Marine natural products†‡

John W. Blunt,*a Brent R. Copp,b Robert A. Keyzers,c Murray H. G. Munro,a and Michèle R. Prinsepd


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.‡
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.7 ‘Marine-sourced anticancer and cancer pain control agents in clinical and late preclinical development’ have been reviewed,8 and ‘New horizons for old drugs and drug leads’ were described.9 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.10 The putative microbial origin of sponge metabolites has been the subject of several reviews and articles.7–11 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.12 Polyketide biosynthesis in dinoflagellates has been reviewed.13 There have been comprehensive reviews for marine nucleosides,14 saxitoxin,15 and tetrodotoxin.16 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.17 ‘AlgaeBase: an on-line

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

Brent Copp received his BSc (Hons) and PhD degrees from the University of Canterbury, where he studied the isolation, structure elucidation and structural–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 diphosphate, protoxin phosphocalyculin C. 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\textsubscript{50} = 36 nM vs. P388), is 5000 times less toxic than calyculin C itself.

A Chinese 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 transformation-associated recombination (TAR) cloning approach was used to capture, activate and express a 67-kb non-ribosomal peptide synthetase (NRPS) biosynthetic gene cluster from Sacccharomonospora 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. Following a putative biomimetic synthesis of heronapyrrole D 19 the metabolite was then detected in cultures of the bacterium, thus validating this approach. Total synthesis of heronapyrrole C 20 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.\(^3^4\)

A deep-sea strain of *Streptomyces*, previously a source of spiroindimicins A–D,\(^3^5\) lynamycins A and D\(^3^5\) and piericidins\(^3^6\) has now led to isolation of a number of bisindole alkaloids; indimicins A–E 21–25, lynamycins F 26 and G 27\(^3^7\) and piericidin E1 28\(^3^8\) using the same modified A1BFe + C medium. Piericidin E1 28 was shown to be an intermediate in the biosynthesis of piericidin A1\(^3^8\) during identification of the biosynthetic gene cluster.

Growth of the strain in modified ISP3 medium yielded heronamides D–F 29–31.\(^3^9\) Violapyrones H 32, I 33, B 34 and C 35\(^4^0\) were obtained from *Streptomyces* sp. (starfish, *Acanthaster planci, Chuuk, Federated States of Micronesia*).\(^4^1\) Violapyrone C 35 has since been synthesised and the absolute configuration determined.\(^4^2\)

A study of the biosynthetic pathway for marineosins\(^4^3\) in *Streptomyces* sp. led to isolation of 23-hydroxyundecylprodiginine 36, 23-ketoundecylprodiginine 37, premarineosin A 38 and 16-ketopremarineosin A 39.\(^4^4\) Syntheses of 23-hydroxyundecylprodiginine 36 (both enantiomers and the
perdeuterated version) and of 23-ketoundecylprodigiosine 37 were reported, as was the feeding of synthetic prodigine analogues which led to the production of novel premarineosins, although these were not fully characterised. 45

The structure of meroclorin 36 has been revised to 40 and a biomimetic synthesis of (±)-meroclorin B 46 has been achieved, 49 while a study of the biosynthesis of the meroclorins 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 Pseudomonas sp. actinoalloteichus (formerly Dermacoccus niopepropionate, phenylacetic acid and \( p \)-coumaric acid and that

Investigation of the biosynthesis of sulfur-containing roseobactoicides 54, 55 produced by Phaeobacter inhibens indicated that these compounds arise from three subunits – dimethylsulfiniopropionate, phenylacetic acid and \( p \)-coumaric acid and that roseobactoicides regulate the symbiosis between \( P. \) inhibens and the microalga Emiliania huxleyi. 58 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. 83–103 The genera Verrucosiscopora and Vibrio also yielded new metabolites 173 and 174. 104, 105 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 light, 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. 115 A number of other total syntheses of bacterial metabolites have been reported. These include syntheses of the depsipeptides, solanamides A 116 and B 116, 117 and arenamides B 118 and C 119, 120 and synthesis of the nucleoside antibiotic A201A. 121, 122 Total synthesis of diixiamycin B 123 was achieved utilising electrochemical oxidation. 124 The alkaloid mansouramycin D 125, 126 was synthesised, as was 5-deoxytetrodotoxin. 127, 128 New biological activities have been reported for sporolide B 129 from Salinispora tropica, 130 for some butenolides 131, 132 and undecylprodigiosin 133 from Streptomyces strains. 134, 135 Biosynthetic studies have been conducted into various bacterial metabolites including arachidonic acid (in Aureispira marina), 136, 137 macrolactins 138 and bacillaene 139 in Bacillus marinus, 140 polybrominated aromatics 141 in Marine mononas mediterranea 142 and Pseudomonaeromonas spp. 143, lomaivitincins 144 in Salinispora pacifica 145, 146 (formerly Micromonospora lomaivitiniensis), tropodiethic acid 147 in (Phaeobacter inhibens), 148 sulfur volatiles 149 in (the Roseobacter clade) 150 and avaroferin 151 and putrebactin 152 in Shewanella sp. 153 Biosynthetic studies within the genus Streptomyces include those on thiocoraline in S. albus, 155 ikarugamycin, 156, 158 antimyccins 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 182 180 and D-I 183–185. 180 with mangromicin A 181 exhibiting potent antitypanosomal and radical scavenging (DPPH) activities. 168, 169 New divergolide congeners 189–192 were obtained from an endophytic Streptomyces strain 179 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 similanesis* 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 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. 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 chondrostereins I 215 and J 216 of which chondrosterein 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 engyodontiumone A–H 219–226 and the phenol derivatives 227–229 were derived from deep-sea derived *Engyodontium album*. Of these, engyodontiumones E–G 223–225 were obtained as racemates.\(^1\) The known polyketide aspergillus one B 196 was also isolated and was a potent inhibitor of settlement of *Balanus amphitrite* (B. amphitrite) larvae.\(^1\) 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.\(^1\)

