Chemical and Biological Aspects of Marine Sponges from the Family Mycalidae

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Abstract

Sponges are a useful source of bioactive natural products. Members of the family Mycalidae, in particular, have provided a variety of chemical structures including alkaloids, polyketides, terpene endoperoxides, peptides, and lipids. This review highlights the compounds isolated from Mycalid sponges and their associated biological activities. A diverse group of 190 compounds have been reported from over 40 specimens contained in 49 references. Over half of the studies have reported on the biological activities for the compounds isolated. The polyketides, in particular the macrolides, displayed potent cytotoxic activities (< 1 µM), and the alkaloids, in particular the 2,5-disubstituted pyrrole derivatives, were associated with moderate cytotoxic activities (1–20 µM). The pyrrole alkaloids and the cyclic peroxides appear to be phylogenetically restricted to sponges and thus might prove useful when applied to sponge taxonomy. The observed diversity of chemical structures suggests this family makes a good target for targeted biodiscovery projects.

Abbreviations

HDAC:	histone deacetylase
PC:	principal component
PKS-NRPS:	hybrid polyketide synthase and non-ribosomal synthase
WPD:	World Porifera Database

Supporting information available online at http://www.thieme-connect.de/products

Introduction

The Porifera is one of the most studied marine phyla for the discovery of novel bioactive natural products [1]. This is not surprising considering the diversity associated with marine sponges, with the phylum comprising over 8500 described species [2,3]. Knowledge of species diversity within the Porifera remains incomplete and the number of species discovered still continues to climb at a constant rate [2,3]. One diverse sponge family that has proven to be a source of biologically important natural products is the family Mycalidae. The family, characterised by the presence of palmate anisochelae spicules, has a worldwide distribution with close to 250 currently valid species [2,4]. Species are organised into two genera, either the larger and more diverse genus *Mycale*, or the smaller genus *Phlyctaenopora* [4]. Due to the high diversity within these genera, they are further divided into subgenera. The genus *Mycale* is comprised of the eleven subgenera, *Mycale (Mycale), Mycale (Aegogropila), Mycale (Anonomycale), Mycale (Arenochalina), Mycale (Carmia), Mycale (Grapelia), Mycale (Naviculina), Mycale (Oxymycale), Mycale (Paresperella), Mycale (Rhaphidotheca)*, and *Mycale (Zygomycale)*, and the smaller genus *Phlyctaenopora* is subdivided into two subgenera, *Phlyctaenopora (Phlyctaenopora)* and *Phlyctaenopora (Barbozia)* [4].

This diverse sponge family has received attention from natural product chemists in pursuit of bioactive natural products with a range of structural classes being reported from its members. These include alkaloids such as 2,5-disubstituted pyrrole derivatives, polyketides such as trisoxazole macrolides, terpenoids such as the mycaperoxides with a 1,2-dioxane attached to bicyclic terpene moieties, and lipids such as the glycosidic steroids, mycalosides. These compounds have also displayed a range of biological activities with cytotoxic, antibacterial, antifungal, and antiviral activities reported. This rich chemical diversity suggests that the family Mycalidae shows promise

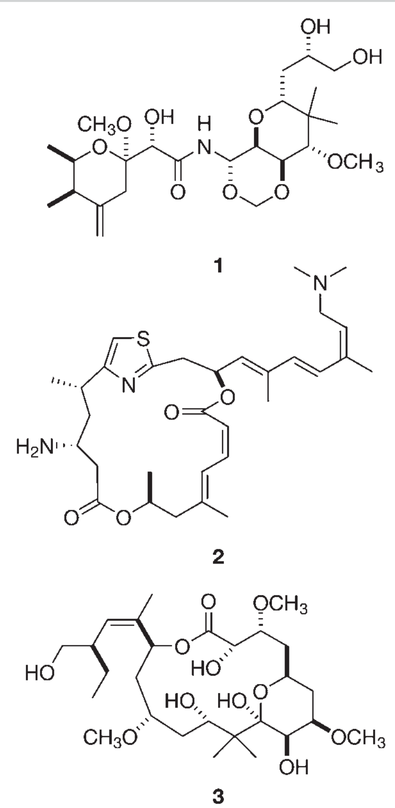

Fig. 1 Mycalamide A (**1**), pateamine (**2**), and peloruside A (**3**).

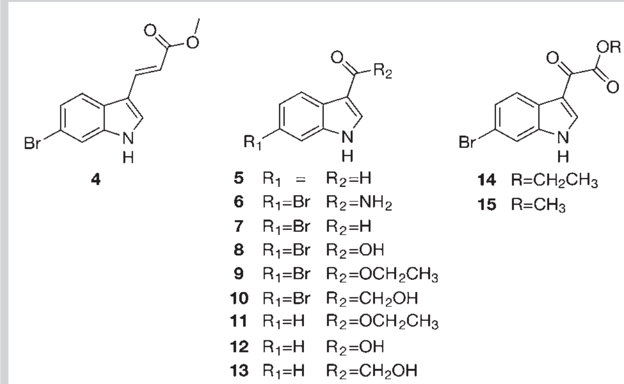

Fig. 2 Chemical structures of monoindole alkaloids.

as a source for potential drug candidates. Good examples of this are the compounds mycalamide A (**1**) [5], pateamine (**2**) [6], and peloruside A (**3**) [7] (**Fig. 1**), all isolated from the sponge *Mycale (Carmia) hentscheli* displaying potent cytotoxicity and yet all these compounds are structurally unrelated.

This review documents the known chemical diversity of the natural products isolated from members of the family Mycalidae. As a result of undertaking this survey, two important questions can be addressed. Firstly, is the family Mycalidae a good resource for biodiscovery? Secondly, are any of the compounds or compound classes reported in the family Mycalidae potentially useful for taxonomic purposes? This review provides a summary of all compounds reported from members of the family Mycalidae prior to June 2015 and their associated biological activity. Sponges identified as members of the family Mycalidae include those that possess currently accepted species names and previous synonyms presented in the WPD [2]. Species names referred to in this review are those currently accepted according to the WPD and include subgenera classifications. Where these are different from the original source, the originally used species name is also provided.

