cell growth in a clonogenic assay over a sustained period of ten days.752

In addition to the mildly antiproliferative epoxyugosters 1266–1271 (Anthopleura midori),754 investigation of MNP chemistry of sea anemones and hydrozoa has identified two new cytolsins (3013 and 3375 Da) from the tentacles of the hydrozoan Olinias sambaqnensis755 and PhcrTx1, a 32 amino acid residue acid-sensing ion channel inhibiting peptide from the sea anemone Phymanthus crucifer756 that represents the first example of a peptide containing an Inhibitor Cysteine Knot scaffold to be isolated from a cnidarian. Further study of the biological activities of previously reported anemone toxins has identified Av3 (Anemonia viridis) to show specificity towards arthropod voltage-gated sodium channels by binding to one of the transmembrane clefs of the channel x-subunit,757 while AnE-1 (Aiptasia diaaphana) prolongs cardiomyocyte action potential duration while lowering peak amplitude via slowing inactivation of sodium channels and enhancing the transient K+ current.758 Mutation of the pore-forming toxin sticholysin 1 (Stichodactyla helianthus) residue tryptophan 111 to cysteine reduced the toxins affinity for membranes by an order of magnitude,759 cystine mutants of phenylalanine 15 or arginine 52 did not alter pore-forming activity but did protect the toxin from peroxynitrite oxidative damage,760 while a third study, using monolayers of phosphatidylycholine and sphingomyelin, determined that the toxin preferentially binds and penetrates membranes which have moderate enrichment in sphingomyelin and membrane fluidity.761 The first total syntheses of alkaloids N-(3-guanidinopropyl)-2(4-hydroxyphenyl)-2-oxoacetamide (Campanularia sp.)762,763 and (±)-tubastrindole B (Tubastrea sp.),764,765 butenolide (+)-hydroxyancepsenolide (Pterogorgia aniceps),766,767 and diterpenes sandresolide B,768 amphilectolide768 and (+)-ileabothaxazole779 (Pseudopterogorgia elisabethae)771,772 have been completed. Conversion of binpinnin J (Pseudopterogorgia bipinnata)773 to intracrence (Pseudopterogorgia kallos)774 via a photochemical pathway has been demonstrated,775 while a photochemical (E/Z) olefin isomerisation was a critical step in the total synthesis of the natural product analog 17-deoxygenoviden.776 Clarification of the structure of the cladiellin diterpene sclerophytin F (Scle-rophytum capitalis)777 has been an ongoing issue, with Frie- drich and Paquette in 2002 proposing the structure should be revised to be the (3S) diastereomer of sclerophytan A.778 Synthesis of this proposed revised structure gave a product whose spectroscopic data differed from those reported for the natural product, suggesting further investigation is needed to resolve this issue.779 A modular approach to a number of cladiellin MNPs using a gold-catalysed tandem reaction of 1,7-dienes has been reported.780 Hippuristanol (Isis hippu-ritus)781 analogues have been evaluated as inhibitors of eukaryotic translation initiation,782 emembranoid and ergosterol MNPs from Vietnamese cnidarians were found to exhibit...
selective in vitro activity against T. brucei, a number of diterpenes (Sinularia maxima) were found to be modest to poor inhibitors of NF-κB transcriptional activation, structurally simpler analogues of fuscol/eunicol exhibit comparable or better anti-inflammatory activity in the mouse ear edema assay, semi-synthetic oxygenated dolabellane diterpenes exhibit in vitro anti-HIV activity, further semi-synthetic examples of hydroxysterols were found to induce pregnane X receptor transactivation, synthetic examples of hydroxysterols were found to induce pregnane X receptor transactivation, 11-epi-sinulariolide acetate inhibits carcinoma cell migration and invasion by suppressing a number of phosphorylation-dependent pathways, 13-acetoxyxarcoraccsosides induces apoptosis in carcinoma cells by activation of p38/JNK and suppression of PI3K/AKT pathways, and cembranoids from Sarcophyton glaucum exhibit cytotoxicity towards a murine melanoma cell line.