*Neosartorya pseudo* [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.\(^1\) 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.\(^1\)

Biosynthetic feeding experiments on *Penicillium citrinum* using \(^{13}\)C 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 201 led to revision of the structure of citrinalin B to 242.\(^1\) 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.\(^1\)

Metabolites 245–254 were also obtained from the genera *Acremonium, Arthrinium, Ascotricha* and *Astrocystis*.\(^2\) 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. flavus*. The known compounds β-aflatoxin,\(^2\) paspalinine\(^2\) and leporine B\(^2\) were

\(^1\) This journal is © The Royal Society of Chemistry 2016

isolated and leporine A\textsuperscript{212} was prepared from the last of these. Configurations were established for each as 258-261 respectively and \textbeta-alatrem and leporine B were isolated for the first time as MNPs.\textsuperscript{213} Other metabolites isolated from the genus 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 Beauveria, Cladosporium, Cochliobolus, Curvularia, Dendrodochiu, Diaporthaceae, Dictomomycetes, Emericella and Eurotium.\textsuperscript{238-250} A pyrrolidinoindoline diketopiperazine dimer, cristatumin E, isolated from Eurotium herbariorum,\textsuperscript{251} appears to be identical to the previously reported eurocristatine.\textsuperscript{252} The genera Hansfodina, Humicola, Isaria, Neoartomya, Nigrospora, Paecilomyces and Paraconiothyrium also yielded the new metabolites 372-399.\textsuperscript{179,225-236} The genus Penicillium was the source of many other metabolites 400-461.\textsuperscript{259-278} Other genera to yield new the metabolites 462-520 were Pseudallescheria, Spicaria, Sphromastix, Stachybotrys, Talaromyces, Trichoderma, Xylaria and 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 (-)-protonobine A 522, (-)-protonobine B 523 (Aspergillus sp.)\textsuperscript{293,294} and (+)-cristatumin C 524 (Eurotium cristatum).\textsuperscript{295,296} Synthesis of the racemate of oxalicumone C (Penicillium oxalicum)\textsuperscript{297} followed by resolution by chiral HPLC and examination of experimental and calculated ECD data, resulted in the configuration of the natural product being assigned as (S)-525.\textsuperscript{298} Culture of a strain of Aspergillus clavatus isolated from the hydrothermal vent crab 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{299} that was isolated for the first time from a natural source and named as clavatusidine C 526. The fungus did not produce clavatustide C 526 when cultured in the absence of zinc.\textsuperscript{300} Percicinone E\textsuperscript{301} (Periconia byssoides) occurs as an enantiomeric mixture in nature and synthesis of the preferred enantiomer (−)-pericosine E 527 has been reported.\textsuperscript{302} First syntheses of a number of fungal metabolites achieved include those of secalonic acids A\textsuperscript{303} (Paecilomyces sp.)\textsuperscript{304} and B\textsuperscript{305} (Gliocladium sp.)\textsuperscript{306,307} (+)-sorbiterrin A\textsuperscript{308} (Penicillium terrestre),\textsuperscript{309} (−)-auroamide C\textsuperscript{310} (Penicillium aurantiogriseum),\textsuperscript{311} calcareitides A–C\textsuperscript{312} (Calcarisporium sp.),\textsuperscript{313} (−)-aspergilazine A\textsuperscript{114} (Aspergillus taiwanchensis),\textsuperscript{315} aspinin\textsuperscript{316} (Aspergillus versicolor),\textsuperscript{317} cochliomycin B\textsuperscript{318} (Cochliobolus lunatus),\textsuperscript{319} dendroides\textsuperscript{320} (Dendrodochiu sp.),\textsuperscript{321} B\textsuperscript{322} and E\textsuperscript{323} paecilocin\textsuperscript{324} (Paecilomyces variotii),\textsuperscript{325} penicimonoterpenes\textsuperscript{326} (Penicillium chrysogenum)\textsuperscript{327} and (+)-penostatin E\textsuperscript{327} (Penicillium sp.)\textsuperscript{328}. The benzaldehyde derivative isoretetrahydro-auroglauzin\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} Oxirapentyns A\textsuperscript{332,333} and B\textsuperscript{334} exhibited growth stimulatory effects on seedling roots of barley and wheat\textsuperscript{335} while isoechinulin A\textsuperscript{336,337} was a strong inhibitor of settlement of larvae of the barnacle B. amphitrite.\textsuperscript{338} 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 (Aspergillus sclerotiorum and A. clavatus) induced biosynthesis of metabolites that were not produced under normal culture conditions: A. sclerotiorum produced aspochracin\textsuperscript{340,341} when stressed with copper and produced stephacidin A\textsuperscript{342} and natoaamides B\textsuperscript{343} and F\textsuperscript{344} under normal culture conditions whilst A. clavatus produced the acetophenone derivative clavatol\textsuperscript{344,345} under stress conditions and deoxytroptoquivaline\textsuperscript{346} and tryptoquivaline A\textsuperscript{146} 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 Alternaria and 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 (Sargassum)-derived Aspergillus species also produced a cyclic peptide, psychrophilin E 531.\textsuperscript{350}
Aspergillus flavipes was the source of the aromatic butyrolactones, flavispen A 532 and B 533 and the previously synthesised 534,535 and 535,532 of which flavispen 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.534 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 1 538 were obtained from endophytic Dothiorella sp. along with three known analogues.535 Of these analogues, dothiorelone G 538 is actually the same as the previously reported cytosporone R,537 also obtained from a mangrove associated species (Leucostoma persoonii). Penipherones A–D 539–543 were obtained from Penicillium dipodomyicola. Of these, penipherone A 539, 540 occurs as a racemate and was separated into its enantiomers by chiral HPLC while penipherones 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 544539 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 545.540 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.541 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.542 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, Rhizidhysteron, Stemphylium and Xylariaceae.543–588

