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REVIEW

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Marine natural products‡

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Covering: 2016. Previous review: *Nat. Prod. Rep.*, 2017, **34**, 235–294

This review covers the literature published in 2016 for marine natural products (MNPs), with 757 citations (643 for the period January to December 2016) 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 (1277 in 432 papers for 2016), together with the relevant biological activities, source organisms and country of origin. Reviews, biosynthetic studies, first syntheses, and syntheses that led to the revision of structures or stereochemistries, have been included.

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1 Introduction

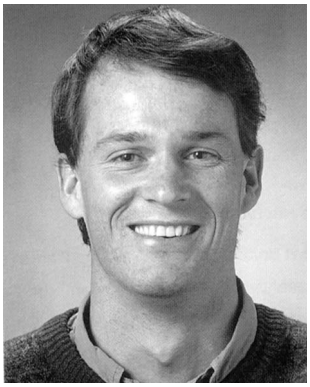
This review is of the literature for 2016 and describes 1277 new compounds from 432 papers, a 5% reduction from the 1340 new compounds in 429 papers reported for 2015.[1] As in previous reviews, the structures are shown only for new MNPs, or for previously reported compounds where there has been a structural revision or a newly established stereochemistry. Previously reported compounds for which first syntheses or new bioactivities are described are referenced, but separate structures are generally not shown. Where the absolute configuration has been determined for all stereocentres in a compound, the identifying diagram number is distinguished by addition of the † symbol. The new format for this review introduced for the previous two reviews[1,2] has been retained, with only a selection of highlighted structures (142) now shown in the review. Compound numbers for structures not highlighted in the review are *italicised*, and all structures are available for viewing, along with their names, taxonomic origins, locations for collections, and biological activities, in an ESI‡ document associated with this review. The Reviews section (**2**) contains selected highlighted reviews, with all other reviews referenced in a section of the ESI.‡ This review welcomes two new authors, Anthony Carroll and Rohan Davis, from Griffith University, Australia into the team.

2 Reviews

A 65% increase in the number of MNP-related reviews appeared in 2016 compared to 2015. Of the 144 reviews published in this

period, 34% focussed on specific compounds or compound classes, 28% related to the bioactivities of MNPs, 29% had an organism or geographic focus while the remainder were more general. The journal Marine Drugs accounted for 29% of all reviews published in the year. Eleven reviews that highlight significant aspects of MNP studies are discussed here and the remaining 133 are listed in the ESI.‡ MNPs reported in 2015 have been comprehensively reviewed.[2] The definitive series of reviews by Newman and Cragg on NPs as drugs has been updated and expanded for the period 1981 to 2014.[3] MNPs as drugs and drug candidates have also been reviewed by the same authors.[4] With the increasing study of MNPs from China, it is timely that a review of the Chinese Marine Materia Medica (CMMM) has appeared.[5] The definition of 'marine derived fungi' has been the subject of ongoing debate and a review highlights this issue and proposes a new consensus definition.[6] Algae are a major source of marine derived fungi and the chemistry of these organisms has been reviewed.[7] A comprehensive review discusses the diversity of holothurian triterpene glycosides and their bioactivities reported over the last six decades.[8] The diterpenoid chemistry of gorgonians and the diverse chemistry derived from *Spongia* species have been reviewed.[9,10] A review of the role of natural product biosynthetic gene-clusters in bacterial ecology and evolution provides an interesting perspective on the drivers of chemical diversity within microorganisms.[11] The challenges of dereplication in MNP studies and LCMS and NMR strategies to efficiently recognise known bioactive MNPs has been reviewed.[12] Updating the MarinLit database[13] continues to be an essential requirement for the preparation of this review and the structures and literature derived from this database form the basis for this review.

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



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 has recently been promoted to Professor.

Anthony (Tony) Carroll initially studied the alkaloid and lignan chemistry of rainforest plants (BSc (Hons) and PhD, Prof Wal Taylor, Sydney University) but marine natural products became a major focus after postdoctoral fellowships at the University of Hawaii with Paul Scheuer and at James Cook University, Australia with John Coll and Bruce Bowden. Fifteen years as head of natural products chemistry for the AstraZeneca/Griffith University drug discovery project expanded his interests to include high throughput purification and structure determination techniques and cheminformatics. Since 2008 he has held a faculty position at Griffith University, Gold Coast where he is currently a Professor.

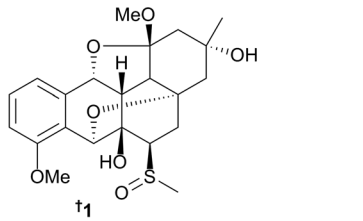
Rohan Davis received a BSc (Hons 1) degree in chemistry and biochemistry from the University of Melbourne (1992). He worked as a research assistant on the AstraZeneca/Griffith University natural product drug discovery program (1994–1996) before undertaking PhD studies (1997–2000) under the supervision of Professors Ronald Quinn and Anthony Carroll. After 2 years of postdoctoral research at University of Utah with Chris Ireland, he returned to Griffith University in 2003 where he is currently an Associate Professor. His current research involves the discovery and development of new bioactive natural products from plants and marine invertebrates and he is currently the Academic Lead for NatureBank, an Australian-based drug discovery platform.

3 Marine microorganisms and phytoplankton

3.1 Marine-sourced bacteria

The number of new natural products from marine bacteria reported in 2016 (179) is a modest increase from the average for those reported in the previous three years (161), but a significant increase from the average for 2010–2012 (115). The genus *Streptomyces* continues to be the dominant force behind the discovery of new and exciting chemistry; numerous compounds from this prolific genus have also provided enticing bioactivities that will no doubt impact chemical biology and drug discovery/development in the future. A sediment-derived *Streptomyces griseus* M268 (Kiaochow Bay, China) was the source of grisemycin **1**, which contains an unusual ether-bridged system and a methylsulfinyl moiety; this is the first sulphur-containing angucyclinone to be reported.[14] Strain M268 had previously been shown to produce the epoxybenz[*a*]anthracene derivative, kiamycin;[15] and both compounds had their absolute configurations assigned following analysis of X-ray diffraction data.[14] Large-scale fermentation of a *Streptomyces* strain (SNM31) (from intertidal mudflats, Buan, Republic of Korea) and extensive chemical investigations yielded the new *p*-aminoacetophenonic acid derivatives mohangic acids A–E **2–6**. Mohangic acid E **6** is the first glycosylated derivative for this particular chemotype. No significant *in vitro* cytotoxicity towards various human cancer cell lines nor antimicrobial activity against pathogenic bacteria and fungi was identified. When all five congeners were tested for cancer chemoprevention, using a quinone reductase (QR) assay at 20 μM, only mohangic acid E **6** displayed any activity (causing a 2.1-fold increase in QR activity compared to the control), suggesting the glucose moiety is important for QR activity in this chemotype.[16]

Additional chemical investigations on the fermentation culture derived from a *Streptomyces* strain CNH189,[17] yielded the ansalactams B–D **7–9** along with the previously identified metabolite, ansalactam A.[17,18] Compounds **7–9** represent three new carbon skeletons and illustrate the plasticity within the ansamycin biosynthetic pathway. Ansalactams B–D displayed moderate antibacterial activity towards MRSA.



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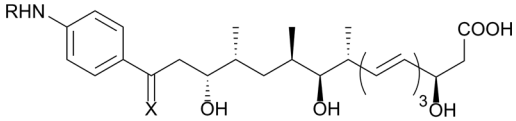
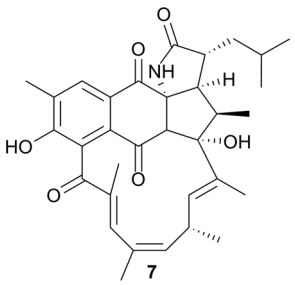


†**2** R = H, X = O
†**3** R = Me, X = O
†**4** R = Ac, X = O
†**5** R = Ac, X = ⁃OH,H
†**6** R = β-glucose, X = O



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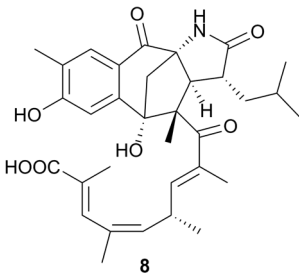

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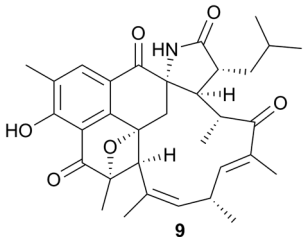

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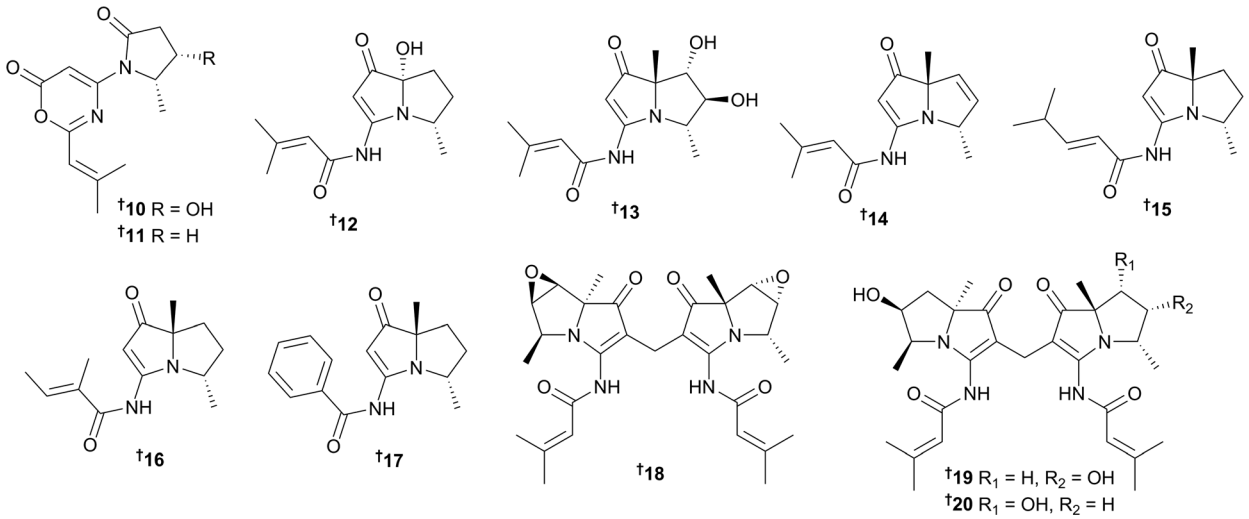
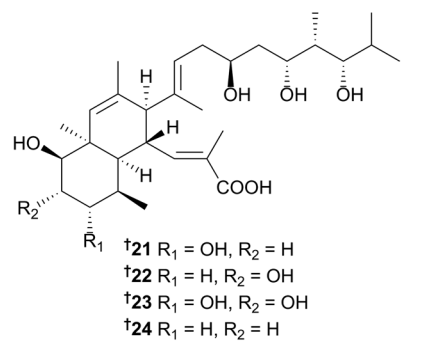
Rob Keyzers carried out his BSc (Hons) and PhD studies at Victoria University of Wellington. His thesis research, carried out under the guidance of Assoc. Prof. Peter Northcote, a former contributor to this review, focused on spectroscopy-guided isolation of sponge metabolites. He then carried out post-doctoral 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.

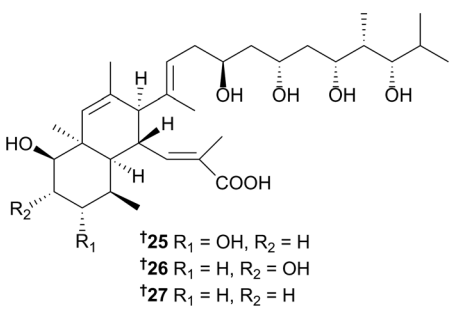
Michèle Prinsep received her BSc (Hons) and PhD degrees from the University of Canterbury, where she studied the isolation and structural elucidation of biologically active secondary metabolites from sponges and bryozoans under the supervision of Professors Blunt and Munro. She undertook postdoctoral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

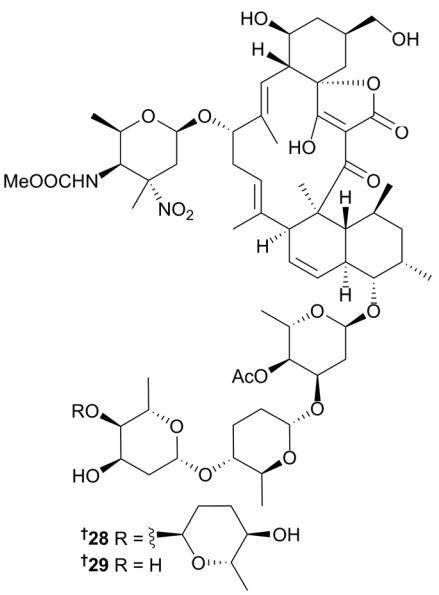


Spinoxazines A **10** and B **11**, which both possess the rare structural motif, 1,3-oxazin-6-one, along with six new bohemamine analogues bohemamines D–I **12–17** were isolated from the extract of *Streptomyces* sp. SNB-048 (sand sample, Bahamian tidal flat).[19] Additional research on another Bahamian-collected bacterial strain, *Streptomyces spinoverrucosus* SNB-032 by the same research group, yielded three new dimeric bohemamines, dibohemamines A–C **18–20** that were subsequently shown to be formed *via* a non-enzymatic process with formaldehyde, which was detected in the culture.[20] This mild dimerisation process was exploited to generate a series of semi-synthetic analogues for biological evaluation. Dibohemamines B and C displayed potent activity against the non-small cell lung cancer cell line A549, with IC_{50} values of 140 and 145 nM, respectively.[20]

Two separate studies on two different *Streptomyces* strains (one collected in Papua New Guinea and the other in China) each yielded new nahuoic acid metabolites.[21,22] Nahuoic acids B–E, along with the known polyketide natural product, nahuoic acid A **21**,[23] were identified and reported from the Chinese strain.[21] Shortly after the first publication of nahuoic acids B–E,[21] another research group published a study[22] using the same trivial names to identify several different congeners. The first total synthesis of one of the new nahuoic acid congeners, nahuoic acid C_i (B_{ii}),[24] presented the authors with the opportunity to correct this situation.[24] The analogues reported in the second study[22] have subsequently been named nahuoic acids B_i–E_i **22**, **23**, **25** and **26** while the congeners from the original study[21] have been named nahuoic acids B_{ii}–E_{ii} **23**, **24**, **27**, and **25**. Thus, a total of seven analogues (including nahuoic acid A **21**) of this architecturally intriguing polyketide structure class have been isolated to date. It should be noted that based on the new terminology, nahuoic acid C_i is the same as nahuoic acid B_{ii}, and nahuoic acid D_i has the same structure as nahouic acid E_{ii}. Several of these polyketides have been shown to display selective inhibition of SETD8 (a lysine methyl transferase) in U20S osteosarcoma cells.[22] With methylation events playing important roles in the epigenetic regulation of gene expression, the discovery of new small molecules that



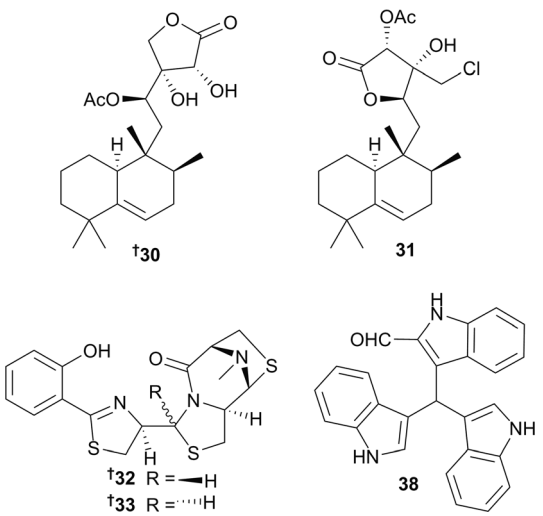




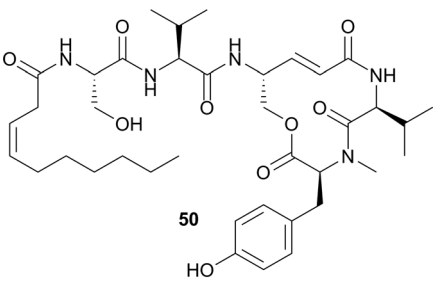
selectively modulate enzymes controlling these events, may impact future cancer research.

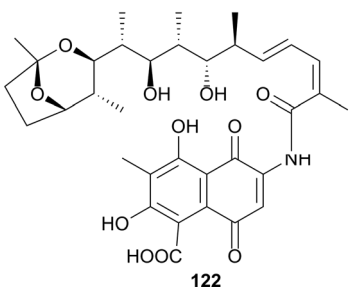
The glycosidic spirotetronates tetrocarcin N **28** and O **29** were isolated from a *Micromonospora* sp. culture (sediment sample, Bohai Bay, Dalian, China) following a PCR-based genetic screening method that targeted the dTDP-glucose-4,6-dehydratase gene.[25] Compounds **28** and **29** displayed modest antibacterial activity against *Bacillus subtilis*. Preliminary structure–activity relationship data indicated that sugar moieties at C-9 and the C-32 formyl moiety found in the previously isolated tetrocarcin congeners (not shown)[26,27] are important for the antibacterial activity of this unique compound class.