9 Bryozoans

There were only three reports (containing 19 compounds) of new metabolites isolated from bryozoans in 2014, which is a large increase on 2013 when only one new metabolite was reported from this understudied phylum. The bromopyrrole alkaloids aspidostomides A–H 1272–1279 and aspidazide A 1280 were isolated from the Patagonian bryozoan Aspidostoma giganteum. Aspidostomide E 1276 exhibited moderate inhibition of the 786-O renal carcinoma cell line. Aspidazide A 1280 is a rare asymmetrical diacylazide and NOE NMR correlations and chemical transformations were utilised in determination of the structure. A series of ceramides neritinaceramide A–E 1281–1285 were obtained from Bugula neritina and exhibited selective but weak activity against two HTCLs. The same sample yielded several sterols 1286–1290. Convolutamidine A 1291 displayed significant anti-inflammatory activity both in vitro and in vivo.

10 Molluscs

The 23 new metabolites reported from molluscs is the average number reported per year over the past decade. Azaspiracid-1 1291 was isolated from contaminated raw shellfish – the epimer forms spontaneously via an equilibrium and formation, as expected, is accelerated by heating. Implication of the latter in relationship to the cooking of shellfish is important as 37-epi-AZA1 was 5-fold more toxic towards Jurkat T lymphocyte cells in vitro than AZA1. Corresponding epimers of the related toxins AZA2 and AZA3 were also detected. Specimens of the Mediterranean sacoglossan mollusc Thuridilla hopei afforded new nor-diterpene aldehydes 1292–1294 in addition to known congeners thuridillin A, B and C. The mollusc feeds on the green alga Derbesia tenuissima, extracts of which only contain a known epoxylactone, supporting the assumption that 1292–1294 are mollusc transformation products. Acetylenic alcohols 1295–1299 were isolated from both the Mediterranean dorid nudibranch Peltodoris atromaculata and one of the nudibranch’s common dietary prey, the sponge Haliclona fulva. In a similar manner, renieramycin-related alkaloids fennebricin A 1300 and B 1301 were isolated from both the nudibranch Jorunna funebris and the sponge Xestospongia sp. The substructurally-related isouquinoline 1302 was only identified in the sponge extract. New diketopiperazines 1303–1306 were reported from Pleurobranchus areolatus – related metabolites have been reported from the ascidian Didemnum sp., a suspected prey of P. areolatus. Further investigation into the origin of tetrodotoxin in Pleurobranchaea maculata demonstrated that the mollusc can accumulate the toxin through its diet however there was no identifiable tetrodotoxin source in the molluscs local environment. Two studies of sea hares identified two moderately cytotoxic sesquiterpenes oculiferane 1307 and epi-obtusane 1308 (Aplysia oculifera) and an anti-inflammatory diterpene dactylo-diterpenol acetate 1309 (A. dactylolomela). 6-Bromooidsatin, typically isolated from muricid molluscs, is weakly antiproliferative towards HT29 cells, and enhances apoptosis in an in vivo colon cancer model. Further structure–activity relationship studies of the cyclic peptide sanguinamide B (Hexabranchus sanguineus) have found that antiproliferative activity is dependent upon both the location of specific amino acids in the macrocycle and their configuration. New synthetic auristatin analogues, being related to the original MNP dolastatin 10 (Dolabella auricularia), bearing changes at the N-terminus showed pronounced antitumour activity. The binding of three examples to tubulin was investigated by co-crystal X-ray studies, identifying an interesting structural feature whereby in the solid state the valine-dolaisoleucine fragment exists in
the cis-configuration, whereas in solution it exists solely in the trans-configuration. In further studies, cholesterol and other simple sterols purified from mussels showed anti-aging and neuroprotective properties,815 synthetic tambujamine analogues show enhanced tumour cell antiproliferative and chloride transport properties,816 and lamellarin D (Lamellaria sp.)817 induces senescence in cancer cells, in a process that includes the generation of intracellular ROS and requires the presence of topoisomerase I.818 Biosynthesis of long chain polyunsaturated fatty acids in the scallop Chlamys nobilis was investigated, revealing the presence of a new elongase, that can elongate 20:4n-6 and 20:5n-3 to C22 and C24 acids, and a Δ4-desaturase.819 A new example of an α47-conotoxin, α-BnIA 1310 was isolated from crude venom of the molluscivorous cone snail Conus bandanus.820 Peptides with the same sequence, MrI.1 and BnI.1, were previously identified by PCR amplification of venom duct cDNA from molluscs C. marmoreus821 and C. bandanus.822 The peptide reversibly inhibited the human α7 nicotinic acetylcholine receptor (nAChR) and blocked nerve-evoked skeletal muscle contractions. Conus bandanus (Vietnam) was also the source of BnIIID 1311, a 15 residue M–1 family peptide containing six cysteines (disulfide connectivity not determined) and three post-translational modifications comprised of a bromotryptophan, γ-carboxy glutamate and amidated aspartic acid residues.823 An unusual α5/5 conotoxin AusIA 1312 was purified from the venom of C. australis – both synthetic globular (natural) and ribbon (different disulfide linkages) configurations inhibited the α7 nAChR.824 A short cyclic hexapeptide Vi804 1313 was isolated from crude venom of C. virgo and the solution structure of it and the βW3 synthetic analogue explored by NMR spectroscopy.825 The high hydrophobicity of γ-conotoxins make them difficult to synthesise by standard peptide synthesis techniques. A recent report describes the use of a Lys4 solubilising C-terminus tag to enable the synthesis and Naκ subtype selectivity of three previously reported C. consors γ-conotoxins, γ-CnVIB, γ-CnVIC and γ-CnVID.826 Further studies have reported on the structure and activity of dicarba analogues of α-RglIA,827 the influence of disulfide connectivity on structure and bioactivity of α-TxIA,828 the influence of acetylcholine to affect the binding of α-MIII at nAChRs,829 the neuronal target selectivity of the Conus textile T-superfamily peptide TxVC,830 and the Ca2+-activated K+ (BK) channel selectivity of the unusual M superfamily conotoxin Vt3.1.831