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 A 636 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.549 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 chymotrypsin590 and the acetylenic lipopeptide kurahyne 639 an inhibitor of the HeLa cell line and inducer of apoptosis.591

Mooreamide A 640 is a cannabinomimetic lipid obtained from Moorea bouillonii and is the most potent marine-derived inhibitor of the neuroreceptor CB2, reported to date.592 Two new aplysiazotaxin analogues, 3-methoxyaplysiazotaxin 641 and 3-methoxydibromoaplysiazotaxin 642 were isolated from Trichodesmium erythraeum and 642, along with the co-isolated known debromo analogues debromoaplysiazotaxin593 and
for itralamide B\textsuperscript{415} and coibamide A\textsuperscript{416} have indicated that the structures of these natural products require revision.\textsuperscript{417,418} Grassypeptolides A–C\textsuperscript{419} were shown to selectively inhibit the dipeptidyl peptidase (DPP8) protease and molecular docking studies indicated that grassypeptolide A binds to the enzyme at two different sites.\textsuperscript{420} Gallinamide A\textsuperscript{421} was shown to be a potent and selective inhibitor of the human cysteine protease cathepsin L.\textsuperscript{422} A genome mining approach was utilised to identify three proteusin rSAM epimerases, enzymes which install multiple \(\varepsilon\)-amino acids in genetically encoded peptide chains, from three strains of cyanobacteria including a marine-derived \textit{Pleurocapsa} strain.\textsuperscript{423} A genome mining approach was also used to show that LanA peptides, linear precursor peptides of lanthionine-containing peptides (lanthipeptides),\textsuperscript{424} are highly diverse among different systems and that closely related lanthipeptide synthetases can be associated with quite different substrate sets.\textsuperscript{425}

### 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 \textsuperscript{658}, from an \textit{Amphidinium} species displayed very potent and selective growth promotion activity on murine bone marrow stromal ST-2 cells. Feeding experiments with \(^{13}\)C single and double labelled acetate indicated that polyketide \textsuperscript{658} comprises a linear C22 chain with two irregular C1 sites (in the terahydrofuran moiety) and four C1 branches.\textsuperscript{426} \textit{Dinophysis acuminata} was the source of the macrolide acuminolide A \textsuperscript{659} which was non-toxic to human tumour cell lines (HTCLs) but a potent stimulator of actomyosin ATPase activity.\textsuperscript{427} Belizentrin \textsuperscript{660}, a 25-membered macrolactam obtained from \textit{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.\textsuperscript{428}

Other genera of dinoflagellates from which the new metabolites \textsuperscript{661–675} were isolated include \textit{Amphidinium}, \textit{Azadinium}, \textit{Karenia} and \textit{Vulcanodinium}.\textsuperscript{429–436} Tentative structures were assigned to ovatoxin-g \textsuperscript{676} and an isomer of palytoxin, the so-called isobaric palytoxin.\textsuperscript{437} The absolute configuration of amphidinin A\textsuperscript{438} was determined as \textsuperscript{677}.\textsuperscript{439} Synthesis of genetically predicted saxitoxin intermediates with identification and quantification in the dinoflagellate \textit{Alexandrium tamarense} and the cyanobacterium \textit{Anabaena circinalis} supports the genetically proposed biosynthetic route\textsuperscript{440} to saxitoxin.\textsuperscript{441} Metabolomic and proteomic analyses indicated that \textit{Karenia brevis} exhibited allelopathy against two competitor diatoms \textit{Asterionellopsis glacialis} and \textit{Thalassiosira pseudonana}. The former, which co-occurs with \textit{K. brevis}, exhibited somewhat more robust metabolism while in the latter, energy metabolism was disrupted and cellular protection mechanisms were impeded.\textsuperscript{442} Other studies examined the biosynthesis of brevetoxin,\textsuperscript{443,444} brevisamide\textsuperscript{445,446} and the genetics of toxin production in \textit{Alexandrium catenella}.\textsuperscript{447}

Other new metabolites \textsuperscript{643–655} were obtained from the genera \textit{Anabaena}, \textit{Lyngbya}, \textit{Moorea}, \textit{Oscillatoria} and \textit{Symphloca}.\textsuperscript{496–498} The absolute configurations of coibacins A and B\textsuperscript{499} have been determined as \textsuperscript{656} and \textsuperscript{657} respectively by total synthesis.\textsuperscript{494} Syntheses of biselyngbyolide A\textsuperscript{495} (\textit{Lyngbya (Moorea)} sp.),\textsuperscript{496} apratocin C\textsuperscript{497} (\textit{Lyngbya (Moorea)} sp.),\textsuperscript{498} malevamide D\textsuperscript{499} (\textit{Symphloca hydnoides}),\textsuperscript{500} micromide\textsuperscript{501} (\textit{Symphloca sp.}),\textsuperscript{502} 12-\textit{epi}-hapalindole Q isonitrile\textsuperscript{503} (\textit{Hapalosiphon laingii}), the latter, energy metabolism was disrupted and cellular protection mechanisms were impeded.\textsuperscript{442} Other studies examined the biosynthesis of brevetoxin,\textsuperscript{443,444} brevisamide\textsuperscript{445,446} and the genetics of toxin production in \textit{Alexandrium catenella}.\textsuperscript{447}
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, bisindole alkaloids isolated from Caulerpa racemosa which are biosynthetically related to the well-established green algal metabolite caulerpin, also from a Caulerpa sp.