A note to the reader

The data summarised here is what is currently available and reported in the literature. Care should be taken when interpreting the patterns presented here. The compounds classes, species, and geographic regions sampled are largely due to research efforts (a summary of research efforts in terms of number of publications within a country over time is available as **Fig. 2S** and **Table 5S**, Supporting Information). Patterns in biological activity should be interpreted with care as the isolation of bioactive compounds (especially cytotoxic ones) could be biased based on targeted research efforts. Additionally, the biological activity data is by no means exhaustive since many compounds have no activity reported because they have not been tested. As the binomial nomenclature ensures there is a universally recognisable scientific name, the inclusion of the subgenus in species names is not required and therefore seldom used in chemical publications. However, since the genus *Mycale* is so taxonomically diverse, for the purpose of assessing the distribution of reported chemistry among this genus, the accepted subgenera for each species (according to the WPD) have also been referred to. Finally, given the nature of sponge taxonomy there is often a limited ability to appropriately identify samples and misidentifications can be misleading.

Chemical Constituents of the Family Mycalidae

Alkaloids

Indole alkaloids

A series of twelve monoindole alkaloids (**Fig. 2**) substituted at position 3 and some brominated at position 6 have been reported in three Mycalid species collected from China, Japan, and India [8–10]. The first report of a monoindole alkaloid from a Mycalid source was the known bromoindole (**4**) from the sponge *M. (Aegogropila) adhaerens* collected from Japan [9]. The known 3-formyl indole (**5**) was isolated from both an Indian specimen of *M. (Carmia) tenuispiculata* [8] as well as a Chinese specimen of *M. (Carmia) fibrexilis* [10]. This Chinese specimen also yielded another ten indole alkaloids comprised of one new brominated indole (**6**) with six other known brominated indoles (**7**–**10, 14**, and **15**) and four known indoles (**5** and **11**–**13**) [10].

Brominated indoles have been reported widely in the sponge class Demospongiae [10] in the orders Dictyoceratida, Poecilosclerida, Tetractinellida, and Suberitida. In particular from the genera *Dysidea* [11], *Iotrochota* [12,13], *Tedania (Tedania)* [14], *Corallistes* [15], *Pleroma* [16], *Hymeniacidon* [17], *Pseudosuberites* [18], and *Spongosorites* [19]. Brominated indoles have also been reported in other non-sponge marine taxa, for example, **12** from the ascidian *Leptoclinides durus* [20] and **14** from bacteria isolated from marine sediment [21]. Indole **4** has displayed nematocidal activity against the parasite *Haemochus contortus* [17].

Pyrrole derivatives

The pyrrole derivatives are the largest group of compounds isolated from the family Mycalidae, with a total of 67 compounds of which 62 have been reported for the first time (**Figs. 3** and **4**). Most of these (55 compounds) are represented by 5-alkylpyrrole-2-carboxaldehyde derivatives and some of these have been given the trivial names mycalazals (vary in alkyl chain length, branching, and saturation) and mycalenitriles (like mycalazals but with a terminal nitrile group). Structural diversity within this group results from variation in the length and structure of the alkyl chain. Variation includes alkyl branching, one or multiple double bonds, and the presence of other functional groups (e.g., terminal nitriles). The remaining 12 compounds, commonly known as mycalazols, have the C-2 aldehyde moiety reduced to a primary alcohol.

The first pyrrole derivatives isolated from Mycalid sponges were **16** from *M. (Mycale) monanchorata* (originally reported as *Mycalecarmia monanchorata*) and **17** from *M. (Carmia) mytilorum*, both collected in India [22]. Both of these compounds, however, were first isolated as a mixture with **18** (and one other pyrrole derivative) from the sponge *Hymeniacidon* sp., order Suberitida (as *Laxosuberites* sp.) [23]. Following this two more 5-alkylpyrrole-2-carboxaldehydes, mycalazals 1 and 2 (**19** and **20**), and twelve 5-acyl-2-hydroxymethylpyrroles, mycalazols 1–12 (**21**–**32**), were characterised from *M. (Carmia) micracanthoxea* collected from Spanish waters [24].

In 1999, compounds **16** and **17** were reisolated from a Venezuelan *M. (Carmia) microsigmatosa* specimen together with ten new 5-alkylpyrrole-2-carboxaldehydes (**33**–**42**) and one new 5-alkylpyrrole-2-carboxaldehyde containing a terminal nitrile (**43**) [25]. In the same paper, the six compounds **16, 17, 35, 36, 40**, and **41** were co-isolated from the sponge *Desmapsamma anchorata* (order Poecilosclerida). An Indian specimen of *M. (Carmia) mytilorum* yielded two new 5-alkylpyrrole-2-carboxaldehydes (**44** and **45**) [26], and another Indian species, *M. (Carmia) tenuispiculata*, was the source of three new compounds including the pyrrole derivative **46**, mycaleoxime (**47**), and the nitrile terminate pyrrole **48** [8]. Mycaleoxime (**47**) differs from the other pyrrole derivatives by the presence of a carbonyl group adjacent to the pyrrole nucleus and a terminal aldoxime group. The new compounds mycalazals 3–13 (**49**–**59**) and mycalenitriles 1–3 (**60**–**62**) (distinguished by a terminal nitrile group) were found in *M. (Carmia) cecilia* from Mexico [27], with the eight known pyrrole derivatives **16, 18, 35, 36, 41, 43, 63**, and **64** [23,25].