11 Tunicates (ascidians)

The 22 new tunicate-derived natural products presented in this review is the second lowest number reported in one year over the last decade. A structurally-diverse range of metabolites were reported, with examples of glycerides 1314 and 1315,821 amino alcohols 1316–1322,823 new didemnaketal congeners 1323, 1324844 and 1325, 1326,845 halogenated alkaloids 1327 and 1328,846 a new rubrolide (R) 1329847 (that unfortunately shares the same letter designation as a related metablite reported from Aspergillus terreus817), pyridoacridine enemidine A 1330852 and sulfated sterols 1331 and 1332.858 Noteworthy was the isolation, structure elucidation and synthesis of a rare example of a modified nuslide bearing a 5’-thiomethyl substituent 1333.859 The same study also led to the reassignment of structure of a known sponge metabolite hamiguanosinol860 from the enol tautomer to the guanosine keto tautomer 1334. The tanjungides A 1335 and B 1336,841 novel dibromomidoenol enamide alkaloids isolated from Diazone cf. formosa exhibit potent cytotoxicity (<1–2 μM) toward a panel of HTCLs. An eleven-step linear synthesis utilising Buchwald vinylidole amidation and peptide synthesis established the absolute configuration of the alkaloids.

Over the years a number of cyclic ribosomal peptides, now known as the cyanobactins, have been reported from ascidians, typically of the genus Lissoclinum. The true producers of these natural products are photosynthetic symbiotic cyanobacteria of the genus Prochloron. The apparent random distribution of cyanobactins isolated from ascidians has now been credited to host phylogeny, with genetic analysis revealing that ‘Lissoclinum patella’ falls into three phylogenetic groups that in turn may contain further cryptic species.842 The implications that local extinctions of such cryptic species may reduce marine natural product diversity is indeed food-for-thought in the context of climate change. A very interesting demonstration of the use of the biosynthetic machinery of cyanobactin production was recently reported, whereby engineered enzymes of the patellamide pathway, in combination with enzymes from other cyanobactin-related pathways, were used for the in vitro production of a small library of cyclic peptides.843 This proof of principle allowed for the preparation of 1–2 mg of each peptide. Total synthesis has led to revision of the original structure proposed for didemnaketal B (Didemnum sp.)844 to 1337, requiring stereochemical inversion of the C-10–C-20 spiroacetel domain of the MNP.845 Such a revision may be of relevance to the ongoing revision of the (sterio)structure of didemnaketal A.846 Syntheses of the reported structures of polycitorols A and B (unidentified ascidian)847,848 and (+)-didemisinolipid C (Didemnum sp.)849,850 suggest that the structures of all three MNPs require revision. Total synthesis has also led to revision of the structure of mandelalide A (Lissoclinum sp.)851 to 1338852 and confirmation of the revised structure of hamauvine B (Apidium haouarianum).853,854 while the structures of distomadines A and B (Pseudodistoma aureum)855,856 and synoxazolidinones A and B (Synocium pulmonaria)857,858 have been confirmed by synthesis. Synoxazolidinones A and C and S. pulmonaria co-metabolites pulmonarins A and B exhibited