Caulerpin featured in studies of antinociception mechanisms and the antituberculosis activities of caulerpin and synthetic analogues.

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, 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.

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, 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.

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, prenylated guaianes, and a xenicane, known analogues and an ethoxylated artifact as well. Three new diterpenoids, a dolabellane, a xenicane, and a prenylated guaiane with five previously characterised compounds were characterised from Mediterranean collections of several Dictyota spp. Three new, and three known dolabellane diterpenoids, were isolated from a Brazilian D. pfalli, and a single crystal X-ray analysis established the absolute configuration of the known 10,18-diacetoxy-8-hydroxy-2,6-dolabelladiene. The meroterpenoids sargachromanol Q and R along with the known sargachromanol J resulted from re-examination of the original extract from Sargassum siliquastrum, while thunberol, is the only new sterol of several isolated from the Chinese Sargassum thunbergii.

Typical brown algal phlorotannins such as eckol and dieckol have stimulated research into a wide range of topics – heme oxygenase-1 expression, oxidative stress, anti-adipogenic activity, anti-HIV-1 and antibacterial activity. Among the studies on the anti-inflammatory properties of phlorotannins 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. The potential therapeutic properties of fucoxanthin and derivatives have been studied as have those of polyphenols such as octaphlorethol and mono- and diacylglycerols.
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 \(^{698}\)–\(^{699}\), halogenated allenes and alkynes \(^{700}\)–\(^{709}\), \(^{710}\)–\(^{711}\) halogenated monoterpenes \(^{712}\)–\(^{713}\), \(^{714}\)–\(^{715}\) sesquiterpenes \(^{716}\)–\(^{719}\), unusual \(^{720}\) seco-laurokamurone \(^{721}\), diterpenes \(^{722}\)–\(^{725}\), brominated aromatics \(^{726}\) and the mahorones \(^{727}\)–\(^{728}\), unusual 2,3-dibrominated 2-cyclopentenones. \(^{729}\)

The use of rapid dereplication tools (UHPLC–PDA–HRMS, 2D HSQC NMR, software tools and databases) for identification of the allenes \(^{730}\) and \(^{731}\) and LC-UV-MS-SPE-NMR for the monoterpenes \(^{732}\)–\(^{735}\) were notable features. A synthesis\(^{736}\) of the brominated sesquiterpene aldingenin C\(^{737}\) showed that the original structure was incorrect, and it was suggested that aldingenin C was probably the known compound caespitol.\(^{738}\) A synthesis\(^{739}\) of the proposed structure of prevezol B\(^{740}\) has shown that the original structure was incorrect. Of the \(~70\) 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.\(^{741}\) An asymmetric total synthesis of \((\pm)\)-bermudynol\(^{742}\) has been accomplished,\(^{743}\) while a total synthesis of the snyderane \((\pm)\)-luzofuran\(^{744}\) has also been made.\(^{745}\) The anti-inflammatory potential of \(5\beta\)-hydroxyypalisadin B\(^{746}\) from \(Laurencia\) \(snackeyi\) has been demonstrated in LPS-stimulated RAW 264.7 macrophages\(^{747}\) and LPS-induced zebrafish embryo.\(^{748}\)

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.

A synthesis\(^{749}\) of the brominated sesquiterpene aldingenin C\(^{750}\) showed that the original structure was incorrect, and it was suggested that aldingenin C was probably the known compound caespitol.\(^{751}\) A synthesis\(^{752}\) of the proposed structure of prevezol B\(^{753}\) has shown that the original structure was incorrect. Of the \(~70\) 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.\(^{754}\) An asymmetric total synthesis of \((\pm)\)-bermudynol\(^{755}\) has been accomplished,\(^{756}\) while a total synthesis of the snyderane \((\pm)\)-luzofuran\(^{757}\) has also been made.\(^{758}\) The anti-inflammatory potential of \(5\beta\)-hydroxyypalisadin B\(^{759}\) from \(Laurencia\) \(snackeyi\) has been demonstrated in LPS-stimulated RAW 264.7 macrophages\(^{760}\) and LPS-induced zebrafish embryo.\(^{761}\)
Sphingoids and taurinated fatty acids and a large number of polyacetylenes 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 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 (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, halogenated alkenes and an amide 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. Reisolation of cyclophilide A from a deep sea Discodermia japonica (Ambon, Indonesia) indicated potent cytotoxicity (IC50 = 60–320 nM). Notably, the viability of cell lines treated with callyspongiolide was not affected by QVD-OPh, a known caspase-inhibitor, suggesting the test compound induces cellular toxicity in a caspase-independent manner.

The stellatolides A–G are a family of cyclodepsipeptides from a Madagascan Ecionemia acervus. The full stereochimical 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 l-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, Pipetela, Reniochalina, Stylissa, Suberites and Theonella have also yielded a large number of peptides. Callyspongiolide 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 (IC50 = 60–320 nM). Notably, the viability of cell lines treated with callyspongiolide 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*, 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. A diketopiperazine 808, a 3-alkylpiperidine 809, seven manzamine-type alkaloids 810–816 and seven 3-alkylpyridines 817–823 have been isolated from the sponge genera *Callyspongia*, *Acanthostrenglyophora* and *Topsentia*. *Axinysa aceatelea* (Okinawa) was the source of protoaculeine B 824 that is a putative novel N-terminal residue for the peptidic toxins aculeines A–C. The structure of this polyanime compound, including identifying its attachment to the peptidic toxins themselves, was determined from detailed synthetic and mass spectrometric studies.