In 2009, **16** and **46** were reisolated from an Indonesian *M. (Carmia) phyllophila* [28]. The 5-alkylpyrrole-2-carboxaldehydes **16, 17, 35, 36, 43, 49, 60**, and **61** were again reisolated from a member of the Mycalidae family, this time from an unidentified *M. (Carmia)* sp. from Palau together with twelve new mycalenitriles 4–14 (**65**–**75**), and seven new mycalazals 14–20 (**76**–**82**) [29]. Finally, in 2013, an unidentified *Mycale* sp. from China also produced **17** [30]. Related structures (e.g., **83**) have been reported from a soft coral-sponge association comprised of a soft coral of the genus *Telesto* and an unidentified sponge [31], and compound **64** has also been reported from the sponge *Oscarella lobularis* (order Homosclerophorida) [32].

Many of these pyrrole derivatives have displayed various biological activities. Mycalazal 2 (**20**) and the mycalazols 1–12 (**21**–**32**) showed cytotoxicity against a panel of cell lines (P388, SCHABEL, A549, HT29, and MEL28) with ED_{50} values of less than 10 µg/mL, and many of these compounds displaying ED_{50} values of less than 2.5 µg/mL. Of these, mycalazol 6 (**26**) was the most active with an

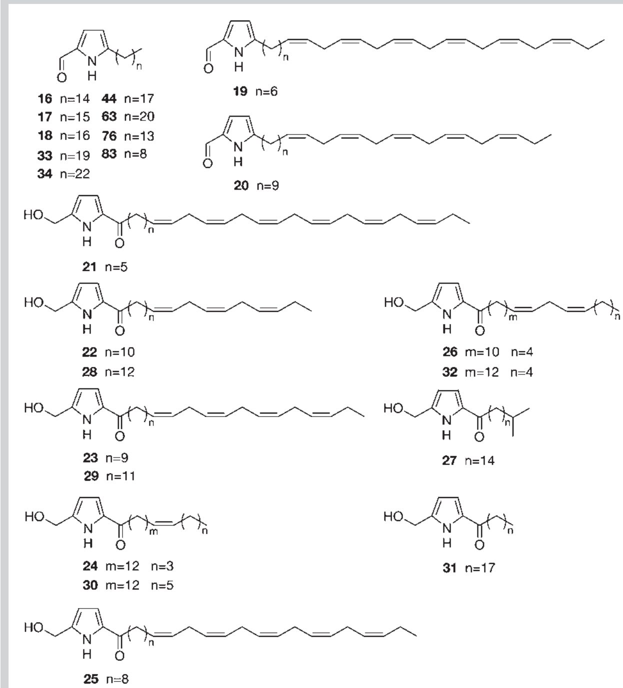

Fig. 3 Chemical structures of 2,5-disubstituted pyrrole derivatives.

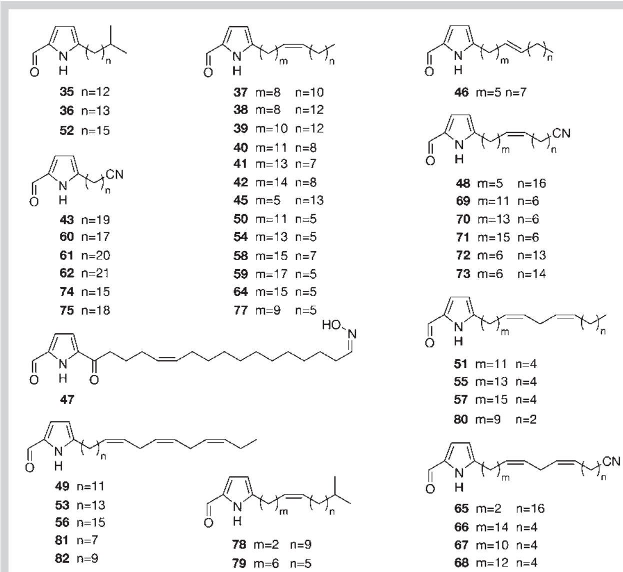

Fig. 4 Chemical structures of 2,5-disubstituted pyrrole derivatives.

ED_{50} value of 2 µg/mL for MEL28 and 1 µg/mL for the remaining cell lines [24]. The nitrile **43** was an active inhibitor of the proliferation of the parasite *Leishmania mexicana* with an LD_{50} value of 12 µg/mL [25]. A library of 22 pyrrole-2-carboxaldehydes including the mycalazals 3–13 (**49–59**), the mycalenitriles 1–3 (**60–62**), and the known pyrrole-2-carboxaldehydes **16, 18, 35, 36, 41, 43, 63**, and **64** were screened against a panel of cell lines (LN-caP, IGROV, SK-BR3, SK-MEL-28, A-549, K-562, PANCI, LOVO, and HeLa cell lines), which resulted in some interesting structure activity observations (see [27] for specific GI_{50} values). The authors

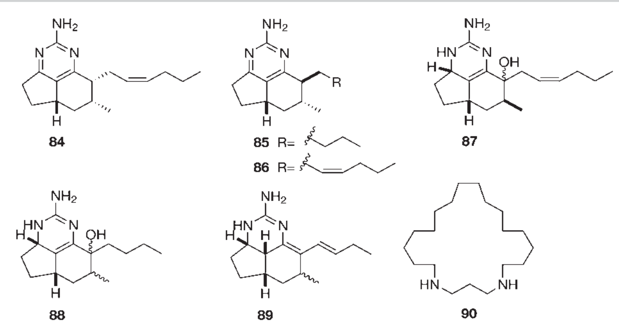

Fig. 5 Chemical structures of mirabilin alkaloids and 1,5-diazacyclohenicosane.

compared the LN-caP cell line inhibition with the structures of the compounds and found that activity was associated with the presence of a single double bond, activity decreased with three double bonds, and was lost completely with two double bonds or saturated alkyl chains [27]. As a mixture, the pyrroles **16** and **46** inhibited the growth of mouse lymphoma cells (L5178Y) with an IC_{50} value of 1.8 µg/mL [28]. Mycalenitriles showed inhibition of hypoxia-induced factor (HIF-1) activation. Mycalenitriles 6 (**67**) and 7 (**68**) were the most active with IC_{50} values of 7.8 and 8.6 µM, respectively. Mycalenitriles 1 (**60**), 5 (**66**), 8 (**69**), and 13 (**74**) were moderately active with IC_{50} values ranging from 10–20 µM [29].