variable levels of anti-biofouling activity against a panel of test organisms, with synoxazolidinone C being particularly potent as both a growth and adhesion inhibitor.\textsuperscript{680} The effects of ascidian extracts on the estrogen receptor-negative breast cancer cell line MDA-MB-231 were investigated by content-rich screening, leading to the identification of eusynstyalamide B (Didemnum candidum, originally isolated from Eusynystyla latericus)\textsuperscript{681} as a moderate cytotoxic (IC\textsubscript{50} 5 \textmu M) causing cell cycle arrest in G2/M and inducing apoptosis.\textsuperscript{682} The potently cytotoxic macrolide jeijimalide C (Eudistoma cf. rigida)\textsuperscript{683} joins congeners jeijimalides A and B as being identified as an inhibitor of the vacuolar-type ATP-driven proton pump (H+-ATPase).\textsuperscript{684} After 24 h treatment, cells also exhibited actin aggregates, but as the MNP does not inhibit actin polymerisation \textit{in vitro}, it was concluded that actin activity was a consequence of disruption of pH homeostasis. Preliminary data suggesting that trabectedin (Et 743) exhibits anti-angiogenic activity towards breast cancer cell lines has been reported.\textsuperscript{685}

12 Echinoderms

The 35 new metabolites reported from echinoderms in this review is 25% lower than the average number reported per annum over the last decade. Beyond the simple sulfonic acid derivative 1339 isolated from the sea urchin Brisaster latifrons\textsuperscript{686} and the highly substituted unsymmetrical binaphthoquinone mirabiquinone 1340 (sea urchin Scaphechinus mirabilis),\textsuperscript{687} the natural product chemistry of echinoderms is dominated by steroidal tri- (1341\textsuperscript{688} and 1342\textsuperscript{689}), tetra- (1343–1352),\textsuperscript{670–673} penta- and hexaoses (1353–1371).\textsuperscript{673–675} The aglycone 1372 was also isolated.\textsuperscript{674} In many cases these MNPs exhibited biological activity including anti-inflammatory,\textsuperscript{686} cytotoxic,\textsuperscript{670,672,674} hemolytic\textsuperscript{670} and antifungal\textsuperscript{673,675} properties.

\[ \text{HO} \text{C} \text{C} \text{O} \text{H} \text{OH} \text{OH} \text{OH} \text{OH} \]

1340

A number of new saponins were identified in extracts of the Australian sea cucumber Holothuria lessoni using solely LC-MS/MS metabolomic techniques.\textsuperscript{676} In a conceptually similar manner, the chemical diversity of saponins present in different organs of the starfish Asterias rubens was investigated by combinations of MALDI-TOF and LC-MS/MS techniques.\textsuperscript{677} The latter study concluded that different organs are characterised by different saponin mixtures and inter-specimen variability exists suggesting influence of sex and/or collecting season on saponin profile. A short octapeptide echinometrin 1373 (sea urchin Echinometra lucunter) was found to exhibit ability to degranulate mast cells leading to an inflammatory reaction.\textsuperscript{678} The sequence of the peptide is an internal fragment of vitellogenin, a nutrient protein present in sea urchin gametogenic cells, suggesting the possibility that echinometrin is a cryptide.\textsuperscript{679}