Other indole 825–829 and β-carboline 830–837 alkaloids were reported from *H. okadai* and *Aaptos* sponges. A biomimetic total synthesis of (±)-dictazole B, isolated from the shallow water sponge *Smenospongia cerebriformis*, has been performed using artificial light to facilitate the [2 + 2] photochemical cycloaddition reaction between aplysinopsin 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 cycloapsinopsins. Fifteen new aaptamine alkaloids 838–852 have been reported from *Aaptos* sponges while a new polycyclic aromatic alkaloid 853 came from an *Ancorina* sp. An unbiased screen of a library of 480 sponge extracts identified the surprisingly simple compound girolline from *Stylissa 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 impairing 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. Guanidine-derived alkaloids 854–863 were reported from *Monanchora pulchra*, *Acanthella cavernosa* and *Biemna labioutei*, while several brominated hymenialdisine-type 864–867 and oridon/oriodin dimer-type 868–877 came from *Callyspongia* sp. and *Agelas* sp., respectively. A highly scalable, multi-gram synthesis of axinellamines A and B (*Axinella* sp.) 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. 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 878–880 and ageliferin and congeners 881–883 as shown here, based upon X-ray crystal structures. Moreover, the massadines had been thought to be rearrangement products from the agelifers, however the absolute configurations of the two series of compounds are antipodal, hence indicating enantiodivergent biosynthetic pathways in vivo to these bromopyrrole alkaloids and invalidating the so-called “Scheuer-hypothesis” for their formation.

Bromotyrosine metabolites 884–893 have been isolated from *Callyspongia*, *Aplysinella* and *Dendrilla* sponges, while *Haliclona*, *Petrosia*, *Phoriospongia* and *Dragmacidon* sponges have yielded substituted purine/pyrimidine compounds 894–898. As usual, sponges continue to be a valuable reservoir of new terpenoid metabolites. Merosesquiterpenoids 899–930 came from the sponge genera *Aka* (*Siphonodictyon*), *Dysidea*, *Dactylospongia* and *Xestospongia*. In particular, xestolactone A 931 and xestosaprol O 932 were isolated from *Xestospongia vansoesi* (Palawan Is., Philippines). Xestosaprol O is twenty times more potent as an inhibitor of indoleamine 2,3-dioxygenase (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.
A meroterpenoid 933 has been reported from Sarcothragus spinulosus.286 Similarly, Axinysa, Dysidea, Ircinia and Topsentia sponges were the sources of a number of sesquiterpenoids 934–964,987–991 some of which had been cleaved, while diterpenoids were obtained from Diacarnus megaspinorhabdosa 965–970,992 Spongia sp. 971–973991 and Darwinella oxedata 974–982.994 A large number of sesterterpenoids 983–1011 were reported in 2014 from the sponge genera Clatharia, Coscinoderma, Hippopospongia, Hyrtios, Petrosaspomgia, Phorbas and Scalarispongia.989,995–999 As always, sponges yielded a variety of steroids 1012–1019,994,995,996,997 and degraded steroids 1020 and 1021,994 and degraded steroids 1022–1024995,996,997 from species of Echinocloathria, Corticium, Haliclona, Ircinia, Petrosia, Plakortis 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 IC50 = 2.9 μM while 1026 was almost 100 times less potent (IC50 = 240 μM), indicating the steric importance of the 9-OH in abrogating activity.997

Cinanthrenol 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 IC50 = 10 nM, as well as altering estrogen-responsive gene expression.608

A series of triterpenoids 1028–1032 have been reported from Jaspis stellifered and Siphonochalinia siphonella.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.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 Plakortis 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 poribacteria 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.613 A comprehensive metagenomic survey of the microbial community associated with the metabolite-rich sponge Theonella swinhoei has uncovered a new bacterial genus, Entothoeonella. This genus is a member of the new candidate phylum Tectomicrobia and appears to be a widespread sponge endosymbiont across many diverse sponge species. Moreover, biosynthetic gene cassettes suitable for production of many “Theonella swinhoei” NRPS and PKS compounds, including the onnamide,614 polytheonamide,615 keramamide616 and cyclotheonamide617 classes, have been identified in the microbial genome.618 A metagenomic approach identified the gene cassette for calyculin A (Discodermia calyx) 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).21,22 again underscoring the importance of symbiotic microbial communities in the production of “sponge” metabolites. The microtubule-stabilising mode of action of laulimalide619 and peloruside A620 has been established through the use of high-resolution crystal structures of the compounds bound to tubulin,620 while aaptamine621 has been shown to have protective effects against cisplatin-induced kidney damage,622 and also prevents photoaging.623 A polybrominated diphenylether624 (Dysidea granulosa) has been shown to inhibit hepatitis C non-structural protein NS3 helicase, a validated antiviral target.625 The four bromotyrosine compounds ianthelliformisamine A–C (Suberea ianthelliformis)626 and spermatinamine (Pseudoceratina sp.)627 were selective and potent inhibitors of human carbonic anhydrase IX (IC50 = 0.20–0.36 μM), with implications for maintaining cellular pH homeostasis and hence application in a variety of disease states.628 The sesterterpenoid heteronemin (Hyrtios sp.)629 inhibited trans-activation response DNA-binding protein 43 kDa (TDP-43), a key factor of several neurodegenerative states. Heteronemin binds to TDP-43 (kD = 270 nM) and altered the aggregation state and localisation of this important neurochemical target.630 The first total syntheses of an all-(Z) octodeca-pentene-3-one (Callyspongia sp.),631,632 strongylodiol G (Stronglylophora...
sp.),
4,515,614 bitungolide B (Theonella swinhoei),
4,515,616 plakortone L (Plakortis clathrata),
6,57,618 epiplakinic acid F (Plakinastrella sp.),
6,59 and its methyl ester (Plakortis halichondrioides),
6,60,641 gracilooether F (Plakinastrella mamilarlis),
6,62,641 laumycins A and B (revised 1033
and 1034, Fascaplysins sp.),
6,641 polydiscamides B–D (Ircinia sp.),
6,647 callipellin M (Latrunculia sp.),
6,648,649 topsentolide A2 (revised 1035, Topsenta sp.),
6,55,613 penarolide sulfate A2 (Penares sp.),
6,615 haliclorensin C (Haliclorella tulearensis),
6,615,617 nakinadine A (revised 1036, Amphimedon sp.),
6,656,67 plakortone A (Plakortis lutea),
6,656,679 (+)-cyanidendrine A (Axinella cylindrata),
6,656,671 ianthelli-formaminasines A–C (Suberea ianthelliformis),
6,62,663 tokaradine C (Pseudoceratina purpurea),
6,664,667 (+)-hemifusilatin 3 (revised 1037, Verongia sp.),
6,71,666 trachycladamines A and B (Trachycladus laevispirulifer),
6,71,669 cyclospongaquinone-1 (Stelospongia conulata),
7,71,671 deoxydesmasponginaquinol (revised 1038) and deoxydesmasponginaquinone (revised 1039, Euryagorgia sp.),
6,73,673 plakamin B (Plakina sp.),
6,73,675 and clionamine D (Cliona celata) have all been completed.