Other alkaloids

Mirabilins A–F (**84**–**89**, ▶ **Fig. 5**) were reported from the sponge *M. (Arenochalina) mirabilis* (originally reported as *Arenochalina mirabilis*) [33]. This is the only report of guanidine tricyclic alkaloids from a member of the family Mycalidae. Several of these mirabilins have since been reported in other sponge species including mirabilins A (**84**), C (**86**), and F (**89**) from *Biemna laboutei* [34], a *Clathria (Isociella)* sp. [35], a *Batzella* sp. [36], and *Monanchora arbuscula* [37,38]. Mirabilins are members of a structurally diverse class of compounds that have been reported in a range of taxa, including both marine and terrestrial microorganisms, invertebrates, and plants (see [39] and previous reviews in series). Related tricyclic alkaloids with a guanidine moiety have been reported in five other sponge genera including *Acanthella* [40], *Batzella* [34,36,41], *Clathria (Isociella)* [35,42], *Monanchora* [37,38, 43,44], and *Ptilocaulis* [45].

Some of these mirabilins have been reported to possess moderate biological activities. Mirabilin A (**84**) has displayed antimalarial activity against *Plasmodium falciparum* (IC_{50} value of 20.7 µM) [34], and mirabilin B (**85**) has been reported to have antifungal activity against the strain *Cryptococcus neoformans* (IC_{50} value of 7.0 µg/mL) as well as antiprotozoal activity against *Leishmania donovani* (IC_{50} value of 17 µg/mL) [38]. Other members of this structure class have also displayed antimalarial activity [34] and several have displayed cytotoxicity to tumour cells [34,37,41].

A new cyclic amine 1,5-diazacyclohenicosane (**90**, ▶ **Fig. 5**) was isolated from a *Mycale* sp. collected from Kenya [46]. Moderate cytotoxic activity was reported against human lung, colon, and breast tumour cell lines (A549, HT29, MDA-MB-231) with GI_{50} values in the micromolar range (ranging from 5.07–5.74 µM) [46].

Polyketides
Macrolides

The trisoxazole family of macrolides (▶ **Figs. 6** and **7**) are macrocyclic lactones with a trisoxazole unit (three contiguous oxazoles) and a side chain with a formyl enamine terminal moiety [47,48]. In total, ten structures have been reported from sponges identified as members of the family Mycalidae. Mycalolides A–C (**91**–**93**) were first characterised from a Japanese *Mycale* sp. [49] followed by the reisolation of mycalolides A (**91**) and B (**92**) from *M. (Aegogropila) adhaerens* of Japanese origin [9]. Mycalolide A (**91**) has been reported in other Japanese Mycalid specimens including *M. (Aegogropila) magellanica* [47], *M. izuensis* [50], and an unidentified *Mycale* sp. [51] and was reported together with mycalolide C (**93**) in the non-Mycalid sponge *Sarcotragus* sp. [52]. Mycalolide C (**93**) has also been reported from the coral *Tubastrea faulkneri* together with the first characterisations of mycalolides D (**94**) and E (**95**) [53], which to date have not been reported from Mycalid (or any) sponges. Mycalolide B (**92**) has also been reported in other Japanese Mycalid specimens, including *M. (Aegogropila) magellanica* [47] and *M. izuensis* [50]. Mycalolides share structural similarity to other trisoxazole macrolides, for example, mycalolide A (**91**) is a hybrid between halichondramide (**96**) and ulapualide A (**97**) [49].

Two sulphur-containing mycalolides, thiomycalolide A (**98**) and B (**99**), were reported from another Japanese specimen of *Mycale* sp. [54]. Several hydroxylated derivatives of mycalolide A (**91**) and B (**92**) have also been characterised from Japanese sponges, including 30-hydroxymycalolide A (**100**), 32-hydroxymycalolide A (**101**), and 38-hydroxymycalolide B (**102**) from *M. (Aegogropila) magellanica* [47] and *M. izuensis* [50]. The *M. izuensis* specimen also yielded 30,32-dihydroxymycalolide A (**103**) [50]. An unidentified *Mycale* sp. yielded 30-hydroxymycalolide A (**100**) in addition to the new compound secomycalolide A (**104**) in which one of the oxazole rings has been cleaved, resulting in a ring opening of the macrocyclic lactone [51]. The trisoxazole family of macrolides occurs in members of five sponge orders including Tetractinellida (*Pachastrissa nux* [55] and *Jaspis* sp. [56]), Suberitida (*Halichondria* sp. [57–59]), Chondrosiida (*Chondrosia corticata* [60]), Poecilosclerida (a number of *Mycale* sp.), and order Dictyoceratida (*Sarcotragus* sp. [52]). Additionally, trisoxazole macrolides have also been reported from other non-sponge sources such as the egg masses of the nudibranch *Hexabranchus* sp. [58,61–63].