The halimane-type diterpenoids micromonohalimane A **30** and B **31** (*Micromonospora* sp. from the ascidian *Symplegma brakenhielmi*, Florida, USA) showed modest antibacterial activity against MRSA. Additional biological evaluation of **31** suggested that micromonohalimane B is bacteriostatic, rather than bacteriocidal.[28] Ulbactins F **32** and G **33** are two polycyclic thiazoline congeners isolated from a culture extract of a sponge-derived *Brevibacillus* sp. (TP-B0800), collected off the coast of Japan. These compounds both inhibited migration of tumour cells in the submicromolar to micromolar range.[29] From the gastrointestinal tract of a fish dredged near the South Orkney Islands (Antartica), a psychrotolerant bacterial strain identified as *Vibrio splendidus* was the source of 15 bis- and tris-indole derivatives, six of which ***34–39*** were new indole alkaloids. Another new bisindole analogue ***40*** was obtained from an additional psychrotolerant strain, *Arthrobacter psychrochitiniphilus*, that was isolated from the excrement of penguins. While some of these indole metabolites showed moderate activity towards several Gram-negative and -positive bacteria, trisindolal **38** was shown to be the most cytotoxic congener from the series following *in vitro* screening against an 11 human tumour cell line (HTCL) panel, being most active towards human breast cancer (MAXF401) and melanoma (MEXF 462) cell lines.[30]



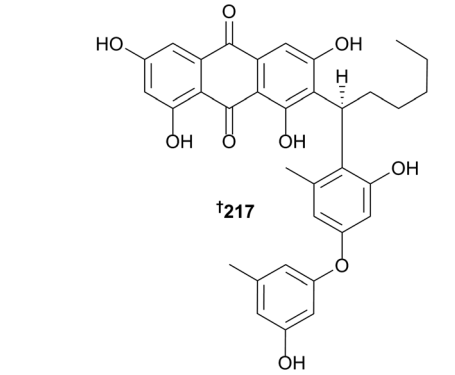
A total of 130 α-proteobacteria belonging to the Rhodospirillaceae family, which were sampled from oceans around the world, have been cultured and investigated for their ability to produce a specific class of lipopeptides, collectively known as the thalassospiramides.[31] Twenty-one new thalassospiramides A6–A11 ***41–46***, B3–B5 ***47–49***, C2 **50**, E2 ***51***, F1–F3 ***52–54***, H ***55***, H1–H3 ***56–58***, I ***59***, I1 ***60*** and J ***61*** were identified and evaluated for not only their ability to inhibit human calpain but also as potential neuroprotective agents. In the calpain *in vitro* assay, 12 thalassospiramides were tested, and several single- and double-digit nanomolar inhibitors were revealed; thalassospiramide C2 **50** was the most potent lipopeptide with an IC_{50} of 1.6 nM. Subsequently, nine of the best calpain inhibitors were chosen for testing in a murine neuroprotective assay; thalassospiramides A4 (previously reported analogue), H ***55*** and H1 ***56*** significantly reduced the neurotoxic response in the mouse model. These studies indicated that this unique class of lipopeptides may have potential use in neurodegenerative conditions such as Alzheimer's disease. Furthermore, the authors of this paper also investigated the diversity of biosynthetic gene cluster (BGC) architectures by sequencing the genomes of 28 Rhodospirillaceae strains, which identified three types of dysfunctional BGCs and four functional BGCs that corresponded to the four thalassospiramide production patterns. This family-wide genome sequencing identified seven BGCs in total, five of which were new to science. This study, which successfully applied biochemical and genomic approaches to the discovery of genes and mechanisms associated with thalassospiramide biosynthesis, will greatly assist scientists that research these novel bioactive lipopeptides in the future.





Additional new metabolites were also identified from the genera *Streptomyces* ***62–121***,[32–62] *Salinispora* **122** and ***123***,[63,64] *Bacillus* ***124–130***,[65–69] *Pseudoalteromonas* ***131*** and ***132***,[70] *Haliangium* ***133***,[71] *Thalassotalea* ***134–138***,[72] *Pseudomonas* ***139*** and ***140***,[73] *Shewanella* ***141***,[74] *Pontibacter* ***142***,[75] *Brevibacterium* ***143–145***,[76] *Streptosporangium* ***146–148***,[77] *Streptomonospora* ***149–152***,[78] *Verrucosispora* ***153***,[79] *Micromonospora* ***154*** and ***155***,[80] *Pseudonocardia* ***156–163***,[81,82] *Nocardiopsis* ***164–176***,[83,84] *Williamsia* ***177***,[85]

and an unidentified metagenome clone ***178*** and ***179***.[86] Several structure revisions were reported during 2016, including thiasporine A ***180***,[87] xiamenmycin A ***181***,[88] and xiamenmycin C ***182***,[89] halichomycin ***183***,[90] and iso-naseseazine B ***184***.[91] Furthermore, total syntheses of a number of bioactive or architecturally attractive MNP scaffolds have also been successfully completed and reported in 2016. For example, the isolation (from *Salinispora arenicola*), structure elucidation and subsequent total synthesis of rifsaliniketal **122** (ref. 63) along with the known and related rifamycin congeners salinisporamycin,[92] and salinketals A and B,[93] were reported. Other total syntheses of marine bacterial metabolites include (±)-spiroindimicins B and C,[94] bacilosarcin C,[95] cyclomarins A[96] and D,[97] cyclomarazines A and B,[98] nitropyrrolins A, B and D,[99] actinophenanthroline A,[100,101] fijiolide A,[102] heronamides A–C,[103] dermacozines A–C.[104] The proposed chemical structure of marineosin A was also successfully synthesised; the structure of the target compound was established following X-ray data analysis.[105] While the NMR data of the synthetic compound showed a high degree of similarity with the previously reported natural product, there were also noticeable differences. Additionally, differences in the physical properties (white solid *vs.* colourless oil) and specific rotation data (opposite signs in the same solvent) indicated that the isolated and synthetic compounds were not the same. It was postulated that these data discrepancies could be potentially attributed to atropisomers, diastereoisomers or structural isomers, however further structure elucidation studies on these unusual spiroaminals are required.[105]



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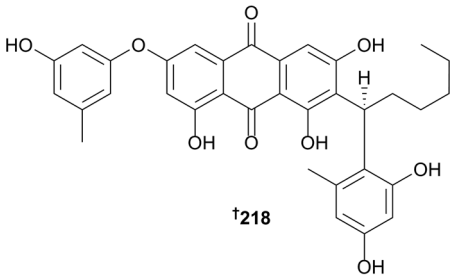

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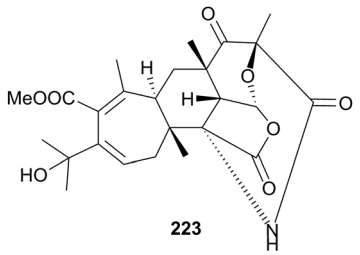

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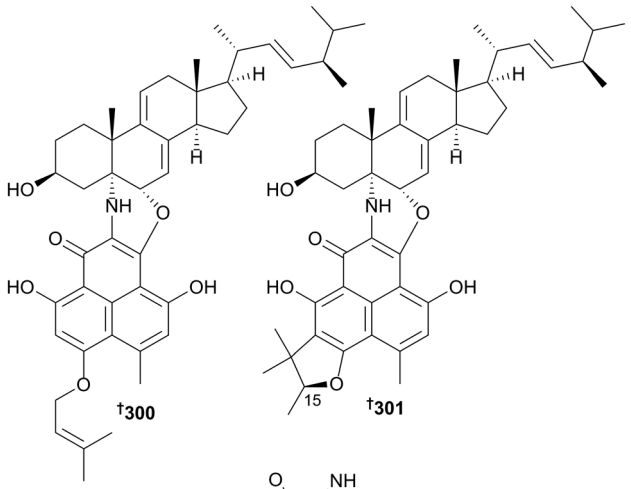
3.2 Marine-sourced fungi (excluding from mangroves)

The number of new compounds reported from marine fungi (not associated with mangroves) has decreased slightly with 328 new compounds reported in 2016 compared to 369 in 2015. A number of new metabolites have been obtained from the genera *Acaromyces* (naphtha-[2,3-*b*]pyrandione analogue ***185*** and thiazole ***186***),[106] *Acremonium* (steroid ***187*** and cyclopentanone derivative ***188***,[107] diterpene glycosides ***189–192***,[108] sesquiterpenoids ***193–207*** (ref. 109) and benzophenone ***208*** (ref. 110)), *Alternaria* (cyclopentenone ***209*** (ref. 111)), *Arthirinium* ((+)-5-chlorogriseofulvin ***210*** (ref. 112)) and *Ascotricha* (polyketide-derived linear ***211–213*** and macrocyclic ***214*** polyesters, hexaketide ***215*** and (−)-orthosporin ***216*** (ref. 113)). The racemate of 5-chlorogriseofulvin has been synthesised but this is the first isolation of (+)-5-chlorogriseofulvin ***210*** from a natural source (simultaneously obtained from *Penicillium canescens* below)[114] and although (+)-orthosporin has been obtained from a terrestrial fungus and (−)-orthosporin has been synthesised, the current report represents the first isolation of (−)-orthosporin from a natural source.[113] The genus *Aspergillus* has again been well studied and has yielded many new metabolites. A deep-sea strain of *Aspergillus versicolor* yielded a series of phenolic compounds aspergilols A–F ***217–222***, of which **217** and **218** possess a new scaffold with a carbon–carbon fusion of an orcinol unit to an anthraquinone.[115]

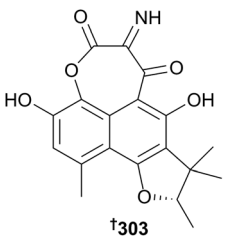
Production of aspergstressin **223**, an unusual hybrid polyketide–terpenoid metabolite was induced in an *Aspergillus* sp. obtained from a hydrothermal vent by cobalt ion stimulation.[116] Other metabolites produced by *Aspergillus* species included meroterpenoids ***224–226***,[117] butenolide derivatives ***227–229***,[118] aromatic nucleoside ***230***,[119] terpenoids ***231*** and ***232***,[120] 2-benzylpyridin-4-one derivatives ***233*** and ***234***,[121] dimeric naphthopyrone ***235***,[122] naphthopyranone ***236***,[123] diorcinol ***237*** (through cocultivation with *Ircinia felina*),[124] α-pyrone polyene ***238*** (ref. 125) (the structure appears in a screening library but no source is given for the compound), chlorinated depsidone ***239***, folipastatin ***240*** and 2-chlorounguinol ***241*** (the last two as first time marine isolates)[126] and sesterterpenoids ***242*** and ***243***.[127] Fumiquinazoline-type alkaloids ***244–254*** (ref. 128) were isolated along with cottoquinazolines B–D, the structures of which were revised to ***255–257***, enantiomers of the structures originally reported.[128] Other compounds isolated from *Aspergillus* species include 20-nor-isopimarane diterpenoids ***258–262***,[129] tetranorlabdane diterpenoids ***263*** and ***264***,[130] cyclic dipeptide ***265***,[131] asteltoxins ***266*** and ***267*** and chromone ***268***,[132] eremophilane sesquiterpenes dihydrobipolaroxin (the configuration of which was determined as ***269***), ***270–273***,[133] phenolic bisabolanes ***274*** and ***275*** (ref. 134) and (*R*)-(−)-hydroxysydnoic acid ***276*** (ref. 135) and the methyl naphthoate ***277***,[136] these last two being obtained as first time marine isolates. Reisolation of pseurotin A_2, from

a different strain of *Aspergillus fumigatus* to that from which it was originally obtained, led to revision of the structure to ***278***.[137]

New metabolites were obtained from the genera *Biscogniauxia* (isopyrrolonaphthoquinone ***279*** and sansalvamide A amide ***280***; the latter a first time MNP),[138] *Chaetomium* (dioxopiperazine alkaloid ***281*** (ref. 139) and cytochalasins ***282*** and ***283*** (ref. 140)), *Chondrostereum* (new triquinane-type sesquiterpenoids ***284–286*** and the sesquiterpenoid anhydroarthrosporone ***287*** as a first time MNP),[141] *Cladosporium* (azaphilones ***288*** and ***289***, bicyclic diol ***290*** and 1-(3,5-dihydroxy-4-methylphenyl)propan-2-one ***291***, the last two as new NPs),[142] *Clonostachus* (isocoumarin ***292*** (ref. 143)) and *Cochliobolus* diethylene glycol phthalate ester oligomers ***293–299***.[144] *Coniothyrium cereale* yielded the unusual nitrogenous heterodimers **300** and **301**, comprising sterol and polyketidic phenalenone portions, triketone ***302*** (obtained as an acetone adduct) and phenalenone derivative **303**, containing an oxepane–imine–dione ring formed *via* an unprecedented imine functionality between two carbonyl groups.[145] Although **301** had previously been isolated from a terrestrial fungus as a C-15 epimeric mixture, it was isolated here as a first time MNP and in an epimeric pure form (15*S*).[145]

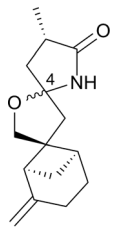


†**300** †**301**



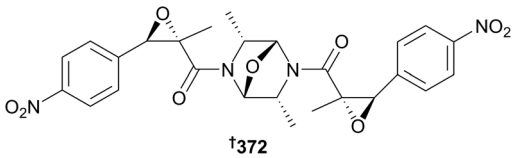
†**303**

Naphthalenones ***304*** and ***305*** and depsidone ***306*** were obtained from the genus *Corynespora*,[146] diketopiperazines ***307–309*** from a *Dichotomomyces* species,[147] asteltoxin derived dimers ***310–312*** from a diethyl sulfate (DES) mutated *Emericella* strain[148] and an indole alkaloid ***313*** (ref. 143) and anthraquinone–xanthone polyketides ***314–319*** (ref. 149) from *Engyodontium* species. The absolute configurations of the known JBIR-97/98 ***320*** and JBIR-99 ***321*** co-isolated from the *Engyodontium* species were also determined.[149] New metabolites were obtained from the genera *Fusarium* (polycyclic quinazoline alkaloid ***322***,[150] β-resorcylic macrolides ***323–326*** (ref. 151) and relgro (absolute configuration determined as ***327*** (ref. 151)), octahydronaphthalene derivative ***328*** (ref. 151) and cyclic hexadepsipeptide ***329*** (ref. 152)), *Hypocrea* (tyrosol derivative ***330*** (ref. 153) and trichodenol B ***331***, the latter as a first time marine isolate (ref. 153)), *Neosartorya* (cyclotetrapeptides ***332*** and ***333***,[154] diketopiperazine derivative ***334***,[154] terpenoids ***335–339*** (the last two of which are reported from a marine source for the first time),[155] 2-naphthoic acid derivative ***340***,[155] isocoumarin ***341***,[155] polyketides ***342*** and ***343***,[156] and benzoic acid derivatives ***344–350*** (ref. 156)), *Nigrospora* (cyclohexadepsipeptides ***351–353***,[157] scopularide A (the configuration of which was determined as ***354*** (ref. 157)) and hydroanthraquinone dimer ***355*** (ref. 158)) and *Paecilomyces* (pyrrolooxazine ***356***,[159] bicyclic fatty acids ***357*** and ***358*** (ref. 160) and indole alkaloids ***359*** and ***360*** (ref. 161)). A compound with the same planar structure as ***360*** was previously obtained from a terrestrial fungus. Sporulaminals A **361** and B **362**, epimeric spiroaminal derivatives, were isolated from *Paraconiothyrium sporulosum* and successfully separated. The epimerisation was found to be induced by temperature, pH and water addition.[162]

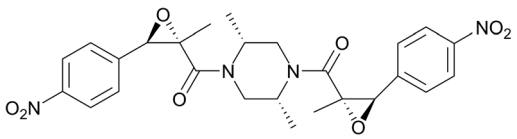


†**361** (4*R*)
†**362** (4*S*)

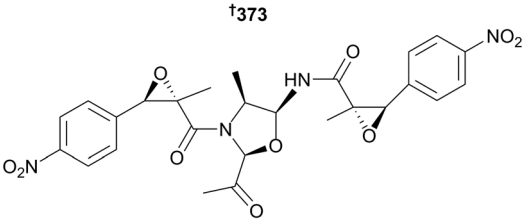
As always, the genus *Penicillium* has been a prolific source of new metabolites, including meroterpenoids ***363–366***,[163] flavone ***367***,[164] spiroketal ***368*** (ref. 165) and macrolides ***369*** and ***370***.[166] A



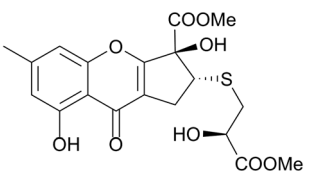
†**372**



†**373**



†**374**

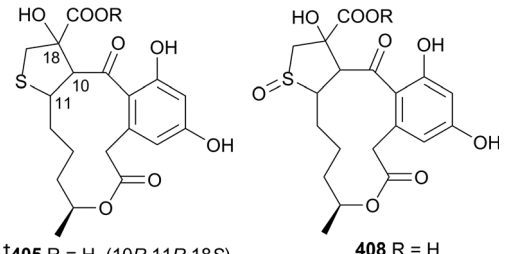


†**375**

bioinformatics tool, MeHaloCoA (Marine Halogenated Compound Analysis) was developed and included in the software R. Integration of the tool into a dereplication approach resulted in identification of known and new halogenated compounds including (+)-5-chlorogriseofulvin ***210*** (ref. 112) and griseophenone I ***371*** from *Penicillium canescens*.[114] Chrysamides A–C **372–374** are dimeric nitrophenyl *trans*-epoxyamides obtained from *Penicillium chrysogenum* (deep sea sediment) of which **372** and **373** possess an unprecedented centrosymmetric dimer skeleton and **374** suppresses production of the pro-inflammatory cytokine interleukin-17.[167] A number of metabolites have been obtained from strains of *Penicillium purpurogenum* mutated by either exposure to neomycin (cyclopentachromone **375** (ref. 168) and cyclic dipeptide ***376*** (ref. 169)) or DES (oxaphenalenones ***377*** (ref. 170) and bacillosporin C ***378***,[170] and alkaloids ***379–382***, with ***382*** representing a structural revision of asperverin[171]). Of these, chromosulfine **375** is the first cyclopentachromone reported to possess a sulfide chain[168] and although bacillosporin C had been isolated previously from both terrestrial and marine fungi, the absolute configuration was reported for the first time.[170]