LRKLMQR

1373

The first synthesis of a pyranonaphthazarin pigment isolated from the sea urchin Echinotrix diadema\textsuperscript{680} has been reported.\textsuperscript{681} Further studies using purified pentahydroxyaphthoquinone echinochrome A\textsuperscript{682,683} have identified it to enhance mitochondrial biogenesis,\textsuperscript{684} to protect cardiomyocyte mitochondria from the effects of cardiotoxic drugs\textsuperscript{685} and to inhibit acetylcholinesterase in an irreversible and uncompetitive mode.\textsuperscript{686} The mechanisms of antioxidant reactivity of the structurally related echinamines A and B\textsuperscript{687} has been investigated using DFT methods.\textsuperscript{688} The benzochromene comparium (Comanthus bennetti)\textsuperscript{689} exhibits anti-inflammatory activity in the carrageenan-induced rat model.\textsuperscript{690} A simple synthesis of ovothiol A\textsuperscript{691} from L-3-hisidine has been reported,\textsuperscript{692} the role of a non-heme iron oxidase enzyme in the biosynthesis of ovothiol A investigated,\textsuperscript{693} NMR-pH titrations used to investigate the microspeciation of the amino acid,\textsuperscript{694} and the antiproliferative activity towards Hep-G2 cell line via an autophagy mechanism identified.\textsuperscript{695} Sterols and fatty acids from the spiny sea-star Marthasterias glacialis exhibit both anti-inflammatory\textsuperscript{696} and cell cycle arrest properties,\textsuperscript{697} while sterols from an urchin and a starfish exhibit selective antiparasitic activity towards \textit{T. brucei}.\textsuperscript{698} Investigation of the structure and bioactivity of chimeric analogues of the starfish cardiac-stomach relaxing SALMFamide neuropeptides S1 and S2 has highlighted the importance of the C-terminus for bioactivity and that the N-terminus confers structural stability.\textsuperscript{699} Treatment of pancreatic cancer \textit{in vivo} in athymic mice using a combination of frondoside A (Cucumaria frondosa)\textsuperscript{700} and the nucleoside anticancer agent gemicitabine was significantly more effective than with either drug alone.\textsuperscript{700} The cytotoxic and apoptotic-inducing abilities of steroids from the cold water starfish Ctenodiscus crispatus\textsuperscript{701} and the triterpene glycosides, including echinoside A, from Holothuria scabra and Cucumaria frondosa have been reported.\textsuperscript{702} Echinoside A and related saponin holothurin A inhibit dietary fat absorption and decrease the adipose tissue accumulation in mice,\textsuperscript{703} and typicosides (Actinocucumis typica)\textsuperscript{704} exhibit a strong immunomodulatory effect on mouse macrophages with marked increase in lysosomal activity and ROS formation.\textsuperscript{705} Complete NMR assignments have been reported for four pentasacide asterosaponins: thornasteroside A, versicoside A, anastoside B and asteronypentaglycoside sulfate (Asterias amurensis).\textsuperscript{706}

13 Mangroves

In addition to a series of mildly antioxidant glycosides, mangroves F–M 1374–1381, reported from the whole fruits of the mangrove Avicennia marina,\textsuperscript{707,708} seco-diterpene 1382 (Ceriops decandra),\textsuperscript{709} cinnamides 1383–1387 (Micromelum falcatum, mangrove associate),\textsuperscript{710} protolimonoids 1388–1394 (Xyllocarpus granatum),\textsuperscript{711} and limonoids 1395–1401, 1402–1404, 1405–
Further investigation of previously reported mangrove MNPs has identified avicequinone C (Avicennia marina) as a 5α-reductase-type 1 inhibitor, catunaregin (Micromelum faicatum) as an angiogenesis inhibitor, the cardiac glycoside nerifolin (Cerbera manghas) as the acicidal component of Panonychus citri, and that leaf extracts and purified components of Avicennia marina exhibit antibacterial activity with relevance to urinary tract infections. Finally, a new biomimetic synthesis and a structure–activity relationship study of the protein tyrosine phosphatase 1B inhibiting properties of the unusual dimeric alkylbutenolide paracaseolide A (Sonneratia paracaseolaris) have been reported.