Trisoxazole macrolides have displayed a range of biological activities, including cytotoxic, proteasome inhibiting, actin-depolymerising, antimalarial, and antifungal activities. Mycalolides A–C (**91**–**93**) have reported cytotoxic activity against B-16 melanoma cells (IC_{50} values ranging from 0.5–1.0 ng/mL) [49], mycalolide B (**92**) has displayed activity against HeLa cells (IC_{50} value of 0.0035 µg/mL) [64], and mycalolides C (**93**) and D (**94**) have shown moderate activity (average LC_{50} values of 2.5 and 0.6 µM, respectively) against the National Cancer Institute's 60-human tumour cell line panel [53]. The sulphated and hydroxylated mycalolides have also shown considerable cytotoxicity. Thiomycalolides A (**98**) and B (**99**) are both active (IC_{50} value of 18 ng/mL for both compounds) against P388 cells [54]. The hydroxylated mycalolides 30-hydroxymycalolide A, 32-hydroxymycalolide A, and 38-hydroxymycalolide B (**100**–**102**) have shown activity against L1210 cells (with IC_{50} values of 0.019, 0.013, and 0.015 µg/mL respectively) [47] and 30,32-dihydroxymycalide A (**103**) has shown activity against HeLa cells (IC_{50} value of 2.6 ng/mL) [50].

The mycalolides secomycalolide A (**104**), mycalolide A (**91**), and 30-hydroxymycalolide A (**100**) have also displayed proteasome

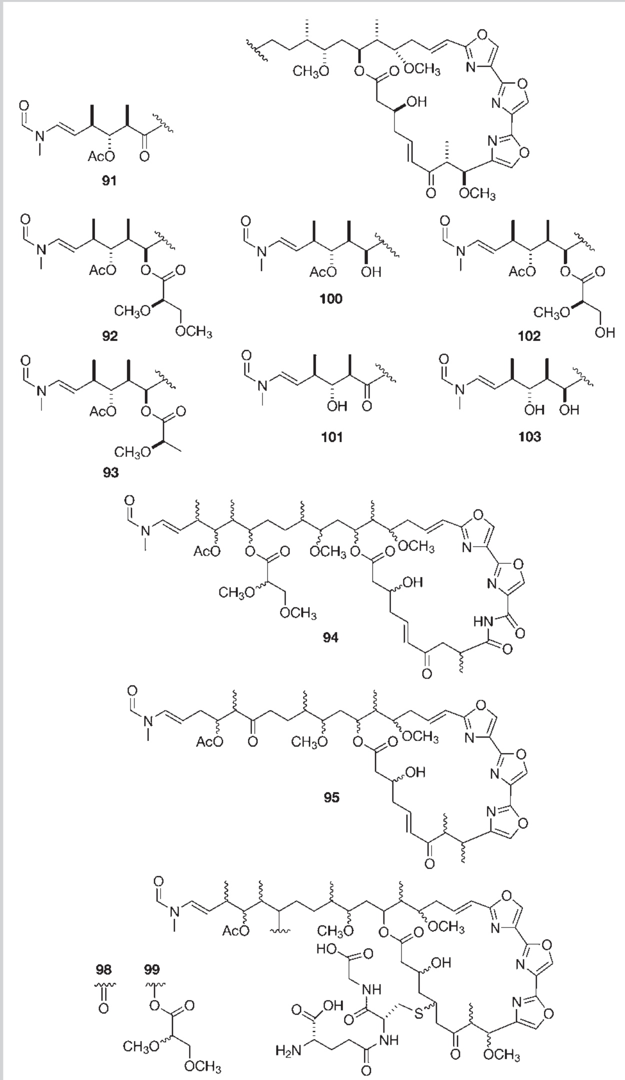

Fig. 6 Chemical structures of macrolide polyketides.

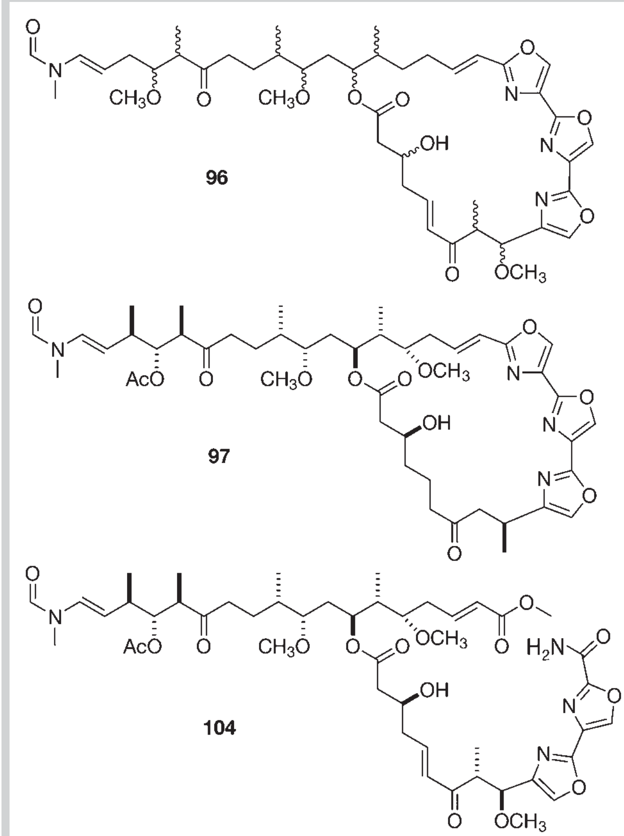

Fig. 7 Chemical structures of macrolide polyketides.

inhibitory activity in an assay using a chymotrypsin-like substrate with IC_{50} values of 11, 30, and 45 µg/mL, respectively [51]. Additionally, the activity of mycalolide B (**92**) has been further explored in an effort to characterise both the actin depolymerising activity [65] and actomyosin inhibitory activity [66]. Through the exploration of an analogue of mycalolide B (**92**), Suenaga et al. [64] documented that the side chain portion of the compound is responsible for actin-depolymerisation activity and that the macrocyclic ring is essential to cytotoxicity.