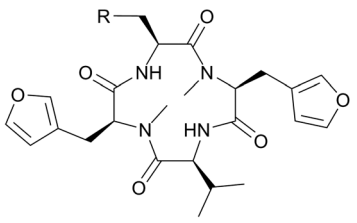
Other metabolites isolated from the *Penicillium* genus include tanzawaic acid derivative ***383***,[172] meroterpenoid ***384***,[173] furan-2-carboxylic acid derivatives ***385–387***,[173] polyketides ***388–398***,[174] ***399*** and ***400*** (ref. 175) and cerebrosides ***401*** and ***402***.[176] The planar structures of ***399*** and ***400*** (ref. 175) appear in a screening library but no source information is given. Cerebrosides ***401*** and ***402*** (ref. 176) were named penicillosides, but that name had already been assigned to some unrelated compounds, previously isolated from a succulent plant.[177] Different culture conditions for a sponge-derived *Penicillium* sp. led to variation in production of some macrocyclic polyketides. Under standard growth conditions, the culture yielded 12-keto-10,11-dehydrocurvularin ***403*** (ref. 178) but application of a previously published procedure of experimental design and chemometric analysis to optimise production of related metabolites, led to production of 15(*S*)-*cis*-10,11-epoxycurvularin ***404*** (ref. 178) and cyclothiocurvularins **405–407** (**405** and **406** diastereoisomeric) and cyclosulfoxicurvularins **408** and **409**; curvularins condensed with a thiolactate residue.[178] Results of biosynthetic feeding experiments utilising [U-$^{13}C_3$ ^{15}N]-L-cysteine and spontaneous formation of cyclothiocurvularins from 10,11-dehydrocurvularin indicated that formation of cyclothiocurvularins may be a detoxification process for the fungus.[178]

Epidithiodiketopiperazines ***410–412***,[179] verrucosidin derivative ***413***,[180] macrolides ***414–417***,[181] azaphilones ***418–421***,[182] diene aldehyde ***422*** (ref. 183) and tetrahydrofuran derivatives ***423–426***,[183] and fatty acid esters ***427*** and ***428*** (ref. 184) were also obtained from *Penicillium* strains as were alkaloids haenamindole and citreoindole, the structures of which were revised to ***429*** and ***430***, respectively based on NMR data and C_3 Marfey's methodology.[185] Citreoindole had previously been obtained from a terrestrial *Penicillium* species but the current isolation[185] was the first from the marine environment. 6-Methylcurvulinic acid ***431***, a known terrestrial plant metabolite, was also isolated from the marine environment for the first time.[186] Reexamination of the published NMR spectral data of (22*E*)-24-methylcholesta-8(14),22-diene-3β,5α,6β,7α-tetraol, isolated from a sponge-associated *Penicillium* sp., indicated that the structure was in fact 5α,6α-epoxy-(22*E*,24*R*)-24-methylcholesta-8(14),22-diene-3β,7α-diol ***432***.[187] New natural products were isolated from the genera *Pestalotiopsis* (chlorinated diphenylmethanes ***433–436***),[188] *Peyronellaea* (isocoumarin derivatives ***437–441***),[189] *Phoma* (isocoumarin derivative ***442***,[190] steroid ***443*** (ref. 191) and ***444–450*** (ref. 192)), *Pleosporales* (azaphilone ***451***),[193] *Pseudallescheria* (diasteroisomeric sesquiterpenes ***452*** and ***453***,[194] cyclopiazonic acid analogue ***454***,[194] diketopiperazines ***455*** and ***456*** (ref. 194) and ***457*** (ref. 195) and lactone derivative ***458*** (ref. 195)). Chromone derivatives ***459*** and ***460*** were obtained from *Rhinocladiella* sp.,[143] and aromadendrane sesquiterpenoids ***461–467*** (ref. 196) from the genus *Scedosporium*. The genera *Scopulariopsis* (xanthones ***468*** and ***469*** and the known AGI-B4, the configuration of the last determined as ***470***, phenolic sesquiterpenes ***471*** and ***472***, alkaloid ***473*** and α-pyrone derivative ***474***),[197] *Simplicillium* (linear peptides ***475–482***),[198] *Spiromastix* (phenolic lactones ***483–495***),[199] *Sporidesmium* (diphenyl ether derivative ***496***)[200] and *Stachybotrys* (isoindolone ***497*** (ref. 201) and phenylspirodrimanes ***498*** and ***499*** (ref. 202)) also yielded

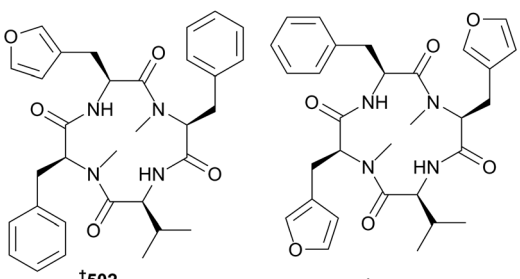


†**405** R = H, (10*R*,11*R*,18*S*)
†**406** R = H, (10*S*,11*S*,18*R*)
†**407** R = Me, (10*S*,11*S*,18*R*)

408 R = H
409 R = Me



†**500** R = *i*Pr
†**501** R =



†**502**

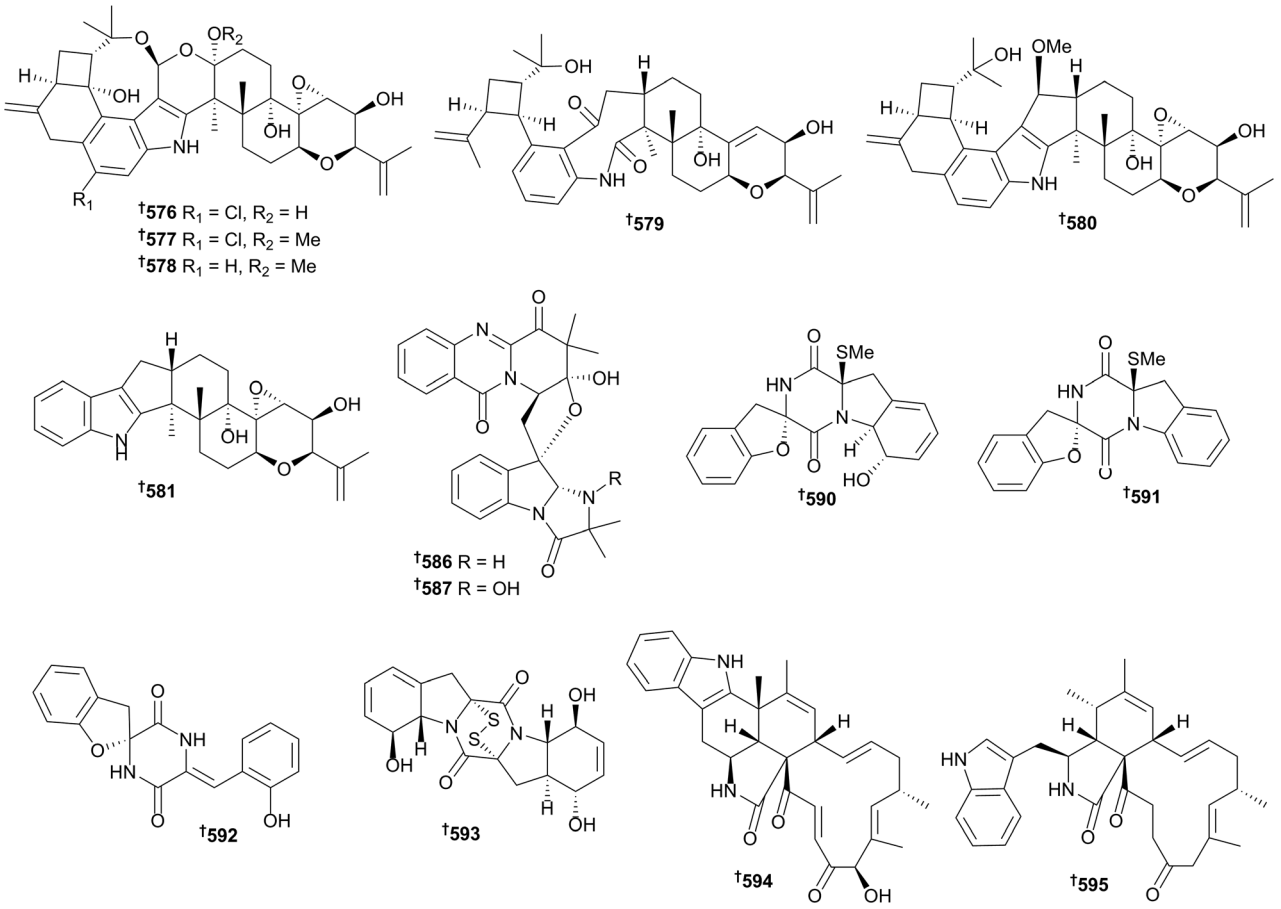
†**503**

new metabolites. Endolides A **500** and B **501**, unusual *N*-methylated tetrapeptides that contain the rare amino acid 3-(3-furyl)-alanine, were isolated from a sponge-derived *Stachylidium* sp.[203] Neither demonstrated any cytotoxicity in a range of bioassays but endolide A **500** showed binding affinity to the vasopressin receptor whilst endolide B **501** possessed selective affinity for the serotonin receptor.[203] Supplementation of the culture medium with phenylalanine produced two further analogues, endolides C **502** and D **503** and negatively affected endolide A **500** production.[204] A series of biosynthetic feeding experiments established that all of the carbon atoms of the rare amino acid were derived from the shikimate pathway except for the *N*-methyl group which arose from the methyl group of methionine.[204]

The genus *Talaromyces* yielded isocoumarin derivative ***504***,[200] diphenylketones ***505*** and ***506*** (ref. 205) and xanthones ***507*** and 1,4,5-trihydroxy-2-methyl-9*H*-xanthen-9-one ***508*** (the latter a known synthetic compound but isolated here as a new NP)[205] whilst *Tolypocladium* sp. yielded decalin-tetramic acids ***509*** and ***510*** (ref. 206) and the *Trichobotrys* genus was the source of macrodiolides ***511–513***.[207] A number of metabolites were isolated from the genus *Trichoderma* including disulfide-bridged dipeptide ***514***,[208] diterpene ***515***,[209] norditerpene ***516***,[210] decalin derivatives ***517*** and ***518*** (ref. 211) and long-chain peptaibols ***519–521***.[212] An azaphilone derivative ***522*** was obtained from *Xylariales* sp.[213] and an unidentified fungus isolated from a brown alga yielded diterpenes ***523–525***.[214] Synthesis of the proposed structure of trichoderin A, an anti-tuberculosis aminolipopeptide originally obtained from a sponge-derived *Trichoderma* sp., has revised the configuration at C-6 from (*S*) to (*R*) as in ***526***.[215] Total synthesis of the originally assigned structure of cereoanhydride C (*Coniothyrium cereale*, green alga *Enteromorpha* sp.), led to reassignment of the structure as spiroketal ***527***.[216] Total synthesis of the tetracyclic cyclopiane diterpenes conidiogenol (*Penicillium chrysogenum*, red alga, *Laurencia* sp.) and conidiogenone B (*Penicillium* sp., sediment), led to revision of their configurations to ***528*** and ***529*** respectively.[217] Total synthesis of the cyclodepsipeptides clavatustide A and B (*Aspergillus clavatus*, crab *Xenograpsus testudinatus*) has been achieved *via* a seven step method from (*R*)-phenyllactic acid.[218] The indole alkaloids notoamides F and R (*Aspergillus* sp., mussel *Mytilus edulis galloprovincialis*) and the related spirooxindole (−)-sclerotiamide, have been synthesised in a convergent manner from commercially available Seebach acetal.[219] A first synthesis of notoamide I was also claimed[219] but the synthesis had already been reported.[220] Denrodolides C and D (*Dendrodochium* sp., sea cucumber *Holothuria nobilis*) have been prepared from commercially available materials.[221] The macrolide gliomasolide C (*Gliomastix* sp., sponge *Phakellia fusca*) has been synthesised,[222] as has the lipopeptide fellutamide A (*Penicillium fellutanum*, fish *Apogon endekataenia*)[223] and the alkaloids penipanoid C and 2-(4-hydroxybenzyl)quinazolin-4(3*H*)-one (*Penicillium paneum*, sediment).[224] A number of new activities were reported for known fungal metabolites. Diorcinol exhibited acetylcholinesterase inhibition,[225] naphthopyrone TMC-256C displayed neuroprotective and anti-neuroinflammatory effects[226] and pannorin, alternariol and alternariol-9-methylether were inhibitors of the signal pathway modulating enzyme glycogen-synthase-kinase 3B, (pannorin ***530*** also a first time MNP).[227] A study which analysed two *Penicillium* strains at different time points throughout the culture period by HPLC-DAD-HRMS indicated that a greater chemodiversity of metabolites may be obtained from the one strain by performing extractions at different times throughout the culture period including early and late growth phases.[228] Studies on the effect of light on the biosynthesis of the anticancer polyketide 1403C (haloroquinone, SZ-685C) in *Halorosellinia* sp., indicated that light significantly increased production of this metabolite (74%) over production in the dark.[229] Comparison of the secondary metabolite profile of a monoculture of *Aspergillus flavipes* with that of a strain cocultured with a *Streptomyces* strain isolated from the same marine sediment, indicated that physical contact with the bacterium induced production of six cytotoxic cytochalasans (such as aspochalasin P) in the fungus.[230]

3.3 Fungi from mangroves

There has been a continued increase in the number of new metabolites reported from mangrove-associated fungi (142 in 2016, 126 in 2015 and 108 in 2014), with the majority coming from endophytic species. An *Alternaria* sp. yielded altenusin derivatives ***531–535*** (ref. 231) and a species denoted "*Ascomycota* sp." (although this is a phylum not a genus) was the source of 2,3-diaryl indone derivatives ***536–538*** (as racemates of *M*- and *P*-helicity enantiomers) and isobenzofuran derivatives ***539*** and ***540*** (also as racemates).[232] Endophytic fungi of the genus *Aspergillus* were the source of sesterterpenoids ***541*** and ***542*** (ref. 233) and isocoumarin derivatives ***543–548***, of which ***545*** and ***546*** are known synthetic intermediates but were obtained as new NPs.[234] Pyrone ***549***, naphthoquinone ***550*** and cyclic urea ***551*** were isolated from *Astrosphaeriella nypae*[235] whilst phenyl derivatives ***552–555*** were obtained from a *Botryosphaeria* sp.[236] *Capnodium* sp. yielded the eremophilane sesquiterpene ***556***,[237] dichlororesorcinol derivatives ***557–559*** were obtained from *Cosmospora vilior*[238] and endophytic *Eurotium rubrum* was the source of enantiomers of a 2-benzofuran-1(3*H*)-one, ***560*** and ***561***, the racemate of which exhibited potent 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity.[239] Endophytic *Lasiodiplodia* species yielded polyketides ***562–565*** (ref. 240) and a series of preussomerin analogues, of which the chlorinated ***566*** and ***567*** were new compounds, ***568*** was a new natural product and ***569–575*** were obtained from the marine environment for the first time.[241] The knowledge that genome mining of a related fungal strain indicated the presence of biosynthetic gene clusters for terpene production, prompted researchers to investigate an endophytic strain of *Mucor irregularis* for secondary metabolite content. This resulted in isolation of rhizovarins A–F **576–581**, structurally unique indole diterpenes.[242] Rhizovarin A **576** possesses an unprecedented linkage of an acetal and a hemiketal whilst rhizovarins B **577** and C **578** possess an acetal linked to a ketal functionality. All three compounds contain an unprecedented eight-membered cyclic ether moiety coupled to five other rings.[242]



Nectriacids A–C ***582–584*** and 12-epicitreoisocoumarinol ***585*** are polyketides obtained from an endophytic *Nectria* sp. of which nectriacids B ***583*** and C ***584*** exhibited potent inhibition of α-glucosidase.[243] Endophytic *Neosartorya udagawae* was the source of four quinazoline-containing alkaloids, neosartoryadins A **586** and B **587** and fiscalins E ***588*** and F ***589*** of which **586** and **587** are representatives of a new class of such alkaloids containing an unique 6/6/6/5 quinazoline ring system directly connected to a 6/5/5 imidazoindolone ring system which was speculated to be biosynthesised from L-tryptophan, anthranilic acid, L-valine and 2-aminoisobutyric acid.[244] Neosartoryadins A **586** and B **587** also exhibited activity against the H1N1 influenza virus (more potent than the positive control).[244] The *Penicillium* genus has been the source of a number of mangrove fungus-associated metabolites including the diketopiperazines spirobrocazine A–C **590–592** and bisthiodiketopiperazine derivative brocazine G **593**, of which brocazine G **593** displayed potent cytotoxicity to sensitive and cisplatin-resistant HTCLs and strong activity against *S. aureus*.[245] Chaetoglobosins penochalasin I **594** and penochalasin J **595** were obtained from endophytic *P. chrysogenum* of which penochalasin I **594** possessed an unprecedented hexacyclic 6/5/6/5/6/13 fused ring system.[246]

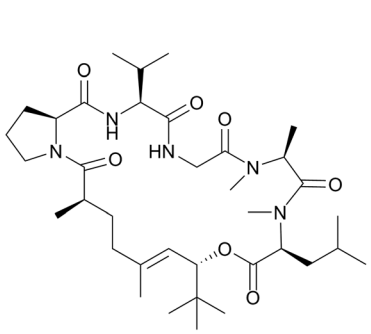
Other metabolites obtained from *Penicillium* strains include benzopyran derivative ***596***,[247] dihydroisocoumarins ***597–599*** (ref. 248) and ***600–602***,[249] polyketides ***603*** (ref. 250) and ***604*** and ***605***,[251] azaphilone ***606*** (ref. 252) and meroterpenoid ***607***.[253] Other genera of mangrove-associated fungi to yield new metabolites included *Pestalotiopsis* (polyketides ***608–613*** (ref. 254) and macrolides ***614–620*** (ref. 255)), *Phomopsis* (chromone derivatives ***621–624*** (ref. 256) and cytochalasins ***625–628*** (ref. 257)), *Pseudolagarobasidium* (sesquiterpenes ***629–648***),[258] *Rhytidhysteron* (chromone ***649–653***),[259] *Stemphylium* (tetrahydroanthraquinone derivatives ***654–656***),[260] *Talaromyces* (isocoumarins ***657–662*** and benzofurans ***663*** and ***664***)[261] and *Trichoderma* (diterpenoids ***665*** and ***666***).[262] Some chamigrane sesquiterpenes ***667–672*** were isolated from a basidiomycetous endophyte which was only identified to family (Meruliaceae).[263] Total synthesis of the purported structures of cephalosporolides H and I and penisporolide B (all obtained from *Penicillium* spp.) and their possible diastereoisomers has indicated that the relative configuration of the tricyclic core should be revised to ***673–675***, and that the sidechains also require an unknown constitutional structure revision.[264] Total synthesis of the proposed structure of a phenylethanol derivative obtained from a *Penicillium* sp. and comparison of the optical rotation and NMR data of the synthetic product with those reported for the natural product, has indicated that the proposed structure must be incorrect,[265] whilst total synthesis of the purported structure of phomolide G (*Phomopsis* sp.) has indicated that the configuration should be revised to ***676***, the C-3 epimer of that originally proposed.[266] Five

gene cluster knockout mutants of a strain of *Apergillus ustus* were obtained and experiments involving the enzymes relevant to terpene synthesis from each gene cluster indicated that biosynthesis of the ophiobolin skeleton involved these five gene clusters and that they are responsible for C15, C20, C25 and C30 terpenoid biosynthesis.[267]