14 Miscellaneous

Two studies of sea grass from the Egyptian Red Sea led to the identification of flavone xyloside 1424 (Thalassia hemprichii) and dihydrochalone diglycoside 1425 (Thalassodendron ciliatum) as antimicrobial and anti-influenza A virus MNPs respectively. Thelepamide 1426 is an unusual ketide-amino acid isolated from the annelid worm Thelepus crispus. The relative configuration of the alkaloid was determined by a combination of heteronuclear J-based configurational analysis and GIAO calculated chemical shifts and DP4 probability analysis. Mild cytotoxicity towards a leukemia cell line was also observed. The arenicins, antimicrobial peptides produced by the polychaet worm Arenicola marina, are constitutively expressed in a range of tissues in the organism suggestive that the peptides play a front-line role in defense against infections. Cypridina luciferyl sulfate 1427 appears to be a more stable storage form of cypridina luciferin, the luminescence precursor of the ostracod Cypridina (Vargula) hilgendorfii. The luciferin could be converted to luciferyl sulfate by action of crude extract of the organism, presumably containing a sulfotransferase, in the presence of 3′-phosphoadenosine 5′-phosphosulfate (PAPS, a sulfate donor), while the reverse reaction took place in the presence of adenosine 3′,5′-diphosphate, a sulfate acceptor.

Extracts of ovary tissue from Takifugu pardalis yielded a new tetrodotoxin analogue, 6-deoxyTTX 1428. The potent voltage-gated sodium channel blocker was also detected by LC-MSMS in other marine animals including snail and octopus. Alanine scanning of the hagfish (Myxine glutinosa) 12-amino acid residue antimicrobial peptide myxinidin has identified a number of critical residues for the observed biological activities and that judicious substitution with arginine led to the identification of more potent analogues. The 33-amino-acid residue peptide pardaxin (flatfish Pardachirus marmoratus) exhibited in vivo activity towards MRSA dermal infection and enhanced wound healing. A range of arsenic-containing lipids have been synthesised, providing valuable reference standards for future studies directed towards understanding the uptake, biotransformation and toxicity of these unusual MNPs.

15 Conclusion

In a recent review the number of new MNPs reported from a range of countries was analysed based on the location of the principal author for each publication. What is not apparent from this analysis is the location of the collecting sites for the organisms. This can be problematical as shown in an extreme example: one prominent MNP chemist based in the Mid-West of the USA, thousands of km from any coastal resource, collected widely (see Fig. 1).

With the biogeographic aspect of the MarinLit database now widely available an alternative perspective is available for viewing the collection data. It is now possible to search by region showing who is collecting where and hence the
interests that MNP chemists have in the various regions of the globe. The 50 years of collecting effort globally is depicted in Fig. 2. The red stars in Fig. 2 represent the collecting sites, described in ~9000 papers, from which ~25 700 new compounds have been obtained. The actual number of unique collection sites is less than the number of papers as multiple collections have often been made at the same sites. Fig. 2 displays those areas that have had high collecting pressures and those where there has been, for whatever reason, lower collecting pressures. An analysis has been made of the collecting effort globally by semi-decade since 1965. For convenience the globe was divided up into 22 regions or countries (see Table 1) and the published papers for each region compiled. Totals for papers (citing collection sites) describing new compounds from 1965 are also listed in Table 1 while Fig. 3 shows the incidence of discovery of new compounds in each region or country by semi-decade since 1965. It is worth noting that since 1965–280 papers contained no biogeographic data, not even a country or an ocean, to describe the origin of new compounds being reported. Fortunately, recent years have seen the increasing use of exact coordinates. The Japanese region, including Okinawa, has been the most productive region with 3877 compounds described. This was followed closely by China with 2915 compounds from the mainland with a further 525 compounds to be included if the regions of the South China Sea and Yellow Sea are also considered. But what is remarkable here is the rapid emergence of MNP chemistry using Chinese-based collections as seen in Fig. 3. Other regions where there have been extensive collections are in the Mediterranean (2358) (which includes the Mediterranean coasts of Spain and France, Italy, the islands of the Mediterranean, Greece, Turkey, Israel, Egypt, the Arabian Peninsula, Black Sea and the Mediterranean African coastlines), Australia (1854), the North (1539) and South (1548) Pacific islands and atolls, and the Gulf of Mexico, Caribbean Sea and islands (1524). Other regions that have been well explored include Taiwan (1350) and Maritime SE-Asia and Papua-New Guinea (1340).