Six other unrelated macrolides with various biological activities have been isolated from the family Mycalidae (▶ **Figs. 1** and **8**). The Japanese specimen of *M. (Aegogropila) adhaerens* afforded a 13-deoxytedanolide (**105**) [9], which is related to the original compound tedanolide (**106**) first isolated from the sponge *Tedania ignis* in 1984 [67] (▶ **Fig. 8**). Further analogues of tedanolide have been isolated from other sponge species of the genera *Ircinia* [68] and *Candidaspongia* [69]. 13-Deoxytedanolide (**105**) has displayed cytotoxicity to P388 murine leukaemia cells with an IC_{50} value of 94 pg/mL [9] and protein synthesis inhibition [70]. Tedanolide (**106**) is known for possessing potent cytotoxicity when tested against cell cultures of human carcinoma of nasopharynx (ED_{50} value of 0.25 ng/mL) and *in vitro* lymphotytic leukaemia (ED_{50} value of 16 pg/mL) and can cause S-phase arrest at a concentration of 0.01 µg/mL [67].

The 19-membered thiazole-containing dilactone macrolide pateamine (**2**, ▶ **Fig. 1**) was isolated from two specimens of *Mycale* sp. and a specimen of *M. (Carmia) hentscheli* from New Zealand [6, 7, 71]. Pateamine (**2**) has attracted considerable interest due to its potent biological activities (see [72] for summary of progress of **2** as a drug target). Pateamine (**2**) has displayed potent cytotoxicity against P388 murine leukaemia (IC_{50} value of 0.15 ng/mL) and antifungal activity against *Candida albicans*, *Trichophyton mentagrophytes*, and *Cladosporium resinae* (MIC of 1 µg/disk, 20 ng/disk, and 0.4 µg/disk, respectively) [6]. Pateamine (**2**) also showed promise as an immunosuppressive agent with an IC_{50} value of 0.46 nM in an interleukin-2 reporter gene assay [73].

Peloruside A (**3**, ▶ **Fig. 1**), a polyoxygenated 16-member macrolide, was characterised from a New Zealand specimen of *Mycale* sp. [7]. The natural congener peloruside B (**107**, ▶ **Fig. 8**) was characterised from a New Zealand specimen of *M. (Carmia) hentscheli* [74]. Peloruside A (**3**) was reisolated from another New Zealand specimen of *M. (Carmia) hentscheli* together with the two new structures peloruside C (**108**) and D (**109**) [71]. Pelorusides share some structural similarity to the geminal dimethyls and polyhydroxylation observed in mycalamides (next section) and the macrolide ring of pateamine (**2**), however, they are not biochemically related [7].

Peloruside A (**3**) was active against P388 murine leukaemia cells at approximately 18 nM [7] and peloruside B (**107**) was active (IC_{50} value of 71 nM) against human ovarian carcinoma (1A9 cells) [74]. Pelorusides A–D (**3, 107**–**109**) were active against human myeloid leukaemia (HL-60 cells) with IC_{50} values of 10 nM, 33 nM, 221 nM, and 2 µM, respectively [71, 74]. Pelorusides have also been shown to arrest cells in the G_2/M phase of the cell cycle, suggesting that the mitotic microtubules are the target for observed cytotoxicity [71, 74, 75]. Peloruside A (**3**) has received large interest due to its ability to alter microtubulin dynamics, leading to cell cycle arrest and apoptosis (see [76] for a review of activity studies), which has led to its consideration as a potential anticancer agent [75].

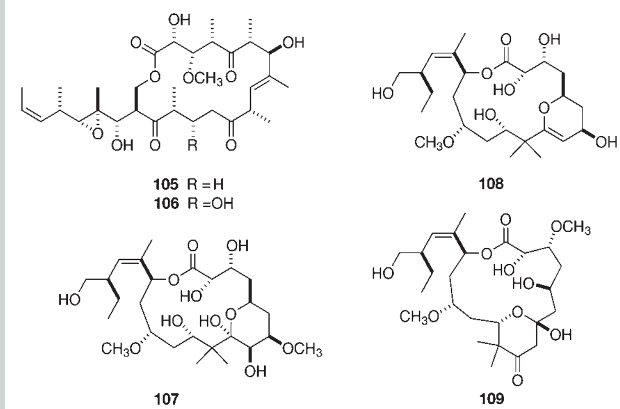

Fig. 8 Chemical structures of macrolide polyketides.

Nitrogen-containing polyketides

During the search for antiviral compounds, mycalamides A and B (**1** and **110**, ▶ **Figs. 1** and **9**) were discovered after the extract of a New Zealand *Mycale* sp. displayed *in vitro* antiviral activity [5, 77]. Since then, mycalamide A (**1**) has been reisolated from several other New Zealand specimens of *Mycale* sp. [7, 78] and *M. (Carmia) hentscheli* [71, 74, 79] together with additional mycalamides. These include mycalamide D (**111**) from a *Mycale* sp. [78] and mycalamide E (**112**) from *M. (Carmia) hentscheli* [79]. Mycalamides have also been isolated in other taxa such as the sponge *Stylinos* n. sp. (mycalamides A and D (**1** and **112**) [80]) and the ascidian *Polysyncraton* sp. (mycalamide A (**1**) [81]). Mycalamides have displayed antiviral activity against *Herpes simplex* type-1 and *Polio* type-1 viruses active at 3.5–5.0 ng/disk for mycalamide A (**1**) and 1.0–2.0 ng/disk for mycalamide B (**110**) [77]. Several mycalamides have shown cytotoxicity against various cell lines with most IC_{50} values at sub-5 nM [78, 79, 82, 83]. Notably, mycalamide A (**1**) was active in the sub-nanomolar range (IC_{50} values from 0.50–0.65 nM against cell lines LLCPK1, H441, and SH-SY5Y) [78, 83] and mycalamide B (**110**) was active in the nanomolar range (IC_{50} values from 0.6–1.5 nM against cell lines P388, HL-60, A549, and HT-29) [82].