3.4 Cyanobacteria

There has been a slight decrease in the number of new natural products from cyanobacteria since 2015, however the numbers of reports over the past 5 years have been consistently low overall (28 in 2016: 31 in 2015; 20 in 2014; 9 in 2013; 31 in 2012). As in previous years, the majority of new metabolites from this phylum are peptidic in nature and most have some biological activity recorded; significant examples include janadolide **677**,[268] wewakazole B **678**,[269] and odoamide **679**.[270]

metabolites share a common mechanism of action.[274] Other new metabolites of either peptidic or non-peptidic nature were obtained from the genera *Hydrocoleum* (***680*** and ***681***),[275] *Leptolyngbya* (***682***),[276] *Lyngbya* (***683***),[277] *Moorea* (***684–686***,[278] and ***687*** (ref. 279)), *Nodularia* (***688–692***)[280] *Synechocystis* (***693–699***),[281] *Nostoc* (***700***),[282] *Okeania* (**701**),[283] *Caldora* (***702***),[284] and *Symploca* (***703***)[285] and one potentially new genus (***704***)[286] that is closely related to *Trichodesmium*, *Okeania* and *Oscillatoria* based on 16S rRNA sequence analysis. The structure of caylobolide B ***705*** was corrected; the *E*-configuration between C-2/C-3 in the original 2010 paper was amended to a *Z*-configuration.[287] The first total syntheses of several cyanobacteria metabolites, such as biselyngbyolide B,[288,289] wewakazole B **678**,[290] odoamide **679**,[291] lyngbyastatin 7 (ref. 292) and cocosolide ***703*** (ref. 285) have been achieved. In order to establish the absolute configuration of the γ-pyrone containing polyketide, yoshinone A, and provide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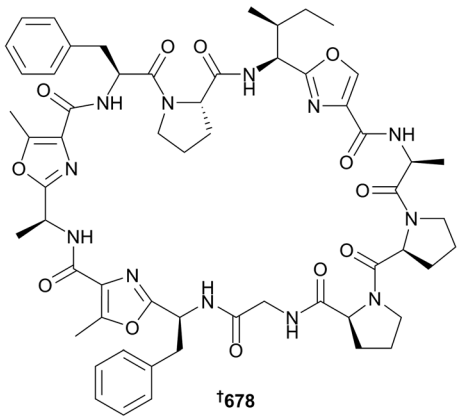
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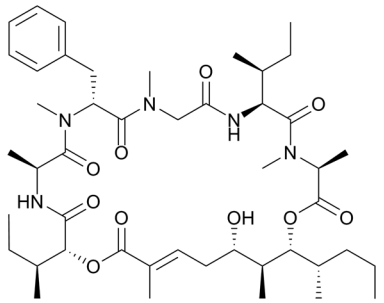

†679

Janadolide **677** (*Okeania* sp., Janado, Japan), a cyclic peptide–polyketide hybrid possessing a rare *tert*-butyl moiety, showed potent activity towards *Trypanosoma brucei brucei* (IC_{50} 47 nM) which was superior to the commonly used therapeutic drug suramin. Furthermore, significant selectivity (>212 fold) towards the trypanosome parasite was identified since no *in vitro* cytotoxicity towards the human cell lines MRC-5, HL60 and HeLa cells was noted at 10 μM.[268] The cyanobactin wewakazole B **678** was obtained using MS-guided isolation from an extract of a Red sea specimen of *Moorea producens* (formerly *Lyngbya majuscula*), and was cytotoxic towards human MCF7 (IC_{50} 0.58 μM) and H460 (IC_{50} 1.0 μM) cancer cell lines.[269] The most potent cytotoxin reported from cyanobacteria in 2016 was odoamide **679**, obtained from bioassay-guided fractionation studies on an extract from a Japanese *Okeania* species. This new 26-membered cyclodepsipeptide had an IC_{50} of 26.3 nM against HeLa S3 human cervical cancer cells.[270] Further biological evaluation on the previously identified cyanobacterial depsipeptide coibamide A[271,272] has shown that this molecule inhibits Vascular Endothelial Growth Factor (VEGF) A/VEGF Receptor 2 (VEGFR2) expression and suppresses tumour growth in a nude mouse xenograft model of glioblastoma (U87-MG). Similarities between coibamide A and apratoxin A[273] biological outputs (cell morphology, VEGFR2 expression, macroautophagy signalling) suggests these two cyanobacterial larger quantities of this bioactive compound for additional testing, the total synthesis of two possible diastereomers was conducted. NMR and optical rotation data comparison of the natural product and synthetic isomers enabled the absolute configuration of yoshinone A to be assigned as ***706***.[293] Koshikalide, a cytotoxic 14-membered macrolide, had its relative configuration reported in 2010, with the absolute configuration unattainable due to scarcity of material (0.3 mg).[294] The first total synthesis of this molecule has confirmed the relative configuration initially assigned, and enabled the assignment of the absolute configuration for this molecule.[295] Studies towards the synthesis of specific structural motifs or fragments (*e.g.* polyhydroxylated moieties common to oscillariolide and phormidolides A–C,[296] the aglycone of lyngbouilloside[297]), and analogues of bioactive products (for example largazoles,[298] calothrins,[299] and aeruginosins[300]) have been undertaken. Collectively, these studies will hopefully expedite and impact synthetic and medicinal chemistry efforts on biologically active cyanobacterial metabolites, and lead to suitable candidates in adequate quantities for future drug development.

3.5 Dinoflagellates

The number of new metabolites reported from dinoflagellates has dropped slightly with 11 compounds reported in 2016 compared

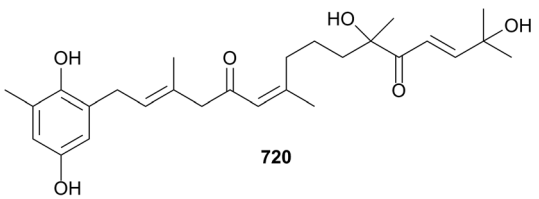
with 15 in each of 2015 and 2014. *Alexandrium ostenfeldii* was the source of gymnodimine D ***707*** with two tetrahydrofuran rings in the macrocycle.[301] The macrolides iriomoteolide-10a ***708*** and -12a ***709*** were obtained from an *Amphidinium* sp.[302] Three new brevisulcatic acids (BSXs), ladder-frame polyethers ***710–712*** were isolated from *Karenia brevisculcata*,[303] two new karlotoxins, polyketides ***713*** and ***714*** were obtained from *Karlodinium veneficum*,[304] and the ladder-frame polyether prymnesin-B1 ***715*** was obtained from the microalga *Prymnesium parvum*.[305] The relative configuration of the C-3–C-12 portion of amphirionin-5 ***716*** was assigned by stereodivergent synthesis of six diastereomeric model compounds and comparison of their NMR spectroscopic data with those reported for the natural product.[306,307] The results of stereoselective and stereodivergent synthesis of the proposed C-79–C-104 fragment of symbiodinolide and stereodivergent syntheses of the C-79–C-97 and C-94–C-104 fragments have led to the reassignement of the relative configuration of this portion of ***717***.[308,309] The complete biosynthetic pathway to the polyketide 13-desmethylspirolide C in *Alexandrium ostenfeldii* has been established by feeding experiments with ^{13}C methyl-labelled methionine and application of the odd-even methylation rule.[310] Feeding ^{13}C-labelled acetates to *Amphidinium* sp. established that all of the carbons of amphidinin A and amphidinolide P were derived from acetates. The polyketide chain of amphidinin A was formed from one triketide and two diketide chains and three unusual isolated C1 units derived from C-2 of cleaved acetates, while the polyketide chain of amphidinolide P was formed from one pentaketide chain, two acetate units, and three isolated C1 units also derived from C-2 of cleaved acetates.[311] Feeding of ^{15}N-labelled intermediates into paralytic shellfish toxins (PSTs) in *Alexandrium circinalis* indicated that biosynthetic intermediates predicted from gene sequences are genuine precursors of PSTs and that a related compound derived from one of these precursors is a shunt product released from cells to reduce PST production.[312]

4 Green algae

Only two new MNPs were reported from the phylum Chlorophyta in 2016 and only a further eight papers and four reviews have described studies on compounds previously reported from green algae. As part of a study of the edible green micro-alga, *Chlorella sorokiniana*, to measure the concentration of the macular protective compound lutein, two new MNPs, sesquiterpene chlorellatin A ***718*** and ergosterol derivative chlorellatin B ***719*** were identified.[313] Both had previously been reported as synthetic derivatives. Studies on the bioactivity of known green algal compounds include the inhibition of red tide algae by extracts and compounds derived from *Ulva intestinalis* and *U. prolifera* with fatty acid esters and carotenoid metabolites being the most active components.[314,315] 4-Hydroxy-2,3-dimethyl-2-nonen-4-olide isolated from *U. pertusa* inhibited pro-inflammatory cytokine production in CpG-stimulated bone marrow-derived dendritic cells in the μM range.[316] A proton NMR-based metabolomics study identified that dimethylsulfoniopropionate and acrylate derived from an unidentified *Ulva* species were sequestered by the sea hare *Aplysia juliana* and used as defensive compounds.[317] The carotenoid astaxanthin[318,319] and sulfolipids[320] continue to be investigated for various biological activities.

5 Brown algae

Twenty eight new compounds were reported from six species of brown algae in 2016 while a total of 46 papers and 11 reviews on brown algae were published. Twelve new meroditerpenoids, cystodiones G–L ***720–725*** and cystones A–F ***726–731*** along with eight known meroditerpenes have been reported from the Spanish brown algae *Cystoseira usneoides*.[321] The compounds were tested for antioxidant and anti-inflammatory activity and all show radical scavenging activity and some (such as **720**) were inhibitors of the production of the pro-inflammatory cytokine TNF-α in LPS-stimulated THP-1 human macrophages at 10 μM. *Dictyopteris divaricata* contained a cadinane sesquiterpene cadinan-4(15)-ene-1β,5α-diol ***732*** along with its known C-5 epimer and the norcadinane *trans*-3-norisocalamenen-4-ol ***733***.[322] An additional sesquiterpene ***734*** was isolated from *Taonia atomaria* along with known compounds; five sesquiterpenes, a unsaturated fatty acid and a unsaturated fatty glycerol ether. A number of the compounds (including ***734***) inhibited bacterial adhesion and barnacle settlement.[323] A study of the edible brown algae *Cladosiphon okamuranus* led to the characterisation of two steroids mozukulin A ***735*** and B ***736***, however neither compound showed activity in an anti-inflammatory assay.[313] A series of six disulfides ***737–742*** and two known disulfides were isolated from the Greek alga, *Dictyopteris membranacea*. None of the compounds showed antibacterial activity against multidrug resistant *S. aureus*, but **740** showed anti-inflammatory activity, inhibiting NO production in a LPS stimulation assay (IC_{50} 3.8 μM).[324]



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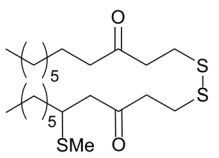


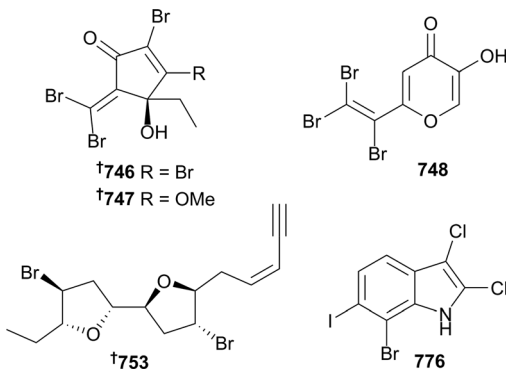
740

Extracts from eight New Caledonian *Lobophora* species (*L. rosacea*, *L. nigrescens*, *L. crassa*, *L. abscondita*, *L. dimorpha*, *L. undulata*, *L. hederacea* and *L. monticola*) were shown to bleach the scleractinan corals, *Acropora muricata* and *Stylophora pistillata*. Three C21 polyunsaturated alcohols lobophorenols A–C ***743–745*** were subsequently isolated from *L. rosacea* and shown to bleach *A. muricata* on contact.[325] Known brown algal-derived meroterpenes have been the

focus of several biological studies with atomaric acid active against *Leishmania amazonensis*,[326] sargaquinoic and sargahydroquinoic acids possessing anti-adipogenic and pro-osteoblastogenic activities[327] and 11-hydroxy-1′-*O*-methylamentadione reducing the effect of dextran sulfate-induced colitis in mice.[328] Dolastane diterpenes from *Canistrocarpus cervicornis* inhibited HIV-1,[329] and spartane diterpenes from *Stoechospermum marginatum* induced apoptosis in melanoma cells.[330] The first total synthesis of dictyoxetane[331,332] and the unnatural enantiomer (−)-erogorgiaene,[333] were reported. Additionally, there were many papers dealing with the biological properties of brown algal lipids,[334–337] polyphenolics[338–348] and carotenoids.[349–360]

6 Red algae

The reporting of thirty-seven new compounds from red algae in eight papers is close to the average for each of the previous five years. Four polybrominated C_4–C_8 hydrocarbons ***746–749*** (*Plocamium australasica*) include the ptilones A–C **746–748** which possess skeletons not previously seen in algal metabolites.[361] Three C_{15}-acetogenins ***750–752*** were isolated from *Laurencia marilzae*.[362] The absolute configuration of elatenyne **753** (*Laurencia elata*[363]) was previously determined somewhat ambiguously by synthesis of a proposed diastereoisomer,[364] but the absolute configuration has now been unambiguously determined by the crystalline sponge method, which enables the crystallographic analysis of non-crystalline compounds on the microgram scale. In this case, only ∼100 μg of elatenyne was required with ∼95% being recovered after the experiment. This represents the first real application of the crystalline sponge method to the determination of the absolute configuration of a natural product.[365] A synthesis of (−)-bisezekayne A ***754*** (*Aplysia oculifera*[366]) has led to a structural revision and the determination of absolute configuration.[367]



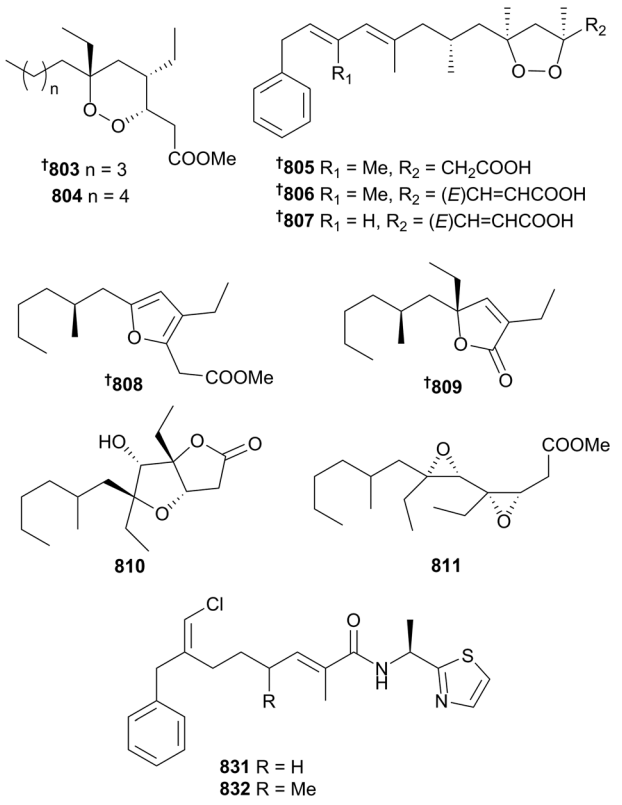
Sesquiterpenoids continue to be commonly encountered in the red algae, with nine brominated chamigrene and cuparane sesquiterpenoids ***755–763*** being obtained from *Laurencia tristicha*,[368] the eudesmane ***764*** from *L. obtusa*,[369] three brominated eudesmanes (selinanes) ***765–767*** and a brominated cycloeudesmane ***768*** from *L. pinnata*.[370] Three meroterpenoids ***769–771*** with variable anti-oxidative activities were characterised from *Hypnea musciformis*.[371] Halogenated indoles are another commonly encountered structural type, with eleven polyhalogenated indoles ***772–782*** from *Rhodophyllis membranacea*, including six which were the first isolation of bromo–chloro–iodo secondary metabolites, as exemplified by **776**.[372] Further related compounds were four brominated indole related alkaloids ***783–786*** (*Laurencia similis*),[373] and bromophenol ***787*** (*Odonthalia corymbifera*).[374]

Papers describing work on new bioactivities for known compounds from red algae include the reporting of the larvicidal potential of obtusol (*Laurencia dendroidea*)[375] against the dengue fever mosquito *Aedes aegypti*,[376] bis(2,3-dibromo-4,5-dihydroxybenzyl) ether (BDDE) (*Odonthalia corymbifera*)[377] as a novel PTP1B inhibitor and potential anti-diabetic agent,[378] immunomodulatory effects of the mycosporine-like amino acids shinorine and porphyra-334 from *Porphyra* sp.,[379] and the insecticidal activity guided isolation of palytoxin[380] from *Chondria armata*. This report also presented refined NMR spectral assignments for palytoxin and claimed this as the first isolation of the toxin from a marine plant.[381] Other studies included the diel variation of sesquiterpene elatol[382] production: a chemical defense mechanism in *Laurencia dendroidea*,[383] the geographic distribution along the SE Brazilian coast of natural products produced by *L. dendroidea*,[384] a study on the sterol biosynthesis pathway in *L. dendroidea* by the cloning and functional characterisation of a cycloartenol cyclase,[385] the biological activities of known compounds from three edible *Gracilaria* spp.,[386] and the design and synthesis of analogues of galaxamide (*Galaxaura filamentosa*)[387] as potential antitumor agents.[388] Other synthetic studies included the first total synthesis of an antibacterial polyhalogenated monoterpene, (−)-anverene (*Plocamium cartilagineum*[389]),[390] and the total syntheses[391] of the *Laurencia marilzae* metabolites 12-epoxyobtusallene IV,[392] obtusallene X,[392] and marilzabicycloallenes C and D.[393]