The total syntheses of the putative structures of 15-
oxopuupehenoic acid (Myrtios sp.),
6,76,767 and astakolactin (Cacos-
spionga scalaris) have also been achieved but the spectro-
scopic data call into question the original identi-
fied 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
highlighted in a study that found that coral and
highlighted in a study that found that coral and
juveniles were repelled from reefs that were over-
dominated.68 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 – alkaloids are only rarely
isolated. In 2014 there were seven examples of alkaloids isolated
from soft corals, comprised of an unusual diketopiperazine
1040
from Menella kanisa,
4,465 and six tetraprenylated purines, malon-
ganenone L–Q 1041–1046, from Echinogorgia pseudosoap.466 In
contrast, cnidarians of the order Zoantharia (zoanthids) were the
sources of five new parazoanthine congener
1047–1051 (Para-
zoanthus axinellae).685 These structures were established using a
metabolomics model, with LCMS/MS fragment analysis being used
to define structures and LC-ECD employed to assign absol-
ute configuration (to 1047, 1048 and 1050).

Other zoanthamine analogues, 1052–1058, were isolated from
Zoanthus sp.660,665 and Zoanthus kuroshio686 as well as a new
42-hydroxypalytoxin diastereomer 1059 from Polythoa
bucculosa.689 Previous studies of an extract of Polythoa toxica identi-
ﬁed the major toxin to be a 42-hydroxy analogue of palytoxin 1060
however the conﬁguration at positions C-41 and C-42 remained unresolved.690 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 P. bucculosa as being (42S)-
hydroxy-(50S)-palytoxin 1059. The relative afﬁnity of palytoxin,
1059 and 1060 towards a mouse anti-palytoxin monoclonal
antibody identiﬁed palytoxin to have the most potent Kd (nM),
while 1059 and 1060 were approximately one and three orders
of magnitude less potent respectively. Similar relative levels of
cytotoxicity towards keratinocytes were also observed, with paly-
toxin 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 Ca2+ coordination.691

A series of butenolide and cyclopentenones 1061–1072 were
reported from Subergorgia suberosa and Sinularia sp. soft
4,692,694 A comprehensive investigation of a Bahamian
collection of Pseudopterogorgia rigida identiﬁed a chlamigene
1073 and seven bisabolanes 1074–1079 as new sesqui-
4,695 The study also reported an extensive number of co-
metabolites 1080–1083 that had been previously reported from
terrestrial plants or as semi-synthetic derivatives 1084–1090.
Other sesquiterpenes 1091–1110 have been reported from
Rumphella antipathies,696,698 Lemnalia philippinensis,699 Menella
kanisa,700 Nepthhea erecta,701 an unidentified gorgonian,702 Den-
dronephthya sp.,703 Sinularia kavarattensis,748 Echinogorgia sar-
sapo reticulata775 and Anthogorgia ochracea.796 Of these
sesquiterpenes, rumphellaoic acid A 1093697 contains a unique
skeleton, while shagenes A 1102 and B 1103702 and ochraceno-
A 1103706 contain rarely reported skeletons. In the case of the
ochracenoid A, absolute conﬁguration was assigned by use of
TDDFT calculated ECD data.

A South China Sea collection of Anthogorgia caerulea yield-
ed, in addition to two known avermectin macrolides, aver-
mectin B, and 22,23-dihydroavermectin A1a,707 two new
congeners B1c 1111 and B1c 1112.708 All four MNPs exhibited
moderate antifouling activities.

Of the thirty-six cembrane related metabolites 1113–1149 re-
ported from cnidarians in 2014,709–722 seccorasmuul 1113
(Lobophytum crassum)727 is notable as it is derived from the
cebrane skeleton via an unusual C-11–C-12 bond cleavage, sinu-
gyroasoline A 1114 (Sinularia gyrosa) is an unprecedented C-4
necrombranoid,728 tortuosenes A 1146 and B 1147 (Sarcophyton
tortuosum)731 represent the first examples of cembranoids con-
taining a C-2–C-20 ring closure, and sinularbols A 1148 and B
1149 (Sinularia arborea) 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
briarine-skeletoned MNPs 1150, gemmacaloids AS–AY 1151–1157,
briarenolide J 1158, juncellolides M–P 1159–1162, fra-
gilisins A–L 1163–1174, dolfulisins A 1175 and B 1176, bri-
violides A–J 1177–1186 and anthrogonoid A 1187 were reported