The six mycapolyols A–F (**113**–**118**, ▶ **Fig. 9**), metabolites of PKS-NRPS, were isolated from a Japanese specimen of *M. izuensis* [84]. Several other compounds have been reported in the literature that contain the dolapyrrolidone unit; a good example of this is dolastatin 15 (**119**) isolated from the mollusc *Dolabella auricularia* [85]. Related compounds have been isolated from various organisms, namely molluscs, sponges, and cyanobacteria, however, these compounds are all thought to be of cyanobacterial origin and either accumulated in animals or are partially modified [85–88]. Mycapolyols showed potent cytotoxicity against HeLa human cancer cells (IC_{50} values from 0.06–0.90 µg/mL) [84], and the related dolastatin 15 (**119**) is known for its potent cytotoxicity (ED_{50} value of 0.0024 µg/mL against P388 cells [85]).

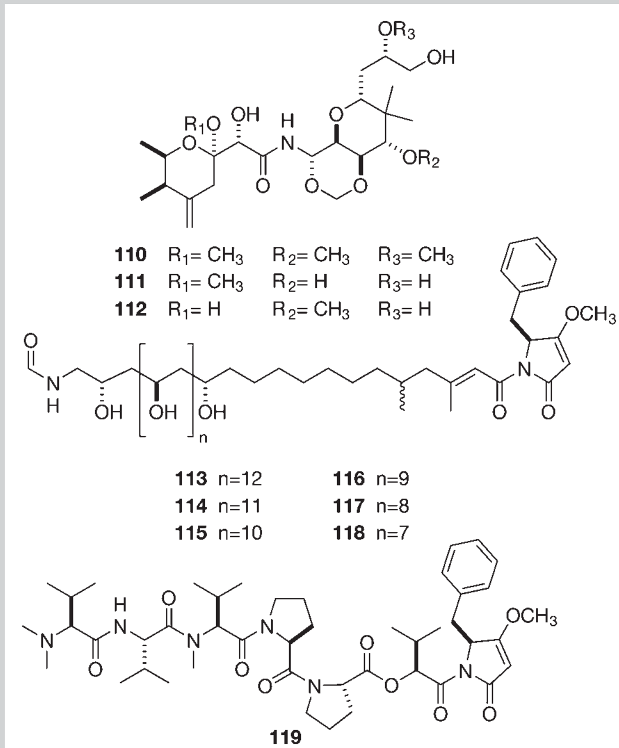

Fig. 9 Chemical structure of mycalamides and mycapolyols.

Other polyketides

Three acetogenins (**120**–**122**, ▶ **Fig. 10**) have been reported from the species *M. (Aegogropila) rotalis* [89, 90]. Since then, **120** and **121** have been reisolated from the red alga *Laurencia paniculata* [91] and other structures similar to **122**, such as **123**, have been reported from *Laurencia intricate* [92]. The brominated dihydroisocoumarin hiburipyranone (**124**) was isolated from the Japanese *M. (Aegogropila) adhaerens* and has exhibited cytotoxicity against P388 murine leukaemia cells with an IC_{50} value of 0.19 µg/mL [9].

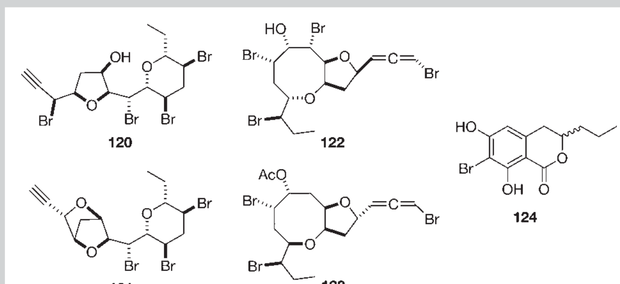

Fig. 10 Chemical structures of other polyketides.

Terpenes and terpenoids

Sesquiterpenes

Five aromatic bisabolene sesquiterpenes (▶ **Fig. 11**) were isolated from an Australian specimen of *M. (Arenochalina)* sp. (as *Arenochalina* sp.) [93]. Two of these compounds, (+)-curcudiol (**125**) and (+)-curcuphenol (**126**), have been characterised previously. The other three isomeric structures, the C-4′ hydroxyl epimers (**127**) and 3′,4′-didehydrocurcudiol (**128**), were reported for the first time [93]. Since the first report of (−)-curcuphenol and related derivatives (e.g., **125** and **126)** from the gorgonian *Pseudopterogorgia rigida* [94], related compounds have been reported from sponge sources including *Discus flavus* [95] and *Myrmekioderma styx* [96]. The new compounds **127** and **128** were later reported together with (−)-curcuphenol and several other aromatic bisabolenes from a gorgonian source, *Pseudopterogorgia rigida* [97].

(+)-Curcuphenol (**126**) has been tested for various activities including cytotoxicity, antifungal, and antibacterial properties. Antitumour properties were recorded against P388 murine leukaemia (IC_{50} value of 7 µg/mL) and human tumour cell lines. Minimum inhibition concentrations were 10 µg/mL for lung (A549) cells and 0.1 µg/mL for both colon (HCT-8) and mammary (MDAMB) tumour cell lines [95]. When tested against *Candida albicans* and *Cryptococcus neoformans*, (+)-curcuphenol (**126**) displayed antifungal activity (IC_{50} value of approximately 15 µg/mL) [95,96] and showed broad inhibition against filamentous fungi in disc assays [98]. Antibacterial activity was recorded against both *Staphylococcus aureus* and methicillin-resistant *S. aureus* (IC_{50} value of less than 20 µg/mL) [96]. (+)-Curcudiol (**125**) showed weak antifungal activity against filamentous fungi [98] and *C. albicans* (MIC value of 250 µg/mL) [95].