7 Sponges

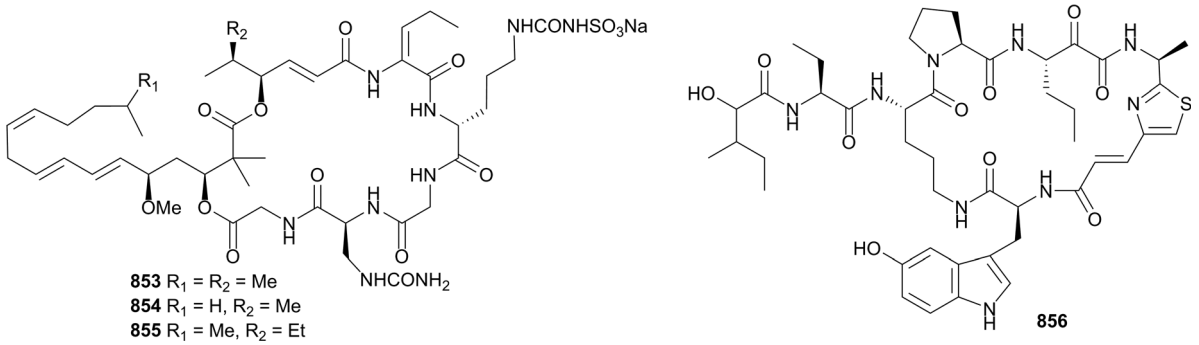
With 224 new and new to marine compounds reported in 2016, compared with 291 in 2015,[1] the impacts of changing focus away from sponges towards microorganisms and other phyla are dramatic; the number of sponge metabolites reported in 2016 is the lowest in over a decade. Nonetheless, sponges are still an important taxonomic group for the discovery of new, bioactive natural products. A number of new glyceride (***788*** and ***789***) and ceramide (***790–793***) lipids have been reported from species of *Theonella* and *Erylus*,[394,395] while branched fatty acids (***794*** and ***795***), polyoxygenated fatty acid amides (***796*** and ***797***) and *N*-acyldopamine glycosides ***798–801*** were sourced from *Asteropus*, *Melonanchora*, *Myxilla* and *Theonella* sponges.[396–399] Unusually, only one new polyacetylene ***802*** was reported in 2016, from *Halichondria panicea*.[400] Examination of the two-sponge association between *Xestospongia deweerdtae* and *Plakortis halichondrioides*, in addition to *P. zyggompha*, resulted in the isolation of 6-*epi*-7,8-dihydroplakortide K **803**, plakortide AA **804**, and three chemically unstable plakinic acids N–P **805–807**. A combination of both Mosher's acid analysis, as well as comparison of density

functional theory (DFT) calculated and experimental ECD spectra were used to establish the absolute configurations of these compounds. The new plakinic acids have inverted configurations compared with other members of the series, although consideration of the likely biosynthesis would suggest they are all generated from a single unified phenylacetic acid (likely phenylalanine derived) starter unit followed by standard iterative ketide additions. Surprisingly, given the sponge extract exhibited antifungal activity against *Cryptococcus gattii*, none of the new compounds showed any bioactivity.[401]

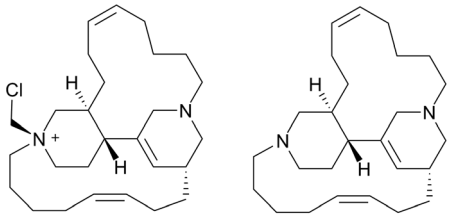


A Chinese (Xisha Islands) *P. simplex* was the source of four plakortin-metabolites, plakorsin D methyl ester **808**, plakilactone I **809**, plakortone Q **810** and the first vicinal diepoxide-containing polyketide plakdiepoxide **811**. Stability testing of the endoperoxide functionality of the most abundant *Plakortis* metabolite reported suggests that many of the polyketides isolated from the genus are likely artefacts from reductive or basic sensitivities. Plakdiepoxide **811** is a potent and selective inhibitor of peroxisome proliferator-activated receptor (PPAR)-γ and hence may have promise as a lead for treatment of Type II diabetes.[402] A large number of quinones have been reported from Australian *Clathria* (***812–815***)[403] and Indonesian *Petrosia* (***816–830***)[404] sponges. Conulothiazoles A **831** and B **832** are chlorinated NRPS/PKS hybrids isolated from a Bahamian *Smenospongia conulosa* that combine features from both the well-known cyanobacterial barbamide and jamaicamide compound classes. As less than 45 μg of each compound was isolated, Marfey's method was used to establish the configuration of the thiazole amide using only 4 μg of isolated compound for ozonolysis and hydrolysis. Unsurprisingly, a severe paucity of material prevented profiling of bioactivity.[405]

As always, a large number of peptidic and peptide-hybrid natural products have been reported from sponges in 2016. Metagenomic analysis has shown that kasumigamide ***833***, a known freshwater cyanobacterial product, is produced by an *Entotheonella* symbiont in a *Discodermia* sponge,[406,407] while other peptides were sourced from the *Theonella* (***834–836***),[408] *Stylissa* (***837–841***),[409,410] *Cribrochalina* (***842***),[411] *Callyspongia* (***843***),[412] *Asteropus* (***845–849***)[413,414] and *Petrosia* (***850–852***)[415] genera. A Japanese (Nakagi, Shizuoka Prefecture) specimen of *Discodermia kiiensis* was the source of sulfolipodiscamides A–C **853–855**, unprecedented *N*-sulfouridyl containing-compounds and essentially the sulfonated analogues of the known lipodiscamides A–C,[416] isolated again concurrently from the same sponge. The sulfonated analogues are approximately two-times more active against P388 murine leukaemia cells than the non-sulfonated, the latter likely to be degradative artefacts of isolation.[417] Only 33 μg of jamaicensamide A **856** was isolated from *Plakina jamaciensis* collected at Plana Cays in the Bahamas, however this was enough material to establish the structure of the cyclic hexapeptide. The configurations of the amino acid portion were secured by Marfey's analysis. The structural similarity of **856** with peptides isolated from other lithistid sponges of disparate genera collected from geographically distinct sites suggest that these compounds are likely produced by cosmopolitan symbionts of the genus *Entotheonella*. A paucity of material prevented biological evaluation of the compound.[418]

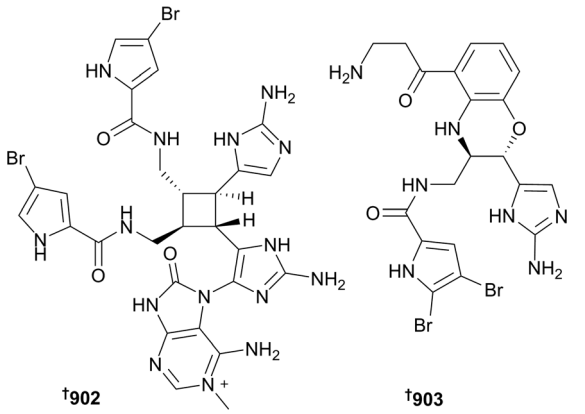


A new diketopiperazine ***857*** was isolated from *Callyspongia* sp.,[419] while macrocyclic alkaloids and their precursors were isolated from *Callyspongia* (***858*** and ***859***)[420] and *Halichondria* (***860–863***)[421] sponges, respectively. Chloromethylhalicyclamine B **864** (*Acanthostrongylophora ingens*, Makassar, Sulawesi, Indonesia) is a selective inhibitor of protein kinase CK1 (IC_{50} = 6 μM *vs.* both γ/ε isoforms) while being inactive against eight other kinases. The chlorinated compound was found to be an artefact of extraction with dichloromethane, reacting with the known compound halicyclamine B **865**,[422] which was itself inactive in the same kinase assays, indicating the extreme sensitivity of observed activity *versus* the structure of the compounds assayed. This study also established the absolute configuration of the known compound **865**.[423]



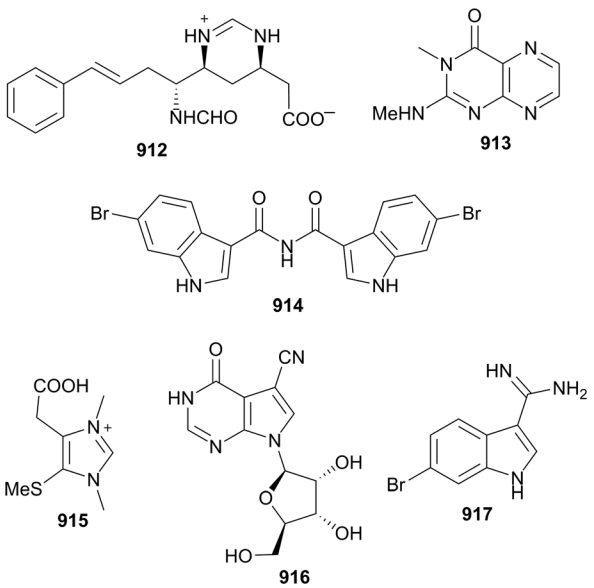
†**864** †**865**

3-Alkylpyridine compounds ***866*** and ***867*** have been isolated from *Xestospongia* and *Halichondria* species, respectively; the synthesis of the former compound was also achieved.[424,425] Indole containing natural products ***868*** and ***869*** (known synthetically),[426] and ***870–874*** (the last of which is known synthetically),[427–430] including β-carbolines ***875*** and ***876***,[431] have been isolated from species of *Acanthostrongylophora*, *Geodia*, *Haliclona*, *Hyrtios* and *Lipastrotethya*, and sourced from Asia, the Middle East and Scandinavia. An aromatic alkaloid ***877*** has been sourced from *Aaptos aaptos* (Vietnam),[432] while two isoquinoline compounds ***878*** and ***879*** were reported from *Xestospongia* sp. (Hainan Province, China).[433] As always, sponges have been rich sources of guanidine-derived metabolites. *Halichondria panicea* (Okinawa) yielded 6-*epi*-monancorin ***880***,[421] while *Monanchora* sponges were the sources of various monanchorin- and crambescin-type compounds ***888–889***.[434,435] In addition, pyrrole and imidazole compounds were sourced from *Agelas* sp. (***890–898***),[436] *Pericharax heteroraphis* (***899***),[437] and *Lissodendoryx* sp. (***900*** and ***901***).[438] Although inactive in anticancer, antibacterial and antifungal screens, unlike other members of the series, 15′-oxoadenosceptrin **902** and decarboxyagelamadin C **903** (*Agelas sceptrum*) are chemically interesting. Like many other congeners, these compounds are highly hydrogen deficient and hence the use of ^{1}H–^{13}C and ^{1}H–^{15}N HMBC experiments were of limited utility for structural elucidation. Rather, DFT calculations of NMR chemical shift data were used to corroborate with those of the detected resonances. Moreover, **902** is the first pyrroloimidazole compound to incorporate adenine.[439]



†**902** †**903**

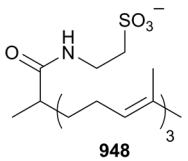
Given their normal prevalence, there were only two reports of new bromotyrosine metabolites in 2016, the first from an unidentified Indonesian Aplysinellidae sponge (***904–910***)[440] and the other from *Acanthodendrilla* sp. collected in Thailand (***911***), the total synthesis of which was also accomplished.[441] Lanesoic acid **912** is a novel zwitterionic acid isolated from a *Theonella* sponge collected at Lanes, Indonesia. The structure of the compound, including an unusual tetrahydropyrimidine cation motif, was established from standard spectroscopic techniques and confirmed by DFT-calculated properties, including confirmation by the DP4+ parameter. Interestingly, **912** was moderately active against the pancreatic cancer PSN1 cell line (IC_{50} = 8.9 μg mL^{-1}) but was inactive against colon, breast and lung tumour cells and hence shows cytotoxic specificity.[442] *Jaspis splendens* was the source of five new alkaloids jaspterin **913**, splendamide **914**, jaspnin A **915**, jaspamycin **916** and 6-bromo-1*H*-indole-3-carboximidamide **917**, the latter two of which are known synthetically.[443] These compounds were discovered through the application of a novel, unbiased, phenotypic screen using a human olfactory neurosphere-derived cellular model of Parkinson's disease. Jaspnin A **915** contains a rare methyl thioimidazole functionality, while jaspamycin **916** in particular displayed a distinctive perturbation of the Parkinson's derived cells and hence may be a useful probe of the molecular basis for the neurodegenerative disease. Additionally compound **917** contains the rare indole-3-carboximidamide motif.[444]



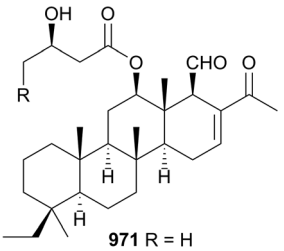
912 **913** **914** **915** **916** **917**

Each year the vast majority of sponge-derived compounds fall into the isoprenoid class and 2016 was no exception. A specimen of *Spongia* yielded two merosesquiterpenoids ***918*** and ***919*** (ref. 445) as did three different collections of *Dysidea* (***920–930***).[446–448] Only two meroditerpenoids ***931*** and ***932*** were reported in 2016,[449] while sesquiterpenoids, their formamides, isocyanides, thiocyanates, isothiocyanates and dimers ***933–947*** (ref. 450–452) were reported from *Axinyssa*, *Dysidea* and *Halichondria* sponges; ***944*** is a known synthetic compound.[453] A novel taurinated norditerpene geodiataurine **948** was reported from a sample of *Geodia macandrewii* dredged in both Nordland and Trøndelag, Norway. The molecule was discovered following a comprehensive LCMS-based metabolomics survey of Norwegian *Geodia* specimens that discovered a statistically different chemotype from the more common barettin-containing species. All four samples of *G. macandrewii* contained **948** and no barettin. Geodiataurine exhibited weak activity ($IC_{50} = 8.5$ μM) against A2058 melanoma cells but with no antibacterial effects.[454] Other diterpenoids, ***949*** and ***950*** (total syntheses also achieved),[455] especially based upon the ubiquitous spongian diterpene skeleton ***951–962***,[456–458] were isolated from *Theonella*, *Dysidea*, *Spongia* and *Dendrilla* sponges, all with varying activities. Several norscalarane ***963–967*** (ref. 459 and 460) and scalarane ***968–970*** (ref. 461 and 462) sesterterpenoids were reported in 2016 from sites in Asia and Egypt. New scalaranes **971** and **972** were isolated from *Carteriospongia* sp. collected at Taitung, Taiwan, as part of a campaign to identify new topoisomerase inhibitors. Compound **971** was a potent disruptor of mitochondrial membrane potential in Molt 4 (leukaemia) cells ($IC_{50} = 125$ nM), inducing apoptosis, and significantly more potent than the other isolates. Detailed mechanistic investigation indicated that the scalaranes inhibited topoisomerase IIα expression, but also induced expression of heat shock protein (Hsp) 70, acetylated tubulin and activated caspase 3, suggesting that the proapoptotic activity of the compounds is due to dual inhibition of Hsp90 and topoisomerase activities.[463]

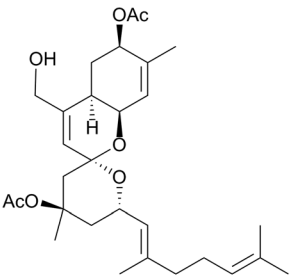
A comprehensive study of a Canadian *Phorbas* sponge (Howe Sound, British Columbia) yielded eight new sesterterpenoids with various carbon skeletons. Alotaketals A **973** and B **974**, and ansellones D–G **975–978** were new congeners of known scaffolds, while anvilones A **979** and B **980** belong to a new class. In addition, **977** possesses the rare 1,2-3,4-bisepoxide moiety, rarely seen amongst natural products. Several of the isolates induced HIV proviral gene expression, through activation of protein kinase C signalling.[464]



948



971 R = H
972 R = Me



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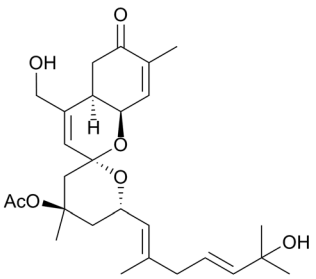

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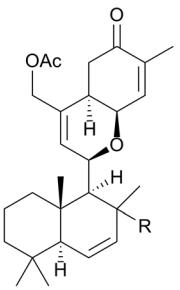
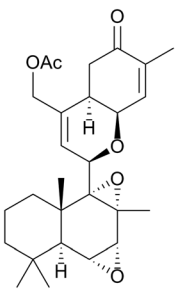
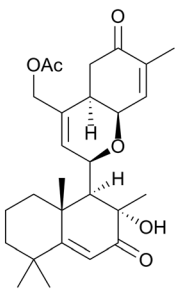