The graph shows very clearly those countries that were most closely studied in the early years. Compounds of Japanese origin were prominent from the 1960s, but the search for MNPs was quickly taken up with compounds from the Mediterranean, North Pacific and North American regions appearing in the early 1970s, followed by Australian and Maritime SE-Asian compounds later in that decade. Prospecting activity in other parts of Asia was relatively slow to start and it was not really until the 1990s that compounds of Mainland SE-Asian, South Korean, Taiwan and Chinese origin started to appear. The output from these regions has rapidly accelerated since, particularly so in the case of compounds of Chinese origin. Fig. 2 and 3, taken in combination, provide a snapshot of the past efforts in marine natural products as well as current endeavours and highlights those areas of the globe that are currently under-explored.

Table 1: The 22 oceanic regions or countries used in the survey giving numbers of publications and new compounds discovered in each region/country over the period 1965–2014

<table>
<thead>
<tr>
<th>Country or Oceanic region</th>
<th>#Compounds</th>
<th>#Papers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacific Russia, sea of Japan</td>
<td>377</td>
<td>167</td>
</tr>
<tr>
<td>China</td>
<td>2915</td>
<td>942</td>
</tr>
<tr>
<td>South China sea and Yellow sea</td>
<td>525</td>
<td>203</td>
</tr>
<tr>
<td>Taiwan</td>
<td>1350</td>
<td>376</td>
</tr>
<tr>
<td>Japan, including Okinawa</td>
<td>3877</td>
<td>1570</td>
</tr>
<tr>
<td>South Korea</td>
<td>848</td>
<td>239</td>
</tr>
<tr>
<td>North Pacific islands and atolls</td>
<td>1539</td>
<td>576</td>
</tr>
<tr>
<td>South Pacific islands and atolls</td>
<td>1548</td>
<td>522</td>
</tr>
<tr>
<td>Maritime SE Asia, Papua-New Guinea</td>
<td>1340</td>
<td>502</td>
</tr>
<tr>
<td>Australia</td>
<td>1854</td>
<td>677</td>
</tr>
<tr>
<td>Mainland SE Asia (including East Malaysia)</td>
<td>457</td>
<td>173</td>
</tr>
<tr>
<td>South Asia</td>
<td>714</td>
<td>333</td>
</tr>
<tr>
<td>Indian ocean and islands</td>
<td>326</td>
<td>155</td>
</tr>
<tr>
<td>Mediterranean, Arabian Peninsula, Black sea</td>
<td>2358</td>
<td>876</td>
</tr>
<tr>
<td>Other African countries</td>
<td>456</td>
<td>154</td>
</tr>
<tr>
<td>Atlantic Europe and the Baltic sea</td>
<td>476</td>
<td>210</td>
</tr>
<tr>
<td>Atlantic ocean and islands</td>
<td>361</td>
<td>140</td>
</tr>
<tr>
<td>South American countries</td>
<td>538</td>
<td>210</td>
</tr>
<tr>
<td>Central America</td>
<td>245</td>
<td>86</td>
</tr>
<tr>
<td>Gulf of Mexico, Caribbean sea and islands</td>
<td>1524</td>
<td>571</td>
</tr>
<tr>
<td>North America</td>
<td>1382</td>
<td>520</td>
</tr>
<tr>
<td>Arctic and Antarctica</td>
<td>330</td>
<td>105</td>
</tr>
</tbody>
</table>
16 Acknowledgements

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17 References

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