This journal is © The Royal Society of Chemistry 2016
from octocoral species *Pennatula aculeata*, *Dichotella gemmacea*, *Junceella gemmacea*, *J. fragilis*, *Ellisella dolfusi*, *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 *Junceella gemmacea* (South China Sea) and *J. fragilis* (also South China Sea), junceellolide O and fragilisinin G 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 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, Muricella sibogae (sibogins A and B, Cladiella sp. (cladieunicellin J, Klyxum molle (klymollins T-X, Cladiella sp. (cladieunicellin M-Q, Cladiella kremptf (kremptfins N-R,
1202–1206, 735,736 and Cladiella hirsuta (hirsutalin N–R, 1207–1211).727 Readers should note that cladieunicellin N 1198 is a structural duplicate of the previously reported Klyxum molle metabolite klymollin Q.738 exhibiting identical spectroscopic, spectrometric and chiroptical properties and that the structure elucidation of cladieunicellin M–Q also led to revision of configuration at C-7 of the structure of litophynin I diacetate to that shown in 1212.

Further examples of diterpenoids, 1213 and 1214,739,1215 and 1216,740 cespitulones A 1217 and B 1218,741 dihydroxysarsolenone 1219, methylidihydroxysarsolenonate 1220, and sarsolilides B 1221 and C 1222,742 have been isolated from soft corals of the genera Cespitularia, Xenia, and Sarcophyton. Structure elucidation and determination of absolute configuration of 1219 and 1220 led the authors to propose a revision of the relative configuration at C-2 of the previously reported MNP sarsolenone (to that shown 1223).743 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 sarcohrechindins A–J 1224–1233.744 In addition, three prostanoids 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 1239–1244746,747 and hydroxylated/polyhydroxylated sterols 1245–1267747–753 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 epoxygersterol 1266–1271 (Anthopleura midiori),749 investigation of MNP chemistry of sea anemones and hydrozoa has identified two new cytolsins (3013 and 3375 Da) from the tentacles of the hydrozoan Olindias sambauquensis755 and PhcrF1x1, 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 (Anemonea viridis) to show specificity towards arthropod voltage-gated sodium channels by binding to one of the transmembrane clefs of the channel α-subunit,757 while AdE-1 (Aiptasia diaphana) 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 cysteine 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 phosphatidyetholine 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 alkaldoids N-(3-guanidinopropyl)-2-(4-hydroxyphenyl)-2-oxoacetamide (Campanularia sp.)762,763 and (±)-tubastrinolide B (Tubastreaa sp.),764,765 butenolide (+)-hydroxyancespensolide (Pterogorgia ances),766,767 and diterpenes sandresolide B,768 amphillectolide769 and (+)-ileabethoxazole770 (Pseudopterogorgia elisabetae)771,772 have been completed. Conversion of bipinnatin J (Pseudopterogorgia bipinnata)773 to intricarene (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-deoxyprovidencin.776 Clarification of the structure of the cladiellin diterpene sclerophytin F (Sclerophythum capitalis)777 has been an ongoing issue, with Friedrach and Paquette in 2002 proposing the structure should be revised to be the (3S) diastereomer of sclerophytin 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-dynes has been reported.780 Hippuristanol (Isis hippocrus)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 (S. maxima) were found to be modest to poor inhibitors of NF-κB transcriptional activation, structurally similar 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, flexible exibilide exhibits in vivo anti-neuroinflammatory activity in rats, 11-epi-sinulariolide acetate inhibits carcinoma cell migration and invasion by suppressing a number of phosphorylation-dependent pathways, 13-acetoxyxarcocrassolide 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 were isolated from the Patagonian bryozoan Aspidostoma giganteum. Aspidostomide E exhibited moderate inhibition of the 786-O renal carcinoma cell line. Aspidazide A was 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 were obtained from Bugula neritina and exhibited selective but weak activity against two HTCLs. The same sample yielded several sterols. Convolutamidine A 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. 37-epi-

Azaspiracid-1 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 Thrudillia hopei afforded new nor-diterpene aldehydes in addition to known congeners thuridillin A, B and C. The mollusc feeds on the green alga Derbesia tenuissima, extracts of which contain a known epoxyalactone, supporting the assumption that are mollusc transformation products. Acetylenic alcohols 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 fennebrin A and B were isolated from both the nudibranch Jorunna funebris and the sponge Xestospongia sp. The substructurally-related isosquinoline was only identified in the sponge extract. New diketopiperazines 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 and -obtusane (Aplysia oculifera) and an anti-neuroinflammatory diterpene dactylo-diterpenol acetate (A. dactylomela). 6-Bromoisatin, 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, synthetic tambjamine analogues show enhanced tumour cell antiproliferative and chloride transport properties, and lamellarin D (Lamellaria sp.) induces senescence in cancer cells, in a process that includes the generation of intracellular ROS and requires the presence of topoisomerase 1. Biosynthesis of long chain polysaturated 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 Δ8-desaturase. A new example of an α4/7-conotoxin, α-BnIA 1310 was isolated from crude venom of the molluscivorous cone snail Conus bandanus. Peptides with the same sequence, Mr1.1 and Bn1.1, were previously identified by PCR amplification of venom duct cDNA from molluscs C. marmoratus and C. bandanus. 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 (disulphide connectivity not determined) and three post-translational modifications comprised of a bromotryptophan, γ-carboxy glutamate and amidated aspartic acid residues. 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. A short cyclic hexapeptide Vi804 1313 was isolated from crude venom of C. virgo and the solution structure of it and the ΔW3 synthetic analogue explored by NMR spectroscopy. 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 Nα subtype selectivity of three previously reported C. consors γ-conotoxins, γ-CNVI, γ-CNVIC and γ-CNVID. Further studies have reported on the structure and activity of dicarba analogues of α-RglIA, the influence of disulphide connectivity on structure and bioactivity of α-TxIA, the influence of acetylcholine to affect the binding of α-MII αt nAChRs, the neuronal target selectivity of the Conus textile T-superfamily peptide TxVc, and the Ca2+-activated K+ (BK) channel selectivity of the unusual M superfamlly conotoxin Vt3.1.