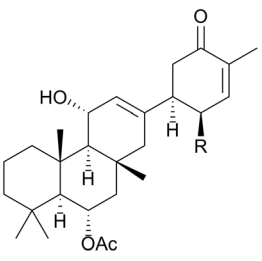
975 R = ····OMe
976 R = ◄OH



977



978



979 R = H
980 R = OAc

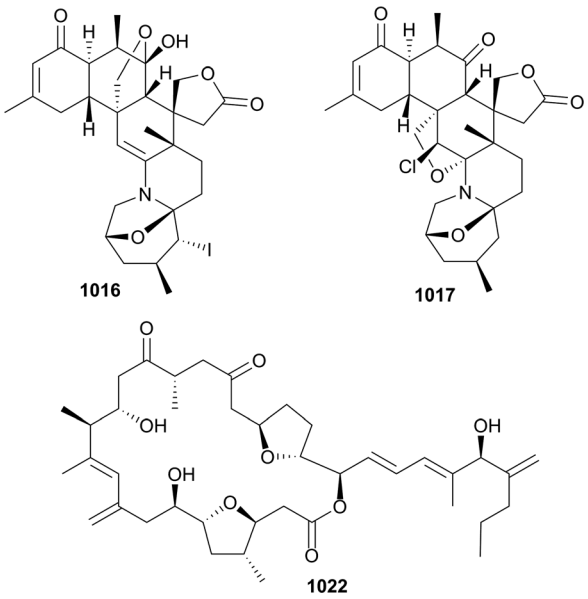
A report of pregnanes ***981–984*** (ref. 465) from a *Myrmekioderma* sponge and four reports of sterols and sterol esters ***985–1000*** (ref. 466–469) were made from *Xestospongia* and *Topsentia* sponges in 2016; compounds ***994*** and ***995*** had been synthesised previously.[470,471] Only two triterpenoid structures were published in 2016, one ***1001*** from *Jaspis stellifera*,[472] and the other ***1002*** from a *Lipastrotethya* sp.[473] Synthetic callipeltins B, E,[474] and M[475] were found to be inactive, whilst natural isolates (*Latrunculia* sp.) were toxic to HeLa cells, suggesting the observed bioactivity was from low levels (~15%) of callipeltins C and H.[476] Leiodermatolide, a polyketide macrolide and potent cytotoxin,[477] has been found to disrupt spindle formation during mitosis, although it does not cause polymerisation or depolymerisation of microtubules and hence has a unique mode of action as an antimitotic agent. Rather, the molecular target of leiodermatolide is likely to be microtubule-associated proteins.[478] Stryphnusin (*Stryphnus fortis*)[479] was discovered as a weak inhibitor of acetylcholinesterase activity. Given its structural simplicity and similarity to other natural acetylcholinesterase agonists, a synthetic campaign produced multiple analogues with strong competitive activity to the target enzyme and additionally butylcholinesterase. Studies of the physiological effects of the library upon muscle function and neuromuscular transmission suggest a novel mode of action and hence stryphnusin represents a new lead for neurodegenerative diseases.[480] Pyrroloiminoquinone metabolites including discorhabdin B[481] and makaluvamine F[482] isolated from an Australian *Latrunculia* sp. inhibited Hypoxia Inducible Factor-1α (HIF-1α) transcription and hence inhibited angiogenesis,[483] while makaluvamine J (*Zyzzya* sp.)[484] was a potent antioxidant.[485] The quintessential MNPs oroidin[486] and sceptrin[487] had antibacterial adjuvant activity and suppressed antibiotic resistance,[488] while the former is also a new lead for HIV antiviral development.[489] Isofistularin-3 (*Aplysina aerophoba*)[490] was found to induce apoptosis, with a novel mode of action *via* inhibition of DNA methyltransferase 1, making it a new anticancer lead.[491] Internet-based tools for scientific research continue to grow in scope and availability. Submission of 71 MNP structures to the Eli Lilly Open Innovation Drug Discovery[492] platform identified several potential leads as inhibitors of VEGF, including araguspongine C[493] and puupehenone,[494] hence both these could be attractive targets for further investigation as angiogenesis inhibitors.[495] The ubiquitous meroterpenoid avarone[496] and several congeners[497–499] enhanced root growth in various terrestrial plants and could have application as agricultural growth stimulants,[500] while a dimeric bisabolenyl urea[501] was found to inhibit protein tyrosine phosphatase 1B (PTP1B) at sub-toxic concentrations, as well as enhancing insulin-stimulated phosphorylation of Akt and hence may be a new lead for Type II diabetes.[502] The common spongian diterpenoids gracilin A,[503,504] H,[505] and L,[506] and additionally tetrahydroaplysulphurin-1,[507] bound strongly to cyclophilin A in a manner similar to cyclosporine A, and hence are new immunosuppressants.[508,509] The highly oxygenated diterpenoid gagunin D[510] inhibited melanin production through inhibition of tyrosinase expression, making it a potential skin whitening cosmetic agent.[511] A large number of first syntheses have been reported in 2016, including vesparioside B,[512,513] strongylodiols C and D,[514,515] lembehyne B,[516,517] the previously unreported xestospongenyne,[518] and petrosiol A.[519,520] The relative configuration of the C-13–C-25 section of hemicalide ***1003*** (ref. 521) has been determined by synthesis.[522] Plakilactone B, C, des-hydroxyplakilactone B,[523] and des-hydroxygracilioether C[524] have been synthesised,[525] as has gracilioether E.[526,527] Peptides are common sponge metabolites and hence are targets of synthetic campaigns. Gombamide A,[528–530] stylissamide G,[531,532] and phakellistatin-15 (ref. 533) were all synthesised in 2016, with the latter compound being inactive while the natural version inhibited the growth of several HTCLS, indicating the presence of a highly potent contaminant in the initial extract.[534] The structures of solomonamide B (*Theonella swinhoei*) ***1004*** (ref. 535 and 536) and microsclerodermin J (*Microscleroderma herdmani*) ***1005*** (ref. 537) were revised following synthesis, the latter study also accomplished the synthesis of the dehydro derivative of microsclerodermin B, dehydromicrosclerodermin B ***1006***.[538] Three separate syntheses established the absolute configuration of callyspongiolide A (*Callyspongia* sp.) ***1007***.[539–542] Aurantoside G[543] has been synthesised,[544] while a synthesis of haliclonin A,[545] consistent with the written description of the configuration of the molecule but opposite to that drawn (incorrectly) in the original publication, has been reported.[546] Renieramycin T[547] has been made,[548,549] while the absolute configurations of isowondonins A ***1008*** and B ***1009***,[550] isolated from *Poecillastra wondoensis*, were established following their syntheses.[551] Other first total syntheses of hyrtinadine B,[552,553] dictyodendrin H and I,[554,555] crambescin A and C,[556,557] clavatadine C,[558,559] cyclosmenospongine,[560,561] strongylophorine 1, 2, 3,[562] 8,[563] and 9,[564,565] arenaran A and B,[566,567] polyrhaphin D,[568,569] hamigeran D,[570] G, L,[571] N–Q,[572,573] and luffarin P[574,575] have been achieved. Both the relative and absolute configurations of furospongin-1 ***1010*** (ref. 576 and 577) and dihydrofurospongin-2 ***1011*** (ref. 578) have been established by synthesis,[579] as has the side-chain configuration of clathsterol ***1012***.[580,581] A detailed combination of genomic and metagenomic analyses has shown that the biosynthesis of polytheonamide (*Theonella swinhoei*),[582] a member of the growing class of Ribosomally synthesised and Post-translationally modified Peptides (RiPPs), includes the first example of a B_{12}-dependent radical *S*-adenosylmethionine C-methylation step.[583] A cautionary tale has been published detailing the need for care when reporting new metabolites from dual sponge associations. Ianthelline is a member of the bromotyrosine compounds commonly found from Verongid sponges, originally *Ianthella ardis*,[584] and later *Stryphnus fortis*.[585] A comprehensive LCMS investigation of a Norwegian (Svalbard) *S. fortis*, and additionally *Hexadella dedritifera* that is commonly found encrusting upon it, has shown that it is actually the latter that is the true producer of ianthelline, and hence great care must be made to try and avoid contamination of one sponge sample with another.[586] An HPLC-based chemical investigation using both diode array and evaporative light scattering detection of compounds from *Aplysina cavernicola* collected around Maire Is., France, has shown that the reproductive state of the sponge has very little impact upon the secondary metabolism of the sponge. Instead, water temperature seems to play the largest role in controlling the bromotyrosine chemodiversity, and hence chemical defence, of the sponge.[587] An analysis of the chemical

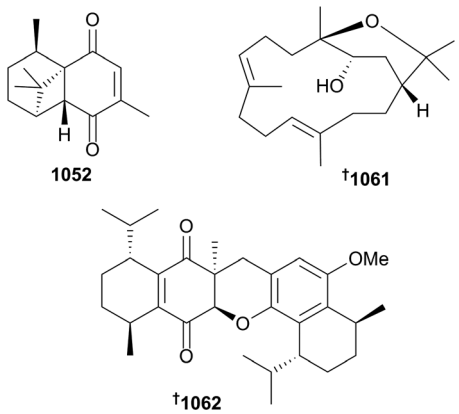
reactivity of the merosesquiterpenoid siphondictyal B (*Siphondictyon coralliphagum*)[588] under aerobic conditions to produce corallidictyals A and B (*Aka coralliphagum*, synonymous with *S. coralliphagum*) and *via* acid to produce corallidictyals C and D was undertaken.[589,590] The oxidative cyclisation proceeds to give the same 1 : 2 ratio of corallidictyals A and B as found in nature, suggesting that they may be products of an autooxidative chemical process rather than enzymatically controlled; the corallidictyals may therefore also be artefacts of isolation.[591] Finally, a study has been undertaken to compare the sterol biosynthetic potential of four fossilised sponge species (*Salpingoeca rosetta*, *Capsaspora owczarzaki*, *Sphaeroforma artica*, *Creolimax fragrantissima*) to try and identify key fossil biomarkers of eukaryote development. In particular, 24-isopropylcholesterol has been suggested as a "molecular fossil" and as the key historical metabolite as evidence of life, but questions arise whether ancient sponges or algae were the source of the compound in previous reports. Genomic data suggest that sponges independently developed genes encoding for C_{30} sterol biosynthesis, including 24-isopropylcholesterol, before other ancient phyla, especially pelagophyte algae. This indicates that it is unlikely that algae are the source of ancient 24-isopropylcholesterol and is consistent with the hypothesis that sponges evolved long before the Cambrian explosion 542 million years ago.[592]

8 Cnidarians

The 202 new compounds reported from cnidarians in 2016 are just below the previous decadal average. Of this total, ten nitrogenous metabolites were reported from hydroids, zoanthids and soft corals, including the cytotoxic ceramide ***1013*** (*Heteroxenia ghardaqensis*),[593] brominated-indoles ***1014*** and ***1015*** (hydroid *Abietinaria abietina*) which were found to activate NF-kB-dependent transcription,[594] and zoanthamines ***1016–1021*** from the zoanthid coral *Zoanthus kuroshio*.[595] Of note were 5α-iodozoanthamine **1016** and 11β-chloro-11-deoxykuroshine A **1017** which are the first reported examples of halogenated zoanthamine alkaloids. New examples of amphidinolides, C4 **1022**, B8 ***1023*** and B9 ***1024***, in addition to the known dinoflagellate-sourced T1, were reported from Brazilian specimens of the octocoral *Stragulum bicolor*.[596] Modest cytotoxicity was observed for **1022** and ***1023***. The simple dinormonoterpenes ***1025*** and ***1026*** were reported from *Sinularia mollis*.[597]

Thirty-one sesquiterpenes were reported, comprised of capgermacrene C ***1027*** (*Capnella* sp.),[598] lochmolin H ***1028*** (*Sinularia lochmodes*),[599] cadinane-type endo- and hydro-peroxides ***1029–1031*** (*Sinularia* sp.),[600] ***1032*** and ***1033*** from *S. verruca*,[601] from which was also reported a rare pyrroloindoline alkaloid ***1034*** in addition to two simpler cyclopentenones ***1035*** and ***1036***, bisabolanes ***1037–1045***, cadinanes ***1046–1051*** and a sesquiterpene bearing a new tricyclic skeleton **1052** (*Pseudopterogorgia rigida*),[602] cadinane ***1053*** (*Menella* sp.),[603] eudesmane-type ***1054*** (*Subergorgia suberosa*),[604] and guaiane lactones ***1055*** and ***1056*** (*Menella woodin*).[605] The final example of a sesquiterpene, cadinane ***1057***, isolated from *Sinularia vanderlandi*, was included in a publication that also reported spartane diterpenoid ***1058***, lipids ***1059*** and ***1060***, and cembrane isodecaryiol **1061** from *S. gravis*.[606] The structure of the latter metabolite, which is a diastereomer of the often reported cnidarian cembranoid decaryiol, was rigorously established and absolute configuration assigned by X-ray crystallography. X-ray crystallography was also used to establish the structure and absolute configuration of the unusual bis-sesquiterpene **1062** (*Rhytisma fulvum fulvum*) – the metabolite is likely derived from dimerisation of the natural product 5-hydro-8-methoxycalamenene.[607] Of six assorted diterpenes ***1063*** and ***1064*** (*Sinularia* sp.),[608] and ***1065–1068*** (*Gersemia fruticosa*),[609] lobane ***1063*** and eunicellane ***1068*** exhibited modest antibacterial activity.

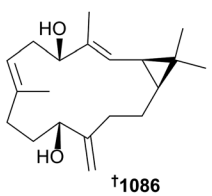




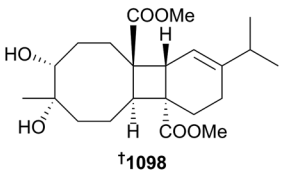
Nearly fifty cembrane-related metabolites were reported from cnidarians in 2016. Amongst these were the 15-acetoxy examples ***1069–1071*** (*Nephthea* sp.),[610] pyranose-containing ***1072*** (*Sarcophyton trocheliophorum*),[611] a mildly anti-Staphylococcal 16-hydroxyl cembranoid ***1073*** (*Sarcophyton* sp.),[612] epoxides trocheliolide B ***1074*** (*S. trocheliophorum*)[613]

and sarcophytonoxides A–E ***1075–1079*** (*S. ehrenbergi*),[614] sinulerectols A–C ***1080–1082*** and degraded cembranoid sinulerectadione ***1083*** (*Sinularia erecta*).[615] The latter study also led to a revision of relative configuration of the previously reported cembranoid sinularectin ***1084***. Further examples of cembranoids or related metabolites included sinularcasbanes M–O ***1085–1087*** (*Sinularia polydactyla*),[616] where the absolute configuration of **1086** was secured by X-ray crystallography, anti-inflammatory uprolides N–P ***1088–1090*** (*Eunicea succinea*),[617] cubitanoids (a scaffold previously speculated as being photochemically-derived from cembranoids) nanoculones A ***1091*** and B ***1092*** and cembranoids nanolobols A–C ***1093–1095*** (*Sinularia nanolobata*),[618] locrassumins A–G ***1095–1102***, (−)-laevigatol B ***1103***, (−)-isosarcophine ***1104*** and sarcophytoxide analogue ***1105*** (*Lobophytum crassum*),[619] casbane-type diterpenoid ***1106*** and diepoxycembranes ***1107*** and ***1108*** (*Lobophytum* sp.),[620] and pambanolides A–C ***1109–1112*** and a *seco*-sinulochmodin analogue ***1113*** (*Sinularia inelegans*).[621] While ***1110*** and **1111** were initially isolated as an inseparable mixture, an X-ray structure of **1111** (pambanolide B_2) was eventually secured. This study also established the configuration of rameswaralide *via* X-ray crystallography. Bis-cembrene trocheliane **1114** and pyran-cembranes sarcotrocheldiol A ***1115*** and B ***1116*** were isolated from *Sarcophyton trocheliophorum* and strong antibacterial activity was reported for **1114**.[622] Finally for cembranoids, the structures of unusual cembrane–capnosane heterodimers bissubvilides A **1117** and B **1118** (*S. subviride*) were secured by combinations of spectroscopic analysis and time dependent DFT (TDDFT)/ECD and NMR calculations.[623] Also of note amongst the cembranoid natural products was the unprecedented carbon skeleton present in locrassumin C **1098** and the use of analysis of an induced CD spectrum resulting from an *in situ* $Mo_2(OAc)_4$ complex to determine absolute configuration.

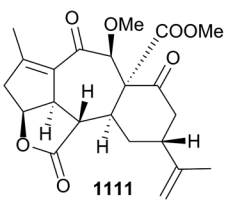
Twenty-one new briarane diterpenes were reported in 2016, comprised of briarenolides M–T ***1119–1126*** (ref. 624) and ZI–ZVI ***1127–1132*** (ref. 625) (both sets of metabolites from the same collection of *Briareum* sp.), and gemmacolides AZ–BF ***1133–1139*** from *Dichotella gemmacea*.[626] Briarenolides M, P, S, T, ZII and ZVI were found to inhibit production of the pro-inflammatory inducible nitric oxide synthase (iNOS), briarenolides N, P and T inhibited the product of COX-2 in LPS-stimulated macrophage cells, and the gemmacolides exhibited low to no cytotoxicity towards two HTCLs and moderate antibacterial activity. The remaining eight diterpenes, all eunicellins, included klymollins Y ***1140*** and Z ***1141*** and klyxumollins A–D ***1142–1145*** (*Klyxum molle*),[627] and cladieunicellins R ***1146*** and S ***1147*** (*Cladiella tuberculosa*).[628] Diterpenes ***1141*** and ***1142*** and ***1147*** exhibited modest cytotoxicity towards HTCLs. Cnidarians, comprising both zoanthids and soft corals, also yielded a variety of steroids including *seco*-sterols pinnigorgiol A–C ***1148–1150***,[629] and D ***1151*** and E ***1152***,[630] pinnisterol A–C ***1153–1155***,[631] (*Pinnigorgia* sp.) and haebaruol ***1156*** (*Clavularia* sp.),[632] *seco*-sterol ***1157*** and epoxy-sterol ***1158***, (*Pinnigorgia* sp.),[633] *seco*-sterol sibogol D ***1159*** and cross-conjugated sterol dienones sibogol E ***1160*** and F ***1161*** (*Muricella sibogae*),[634] pregnanes subergorgol T–X ***1162–1166*** (*Subergorgia suberosa*),[635] cross-conjugated dienones petasitosterone A–C ***1167–1169*** (*Umbellulifera petasites*),[636] ecdysones zoanthone A ***1170*** (*Zoanthus* sp.)[637] and palythone A ***1171*** (*Palythoa mutuki*),[638] 18-oxygenated sterol ***1172*** (*Nephthea* sp.),[639] 19-oxygenated sterol ***1173*** (*Pacifigorgia senta*),[640] sterols including cyclopropylated (gorgosterol) examples ***1174–1177*** (*Pinnigorgia* sp.),[641] ***1178*** (*Lobophytum lobophytum*),[642] klyflaccisteroids G–J ***1179–1182*** (*Klyxum flaccidum*),[643] and ***1183*** and ***1184*** (*Sinularia microspiculata*),[644] 4α-methylated sterols ***1185–1191*** (*Litophyton mollis*),[645] polyhydroxylated sterols ***1192–1209*** (*Gorgonia* sp.),[646] 24-methylene sterols ***1210*** (*Nephthea columnaris*)[647] ***1211*** (*Sinularia* sp.)[648] ***1212*** and ***1213*** (*Nephthea erecta*)[649]



†1086



†1098



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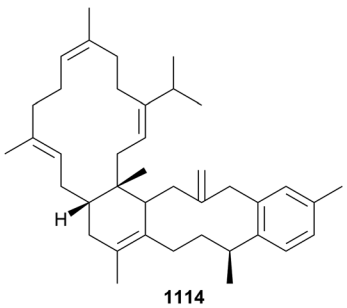

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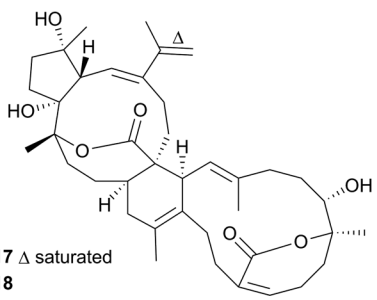
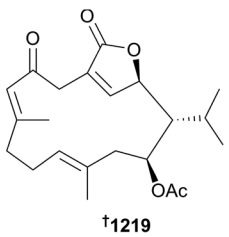


†1117 Δ saturated
†1118



†1219

and ***1214*** (*Sinularia nanolobata*),[650] 24-epoxy sterol ***1215*** (*S. nanolobata*),[650] and steroidal glycosides ***1216–1218*** (*Astrogorgia dumbea*).[651] The structure of sarcophytonolide H has been confirmed by total stereospecific synthesis: the same study led to revision of the relative configuration of the 14-acetoxy substituent of isosarcophytonolide D to **1219**.[652]

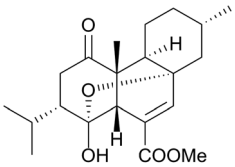
An enantioselective synthesis of (1*S*)-suberosanone led to configurational assignment of the related suberosenol A.[653] Unfortunately the potent HTCL cytotoxicity reported for naturally occurring (1*S*)-suberosanone was not observed for the synthetic material. An organocatalytic system was used to prepare non-natural enantiomer (1*R*)-suberosanone,[654] and first syntheses of malonganenone J[655] and *seco*-pseudopteroxazole[656] have been reported. Further biological studies have identified that hydrogen peroxide derived from peroxy sesquiterpenoids induced apoptosis in HCT116 cells,[657] pseudopterosin protects synaptic function during oxidative stress suggesting a potential role as a neuromodulatory agent,[658] a metabolomics approach has identified that flexibilide-treated HCT116 cells suffer TCA cycle down-regulation and up-regulated levels of sphingosine-1-phosphate,[659] sinularin suppresses the proliferation of gastric tumour cells and induces apoptosis *via* mitochondrial dysfunction,[660] 5-*epi*-sinuleptolide inhibits early biofilm formation of the human pathogenic Gram negative bacterium *Acinetobacter baumannii*,[661] 11-dehydrosinulariolide exerts antiapoptotic and anti-inflammatory effects at different time points after spinal cord injury[662] and also exerts a neuroprotective effect in models of Parkinson's disease,[663] 11-*epi*-sinulariolide acetate exhibits cytotoxicity towards HA22T hepatocellular carcinoma cells inducing apoptosis through mitochondrial dysfunction and endoplasmic reticulum stress pathways,[664] a sterol from the hard coral *Acropora formosa* induces p53-mediated apoptosis in A549 human non-small cell lung cancer cell-line,[665] and the carotenoid peridinin exerts anti-proliferative and pro-apoptotic effects against human T-cell leukemia virus type 1-infected T-cell lines by suppressing NF-kB and Akt signalling[666] and anti-viral properties.[638] Comprehensive LCMS analysis of organisms living in close proximity to *Palythoa tuberculosa* on an Okinawan reef, has detected the presence of palytoxin and 42-hydroxy-palytoxin exclusively in the coral.[667]

9 Bryozoans

In contrast to 2015 when nine new compounds were reported, there were no new metabolites reported from this understudied phylum in 2016. There were two reports relating to compounds previously isolated from the phylum however. The cytotoxicity to HeLa cells of the alkaloid pterocellin A, a metabolite of the New Zealand endemic species *Pterocella vesiculosa*, was shown to occur *via* mitochondrial apoptotic processes.[668] Amathaspiramides A–F originally isolated from the Australasian endemic species *Amathia wilsoni*, and four analogues have been synthesised and tested for antiproliferative activity against four HTCLs.[669] In contrast to the original report in which all amathaspiramides were shown to be inactive towards P338 murine tumour cells at 25 μM,[670] amathaspiramide C was the most active compound showing weak (IC_{50} 5.8 μM) activity towards the MiaPaCa-2 pancreatic cancer cell line. Furthermore only amanthaspiramindes A, C and E containing a pyrrolidine and 8*R* configuration of the *N*-acyl hemiaminal moiety showed antiproliferative activity. A series of simplified bryostatin analogues[671] and salicylate-derived bryostatin analogues[672] were prepared and exhibited very potent anti-Chikungunya virus activity.[671,672]

10 Molluscs

The 24 new metabolites reported in 2016 from molluscs is close to the average number reported per year over the past decade. New metabolites reported from molluscs included polypropionates exiguapyrone ***1220*** and exiguaone ***1221*** (cephalaspidean (bubble snail) mollusc *Haminoea exigua*),[673] kahalalide analogues Z_1 ***1222*** and Z_2 ***1223*** (sea hare *Elysia ornata*),[674] rearranged diterpenes and norditerpenes ***1224–1238*** from Australian specimens of the nudibranchs *Goniobranchus verrieri*, *G. splendidus*, *G. cf. splendidus* and *G. daphne*,[675,676] diterpenes ***1239–1242***, including one **1239** which was identified as being a potent fish feeding deterrent, from the aeolidoidean *Phyllodesmium longicirrum*,[677] and two new secosterols ***1243*** and ***1244*** from the sea hare *Aplysia kurodai*.[678]



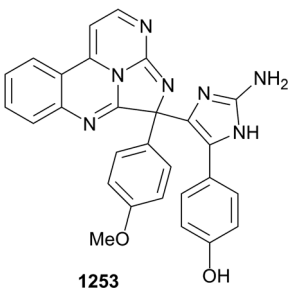
1239

Of note were the structure elucidations of the *Goniobranchus* metabolites, many of which were isolated in submilligram quantities. In a beautiful exposition of the utility of total synthesis, the putative linear contiguous polyketide precursor of the mollusc metabolite dolabriferol has been shown to undergo regioselective *retro*-Claisen fragmentation to form the natural product under mild conditions.[679] Total syntheses of (+)-panacene,[680] brominated chamigrene sesquiterpenes, including aplydactone,[681,682] the protein synthesis inhibitor chlorolissoclimide,[683] and (−)-chromodorolide B[684] have been reported. Carotenoid mytiloxanthin, originally reported from the sea mussel *Mytilus californianus*, quenches singlet oxygen and inhibits lipid peroxidation.[685] The mode of binding of aplysiatoxin to protein kinase Cδ C1B domain in a model bilayer membrane has been studied using molecular dynamics simulation,[686] while surface plasmon resonance was used to analyse the actin-tubulin protein–protein interaction induced by aplyronine A.[687] Latrunculin A is selectively accumulated in the rim of the mantle of *Chromodoris* nudibranchs, with the implication that, being the most exposed part of the mantle, the natural product is used as a predator deterrent.[688] Latrunculin A demonstrated potent antifeedant activity towards rock pool shrimps (*Palaemon*

serenus). New examples of conotoxins purified from venom of *Conus* species molluscs were reported: PiVIIA,[689] a 25-mer producing significant increases in Ca^{2+} currents (*C. princeps*); Im10A,[690] an 11-mer bearing four cysteine residues (*C. imperialis*); Lo6/7a and Lo6/7b,[691] 24- and 27-mers, respectively, which are examples of framework VI/VII conotoxins from *C. longurionis*; Asi3a a framework III 15-mer and Asi14a a framework XIV 17-mer, both[691] from *C. asiaticus*; and AusB, an unsual 18-mer example bearing only one disulfide bond, isolated from *C. australis*.[691] Screening of a library of synthetic conotoxin variants has identified a peptide that upon further structure–activity relationship tuning, led to analogues that were potent and selective agonists of the κ-opioid receptor.[692] Large quantities of the nAChR antagonist, α-conotoxin LvIA, have been prepared *via* an *E. coli* recombinant expression system.[693] Some carnivorous cone snails, including worm-hunting snails of the subgenus *Rhizoconus*, have evolved two distinct venoms – one set of peptides for defence, and another set for predation.[694] A phylogenetic and molecular evolution analysis of αD-conotoxins suggests that they evolved as part of a defensive strategy in this subgenus.

11 Tunicates (ascidians)

The ten new tunicate-derived natural products presented in this review is the second lowest number reported in one year since 2002. The metabolites reported included a phosphorylated polyketide ***1245***,[695] a new glycosylated macrolide mandelalide E ***1246***,[696] an acetylenic amino alcohol ***1247*** and *N*-hydroxylated-1,2,3,4-tetrahydro-β-carboline ***1248***,[697] neuroactive guanidine alkaloids ***1249–1252***,[698] another example **1253** of the unusual tetracyclic-cored eudistidine alkaloid family,[699] and a disulfated steroid ***1254***.[700] Noteworthy was the added-complexity, compared with congeners reported in 2015, of eudistidine C **1253** reported from *Eudistoma* sp., collected in Palau.[699] The racemic natural product was synthesised by a straight-forward nucleophilic substitution reaction using eudistidine A as starting material, simple extension of which led to preparation of a library of un-natural analogues. Chiral HPLC allowed for resolution of the two enantiomers of the natural product, with absolute configuration assigned to each by comparison of experimental ECD spectra with those calculated using TDDFT calculations. (−)-(*S*)-Eudistidine C was a modest inhibitor of p300-HIF-1α protein interaction.

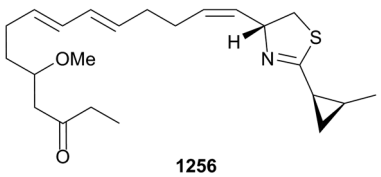


1253

Also of note in 2016, was a report on the effectiveness of chemical shift calculations in the structure elucidation of the complex marine natural products the mandelalides (tunicate) and coibamide A (cyanobacterium).[701] Total syntheses of obscuraminol A,[702] crucigaterin 277,[703] polycarpathiamines A and B,[704] and iheyamine A[705] have been reported, and in all cases, the structures of the reported natural products were confirmed. Novel rigidin analogues targeting β-tubulin have been found to exhibit potent antitumour activity *in vitro* and *in vivo*,[706] while clavaminol A and diacetyl clavaminol H exhibit antibacterial, antifungal and biofilm inhibiting activities.[707] The chemistry and biology of the mandelalides continues to attract attention with new synthetic routes and biological activities reported.[708–710] Semi-synthesis of a library of 2′-*N*-acyl derivatives of ecteinascidin 770 has identified two analogues, an isoxazole amide and an 4-methoxyphenyl amide, to be more potent *in vitro* cytotoxins than the natural product.[711] Analogues of the amino-imidazole alkaloids polycarpine and polycarpaurines A and C have been identified as antivirals (against tobacco mosaic virus) and fungicidal against a set of plant pathogens.[712] Copper(II) complexes of cyclic peptides related to patellamide exhibit glycosidase and β-lactamase-like activity,[713] while the effects of unnatural amino acid variation on the open/folded conformations of ascidiacyclamide have been investigated by NMR, CD and X-ray crystallography.[714] A yeast-based chemical genetics approach was used to identify the cellular target of eudistomin C as being the uS11-containing ribosomal subunit and that it is a potent inhibitor of protein translation.[715] Eudistomin U is a weak DNA binder.[716]

12 Echinoderms

The forty-six new metabolites reported from echinoderms in this review is about average for the number reported per annum over the last decade. A new radical-scavenging aminonaphthoquinone, spinamine E ***1255***, was reported from the urchins *Strongylocentrotus pallidus* and *Mesocentrotus nudus*,[717] while trace amounts of curacin E **1256** were isolated from the brittle star *Ophiocoma scolopendrina* using bioassay-guided fractionation.[718] What is unusual about the latter metabolite is that it is structurally related to curacin A,[719] an antimitotic reported from a cyanobacterium. Absolute configuration about the thiazoline ring was related to the known configuration of the same ring system in curacin A *via* analysis of ECD data.



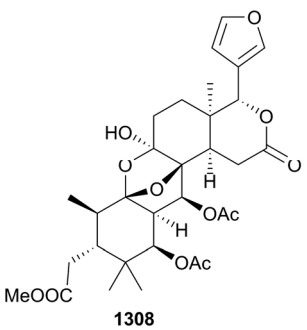
1256

The remaining metabolites reported from echinoderms were dominated by anthraquinones ***1257*** and ***1258*** (crinoid *Comatula rotalaria*),[403] pyrrole oligoglycosides ***1259*** and ***1260*** (starfish

Acanthaster planci)[720] and sterols ***1261–1263*** (starfish *Archaster typicus*)[721] and their glycosides including ***1264–1267*** (starfish *Protoreaster lincki*),[722] ***1268–1277*** (starfish *Anthenea aspera*),[723] ***1278*** and ***1279*** (starfish *Acanthaster planci*),[724] ***1280–1282*** (starfish *Pentaceraster regulus*),[725] ***1283–1285*** (starfish *Craspidaster hesperus*),[726] ***1286*** (sea cucumber *Colochirus robustus*),[727] ***1287*** (starfish *Aphelasterias japonica*),[728] ***1288–1291*** (sea cucumber *Colochirus robustus*),[729] ***1292–1295*** (ref. 730) and ***1296–1299*** (ref. 731) (both sets from sea cucumber *Cucumaria fallax*) and ***1300*** (sea cucumber *Astichopus multifidus*).[732] Two synthetic routes to spinamine E ***1255*** (2-amino-3,6,7-trihydroxynaphthazarin) have been reported[733] as has the first synthesis of the pentacyclic naphthazarin-derived dimer mirabiquinone A.[734,735] The structure of the complex sialic acid embedded octasaccharide ganglioside GP3 (*Asterina pectinfera*)[736] has been confirmed by total synthesis.[737] The sea cucumber triterpenoid glycoside frondoside A[738] exhibits activity in a human pancreatic mouse xenograft model but only when given intraperitoneally (oral gavage delivery had no effect).[739] It also exhibits activity towards prostate cancer cell lines *in vitro* and *in vivo*.[740] A related sea cucumber triterpenoid glycoside, echinoside A,[741] exhibited diurnal time-dependent inhibition of fatty acid biosynthesis in mice while enhancing mitochondrial fatty acid β-oxidation.[742] The tetrasaccharide saponin echinoside A[743] has higher bioavailability than the hexasaccharide saponin holotoxin A_1 (ref. 744) as measured using the Caco-2 cell model and single-pass intestinal perfusion.[745] Pentasaccharide saponin, cucumarioside A_2-2,[746] activates cellular immunity by interacting with P2X receptors on macrophages.[747]

13 Mangroves

Mangroves or their associates were the sources of a moderately antiplasmodial embelin analogue ***1301*** (*Aegiceras corniculatum*),[748] two dolabranes tagalsin V ***1302*** and W ***1303*** (*Ceriops tagal*),[749] a new tirucallane ***1304*** and two tetranortriterpenes ***1305*** and ***1306*** (seeds of *Xylocarpus moluccensis*),[750] a further eight tetranortriterpenoids ***1307–1314*** (leaves and twigs of *X. granatum*),[751] and limonoids ***1315–1318*** (*X. moluccensis*).[752] The structures of xylogranatumin A **1308** and thaixylomolins O **1315** and P **1316** are notable, with the former containing an unusual oxygen-bridging arrangement, and the latter two with their orthoacetate bridge. Absolute configurations were assigned to ***1307*** and ***1318*** by TDDFT calculated ECD analysis, to **1315** and ***1307*** by single crystal X-ray diffraction studies and to **1316** by comparison of ECD spectra.



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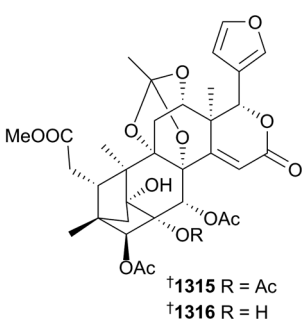
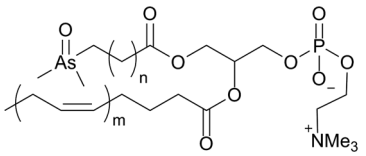


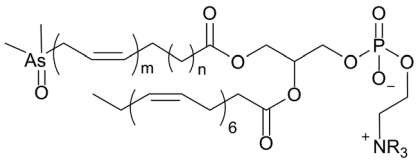
†**1315** R = Ac
†**1316** R = H

14 Miscellaneous

Norwegian sea herring caviar (*Clupea harengus*) contain arsenolipids **1319–1324**.[753] The metabolites were characterised solely by MS/MS analysis, meaning that the structures are only proposals, with the glycerol ester point of substitution and position and geometry of alkene double bonds not determined.



1319 n = 13, m = 5
1320 n = 13, m = 6
1321 n = 15, m = 6



1322 n = 4, m = 5, R = Me
1323 n = 2, m = 6, R = Me
1324 n = 2, m = 8, R = H

15 Conclusion

The rich and unique chemical diversity of NPs have long been an important source of drugs and drug leads.[3] Comparisons of

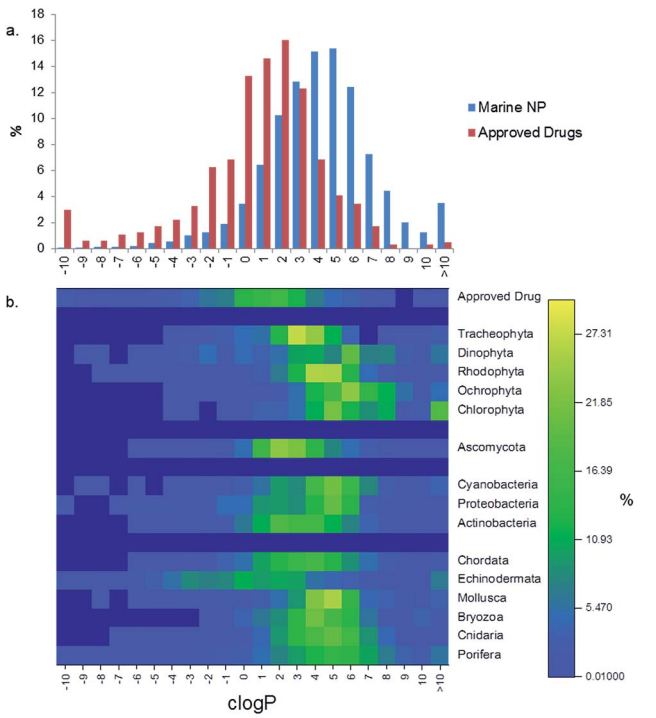


Fig. 1 clog *P* distribution of MNPs and approved drugs. (a) Proportion of clog *P* between −10 and 10 for all MNPs isolated since 1957 compared to approved drugs. (b) Heatmap of clog *P* proportions for the 15 most abundant MNP-producing phyla.