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, amino alcohols 1316–1322, new didemnaketal congeners 1323, 1324 and 1325, 1326, halogenated alkaloids 1327 and 1328, a new rubrolide (R) 1329 (that unfortunately shares the same letter designation as a related metabolite reported from Aspergillus terreus17), pyrdoacridine enemidine A 1330 and sulfated steroids 1331 and 1332. Noteworthy was the isolation, structure elucidation and synthesis of a rare example of a modified norseside bearing a 5-thiomethyl substituent 1333. The same study also led to the reassignment of structure of a known sponge metabolite hamiguanosinol60 from the enol tautomer to the guanosine keto tautomer 1334. The tanjundigines A 1335 and B 1336, novel dibromindoole enamide alkaloids isolated from Diazona cf. formosa exhibit potent cytotoxicity (<1–2 μM) towards 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 phylegetic groups that in turn may contain further cryptic species. 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. 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.) to 1337, requiring stereochemical inversion of the C-10–C-20 spiroacetal domain of the MNP. Such a revision may be of relevance to the ongoing revision of the (stereo)structure of didemnaketal A. Syntheses of the reported structures of polycitols A and B (unidentified ascidian) and (+)-didemsmierinolipid C (Didemnum sp.) 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.) to 1338 and confirmation of the revised structure of haouamine B (Apidium haouarium). While the structures of distomadines A and B (Pseudodistoma aureum) and synoxazolidinones A and B (Sinoicium pulmonaria) 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 synxazolidinone C being particularly potent as both a growth and adhesion inhibitor. 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 eusynsteylalamide B (Didemnum candidum, originally isolated from Eusynsteyla latericrus) as a moderate cytotoxin (IC_{50} 5 mM) causing cell cycle arrest in G2/M and inducing apoptosis. The potently cytotoxic macrolide iejimalide C (Eudistoma cf. rigida) joins congeners iejimalides A and B as being identified as an inhibitor of the vacuolar-type ATP-driven proton pump (H^+ -ATPase). After 24 h treatment, cells also exhibited actin aggregates, but as the MNP does not inhibit actin polymerisation 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.

12 Echinoderms

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

A number of new saponins were identified in extracts of the Australian sea cucumber Holothuria lessoni using solely LC-MS/MS metabolomic techniques. 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. 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. 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.

13 Mangroves

In addition to a series of mildly antioxidant glycosides, marine MNPs 1374-1381, reported from the whole fruits of the mangrove Avicennia marina, seco-diterpene 1382 (Ceriops decandra), cinnamides 1383-1387 (Micromelum falcatum, mangrove associate), protolimonoids 1388-1394 (Xylocarpus granatum), limonoids 1395-1401, and asteroypentaglycoside sulfate (Asterias amurensis).
1408,944 1409–1418,953 1419–1422936 and 142397 (X. rumphii and X. granatum) were also isolated from mangroves or their associates. The absolute configuration of the unusual spiro-seco-abietane decandrinin 1382 was secured via analysis of experimental and calculated ECD and ORD chiroptical data909 while of the limonoids reported, the structures of xylorumpphin G 1398,922 xylorumppyridine A 1402,931 granatumin L 1409946 and granatumin Y 1422936 were established by single crystal X-ray diffraction studies.

Further investigation of previously reported mangrove MNPs has identified avicequinone C (Avicennia marina)948 as a 5α-reductase-type 1 inhibitor,949 catunaregin (Micromelum falcatum)928 as an angiogenesis inhibitor,929 the cardiac glycoside nerifiolin (Cerbera manghas)922 as the acicardial component of Panonychus citri,923 and that leaf extracts and purified components of Avicennia marina exhibit antibacterial activity with relevance to urinary tract infections.924 Finally, a new biomimetic synthesis925 and a structure–activity relationship study of the protein tyrosine phosphatase 1B inhibiting properties926 of the unusual dimeric alkylbutenolide paracaseolide A (Sonneratia paracaseolaris)937 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)928 and dihydrochalcone diglycoside 1425 (Thalassodendron ciliatum)929 as antimicrobial and anti-influenza A virus MNPs respectively. Thlelepamide 1426 is an unusual ketide-amino acid isolated from the annelid worm Thelepus crispus.940 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,931 are constitutively expressed in a range of tissues in the organism suggestive that the peptides play a front-line role in defense against infections.942 Cypriodina luciferyl sulfate 1427 appears to be a more stable storage form of cypridina luciferin, the luminescence precursor of the ostracod Cypridina (Vargula) hilgendorfi.943 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 1428.934 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)925 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.936 The 33-amino-acid residue peptide pardaxin (flatfish Pardachirus marmoratus) exhibited in vivo activity towards MRSA dermal infection and enhanced wound healing.937 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.938

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.9 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 database9 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>
<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>

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.
16 Acknowledgements

We thank Dr Serin Dabb and Dr Helen Potter (Royal Society of Chemistry) for the provision of data used in this review, from the MarinLit database.\(^{18}\)

17 References

Review

Natural Product Reports

This journal is © The Royal Society of Chemistry 2015

Open Access Article. Published on 03 February 2016. Downloaded on 6/18/2019 3:51:01 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 International Licence.


676 R. A. Keyzers, J. Daoust, M. T. Davies-Coleman, R. Van Soest, A. Balgi, E. Donohue, M. Roberge and