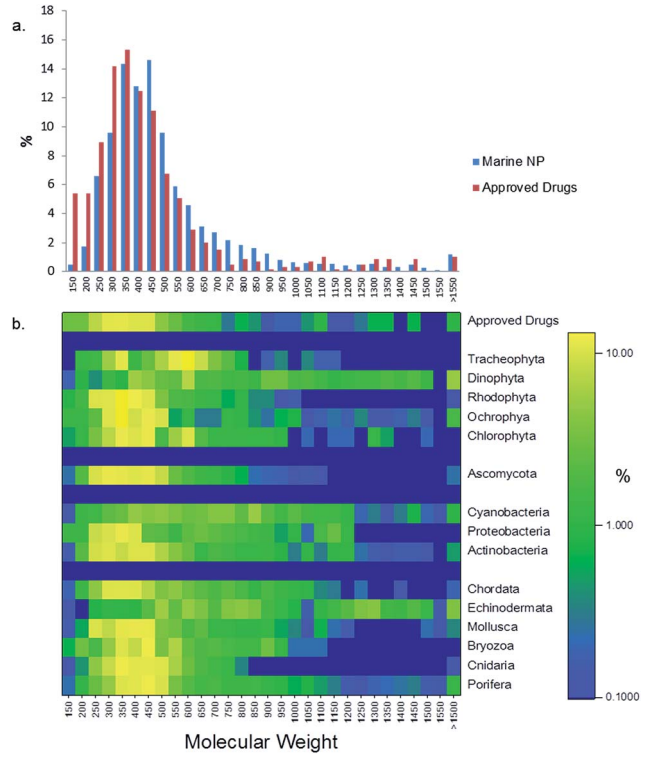


Fig. 2 Molecular weight distribution of MNPs and approved drugs. (a) Distribution of MW for all MNPs isolated since 1957 compared to approved drugs. (b) Heatmap of MW distributions for the 15 most abundant MNP-producing phyla.

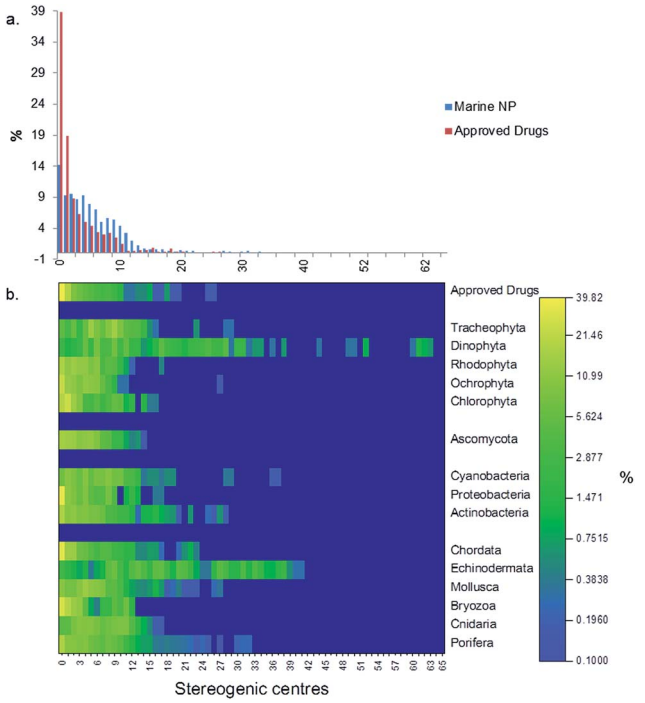


Fig. 3 Distribution of the number of stereogenic centres per molecule in MNPs and approved drugs. (a) Distribution of chiral centre count per molecule for all MNPs isolated since 1957 compared to approved drugs. (b) Heatmap of stereogenic centre counts per molecule for the 15 most abundant MNP-producing phyla.

the chemical diversity of drugs compared to NPs and synthetic libraries have shown that NP chemical diversity is more closely aligned with drugs than synthetic libraries.[754] This is unsurprising since over half of all drugs are either NPs, NP-derived or NP-inspired.[3] Chemical diversity has been reported to align with biological diversity and marine collection efforts over the years have focused on obtaining diverse biota to maximise the potential chemical diversity that they might contain.[755] It has also been recognised that some MNPs isolated from macro-invertebrates may actually be produced by micro-organisms and in recent years this has, in part, led to an increasing trend towards the study of marine micro-organisms with reduced efforts focusing on other taxa.[755] With 28 609 MNPs having now been reported from a variety of marine sources[13] it is timely to assess the chemical diversity found within these organisms and to compare this diversity to that of approved drugs. In this conclusion 11 physico-chemical descriptors, clog *P*, molecular weight (MW), polar surface area, counts of stereogenic centres, small rings, aromatic atoms, sp^3 atoms, hydrogen bond donors and acceptors, basic nitrogens and acidic oxygens, were calculated for 28 609 MNPs reported since 1957 and 2908 approved drugs derived from the SWEETLEADS database.[756] Principal component analysis (PCA) of these descriptors was then undertaken. Pairwise cluster analysis of the MNPs from the 15 phyla (refer to *y* axis in Fig. 1) from which the majority of MNPs have been reported was also carried out using the FragFp (substructure fragment dictionary) descriptor generated in the free chemiformatics software Osiris Datawarrior.[757] Two of the Lipinski criteria for "drug-likeness", MW and log *P*, are presented in Fig. 1 and 2. Although on average the clog *P* for MNPs are shifted three log units higher compared to approved drugs, the trend is different for different phyla, with compounds reported from Actinobacteria, Ascomycota, Chordata (predominantly tunicates) and Bryozoa possessing the most similar profile to approved drugs. The MW histograms for MNPs and approved drugs are very similar with approved drugs containing a slightly higher proportion of low MW compounds. Comparison at the phylum level tells a different story with Echinodermata, Dinophyta, Cyanobacteria and Tracheophyta (mangroves) containing proportionately higher MW compounds. A distinguishing feature of NPs compared to synthetic compounds is their abundance of stereogenic centres. On average 58% of approved drugs have one or no stereogenic centre compared to only 25% of MNPs (Fig. 3). Bryozoa, Chordata and Proteobacteria show the closest match to approved drugs, while Echinodermata, Dinophyta, Cnidaria, Mollusca and Tracheophyta on average contain molecules with a larger number of stereogenic centres. A plot of principal component 1 (PC1) *vs.* PC2 (accounting for 80% of the variability in the PCA data) (Fig. 4 and 5) reinforces the above conclusions indicating that compounds reported from Echinodermata and Dinophyta occupy complementary but

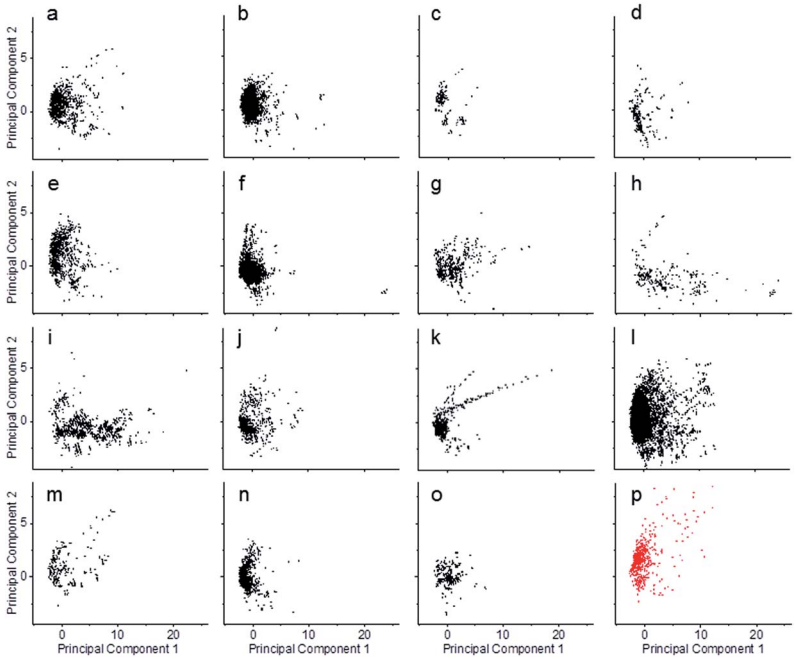


Fig. 4 Principal component analysis of 11 physico-chemical properties calculated for compounds reported from the top 15 MNP-producing phyla and approved drugs. (a) Actinobacteria (1134), (b) Ascomycota (3398), (c) Bryozoa (238), (d) Chlorophyta (272), (e) Chordata (1161), (f) Cnidaria (5473), (g) Cyanobacteria (563), (h) Dinophyta (311), (i) Echinodermata (1396), (j) Mollusca (1178), (k) Ochrophyta (1311), (l) Porifera (8778), (m) Proteobacteria (274), (n) Rhodophyta (1783), (o) Tracheophyta (339), (p) approved drugs (2908).

different areas of chemical space compared to the other 13 phyla (and approved drugs). Ochrophyta (brown algae) compounds occupy a unique area of chemical space, while Cnidaria, Cyanobacteria, Mollusca, Cyanophyta and Rhodophyta (green and red algae) contain a higher proportion of molecules with either a large number of stereogenic centres, sp^3 carbons and/or rotatable bonds. The myriad compounds reported from Porifera show a range of chemical properties and this is reflected in the broad area of chemical space occupied by these compounds compared to those reported from the other 14 phyla. But how useful is a PCA comparison in defining chemical diversity? Pairwise cluster analysis of the compounds isolated from the top 15 phyla and similarity analysis of their shared clusters indicates that although compounds often occupy a similar area of chemical space, their structures are different, with on average less than an 8% overlap of clusters shared between two phyla (Fig. 6). An exception was the compounds reported from Mollusca, organisms that are known to sequester compounds from dietary sources, and these compounds shared a higher (10–17%) similarity with most other phyla except Bryozoa, Tracheophyta and Proteobacteria. Finally, MNPs are diverse since 6264 clusters were generated from the 28 609 compounds analysed and the majority of the compounds were represented in clusters of less than ten members (Fig. 7). Only the Cnidaria, Echinodermata, Cyanobacteria and Tracheophyta contain individual clusters that represent >30% of the total compounds reported from each phylum. The take home messages from these analyses are that the chemical space occupied by approved drugs overlaps with that of MNPs, chemical diversity within marine organisms is high and that targeting one group of marine organism over another is perilous if one is to trying to maximise the exploration of chemical diversity. Likewise the trend towards targeted microorganism collections at the expense of invertebrate and algae collections is likely to lead to unique chemical diversity being overlooked.

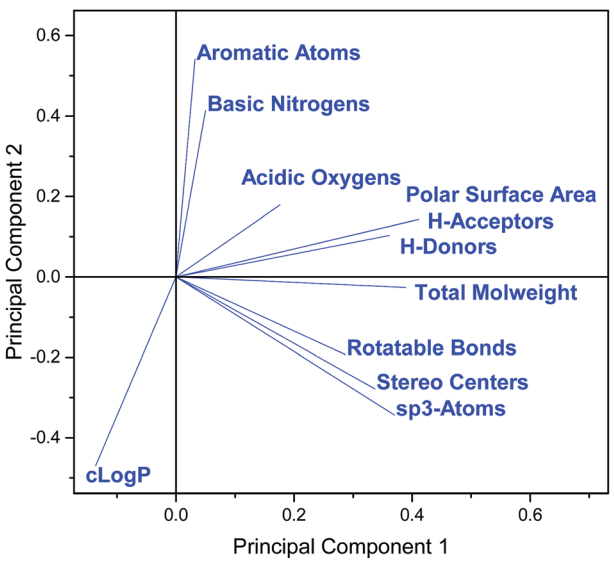


Fig. 5 Loadings plot for the PCA in Fig. 4.

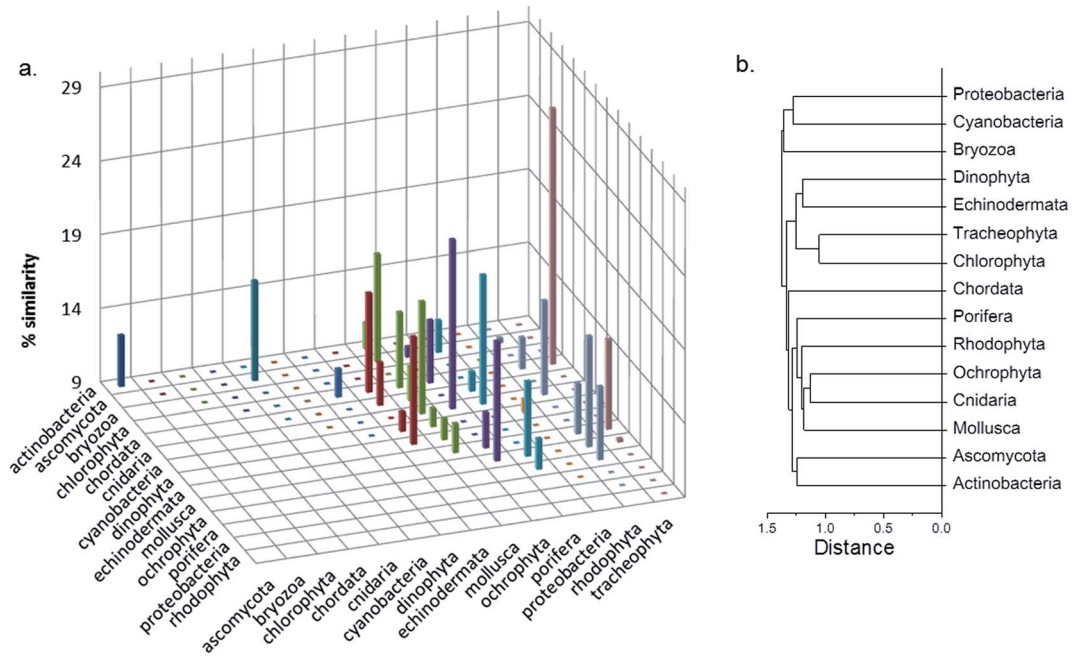


Fig. 6 Similarity analysis of compound clusters (6264) in the 15 most abundant MNP-producing phyla. (a) % similarity of clusters between phyla (*z* axis minimum is set at 9% and all dots represent similarities less than 9%), (b) Euclidian cluster analysis of similarity indices.

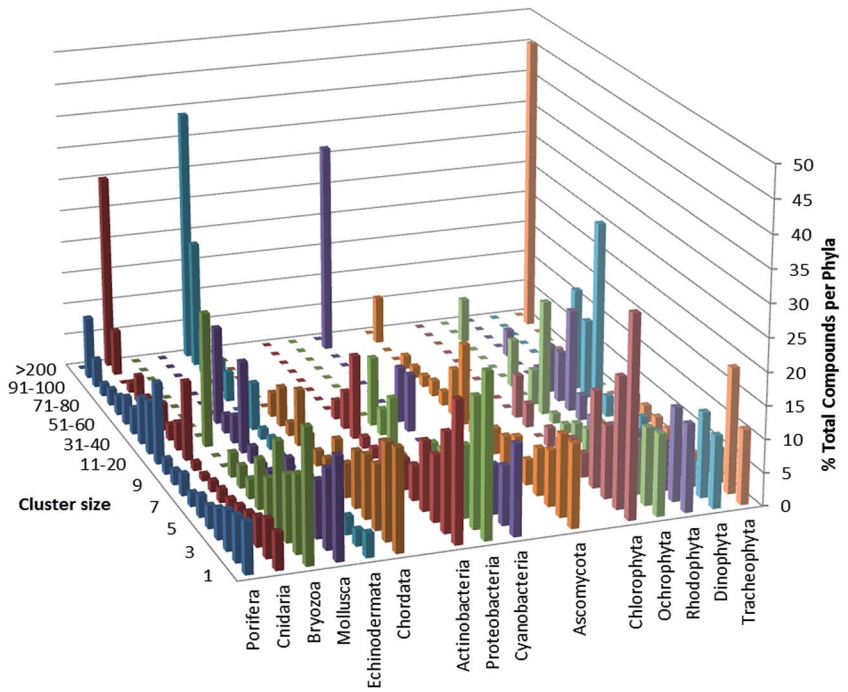


Fig. 7 Compound cluster analysis. Proportion of compounds in each phylum that are members of clusters of varying size.

16 Conflicts of interest

There are no conflicts to declare.

17 Acknowledgements

We thank Dr Helen Potter (Royal Society of Chemistry) for the provision of data used in this review, adapted from the MarinLit database with permission from the Royal Society of Chemistry.[13] This review closes a chapter of dedicated and insightful contribution by Professor John Blunt and we wish him well for the future. Professor Blunt has been the corresponding author for the last fifteen issues and has provided exceptional guidance, oversight and mentorship to the authorship team. John has been the engine room of the review. He has liaised with the editorial team at NPR and RSC, coordinated the contributions of the co-authors,

and with his longtime colleague Professor Murray Munro compiled the text and all of the structures and generated the ESI‡ files as well as writing individual review sections. His ability to coordinate the contributions of the co-authors, seamlessly compile their individual contributions and organise the 1000+ new structures each year, to produce such a quality annual review is testament to John's high standards. The database, MarinLit, was the "brainchild" of Professors Blunt and Munro and it is this database (now administered by RSC) that has provided the backbone upon which the annual review has been compiled. It has been a true pleasure working with John and we wish to thank him for his leadership in MNP research and his outstanding contributions to these reviews.

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