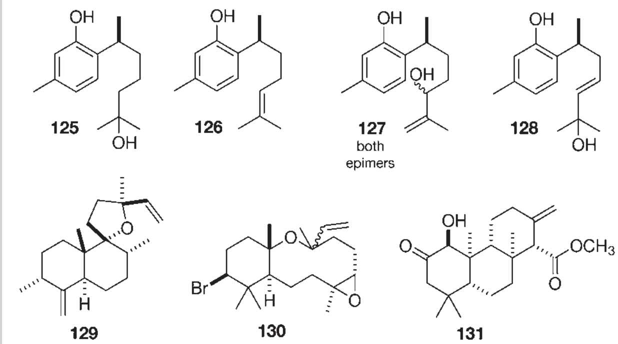

Fig. 11 Chemical structures of aromatic sesquiterpenes and diterpenes.

Diterpenes

The first Mycalid diterpenes, rotalin A (**129**) and B (**130**) (▶ **Fig. 11**), were characterised from a Sicilian specimen of the species *M. (Aegogropila) rotalis* [99]. Rotalin A (**129**) resembles the labdane family of plant-derived diterpenoids containing a rearranged labdane skeleton [99], while rotalin B (**130**) is a brominated diterpene. The new diterpene mycgranol (**131**), with an isocopalane skeleton, was reported in the species *M. (Arenochalina)* aff. *graveleyi* collected from Kenya [100]. The isocopalanes are a class of diterpenoids that exist in two enantiomeric forms and are restricted to the marine environment [101]. These compounds have been reported from organisms such as nudibranchs (e.g., *Anisodoris fontaini* [102]) and sponges (e.g., *Coelocarteria* cfr. *singaporensis* [101] and *Spongia zimocca* [103]). No activity has been reported for these Mycalid diterpenes and little activity has been reported for the related compounds.

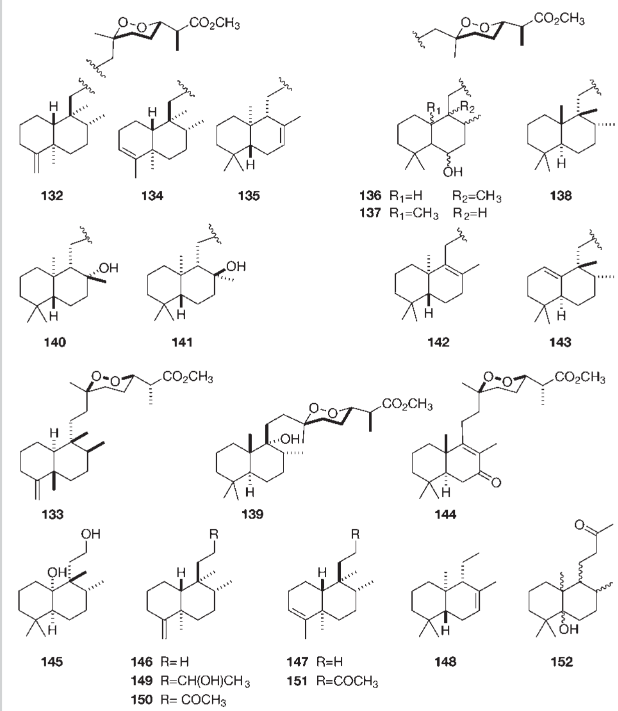

Fig. 12 Chemical structures of cyclic peroxides and related norterpenes and norterpenoids.

Cyclic peroxides

Cyclic peroxides are norsesterterpenes containing a 1,2-dioxane ring (▶ **Fig. 12**) that usually exist as carboxylic acids, but are more easily isolated as their methyl esters and have displayed various bioactivities [104–106]. The first cyclic peroxide isolated from a Mycalid source was *enantio*-sigmosceptrellin A (**132**) isolated from an Australian *M. (Aegogropila)* cf. *ancorina* [107]. This is the enantiomer of sigmosceptrellin A (**133**), which was originally isolated from the sponge *Diacarnus laevis* (originally reported as *Sigmosceptrella laevis*) [108,109] but where the absolute configuration was later corrected by Capon and MacLeod [107]. Later, **132** was again isolated from an Australian *M. (Grapelia) ancorina* together with the two new cyclic peroxides **134** and **135** that are isomeric with *enantio*-sigmosceptrellin A (**132**) [110]. The Australian sponge *M. (Carmia)* cf. *spongiosa* was the source of two new cyclic peroxides that were later named mycaperoxide E (**136**) and F (**137**) [104]. A Thai *Mycale* sp. yielded the two cyclic peroxides mycaperoxide A (**138**) and B (**139**) [111] and two further mycaperoxides, C (**140**) and D (**141**), were isolated from an Australian *Mycale* sp. in addition to the known compounds *enantio*-sigmosceptrellin A (**132**), **134**, and **135** [106]. The known mycaperoxide F (**137**) was reisolated from an Australian *Mycale* sp., and the new mycaperoxide G (**142**) was characterised from another individual of unidentified *Mycale* sp. [112]. Mycaperoxide H (**143**), isolated together with mycaperoxide B (**139**), was characterised from another Thai *Mycale* sp. [113], and mycaperoxide A (**138**) was reisolated from an Indonesian *M. (Arenochalina) euplectellioides* [114].

Cyclic peroxides have also been reported in other sponge genera, mainly *Diacarnus* [108, 109, 115, 116], *Latrunculia* [107, 117], *Negombata* [118] and *Sigmosceptrella* [119], which are all from the order Poecilosclerida. Bicyclic peroxides that share similar structural characteristics to the mycaperoxides include the sigmosceptrellins (e.g., sigmosceptrellin A **133**) isolated from the sponge *Diacarnus laevis* [108, 109] and diacarperoxides (e.g., diacarperoxide F **144**) from the sponge *Diacarnus megaspinorhabdosa* [116].

Mycaperoxides A (**138**) and B (**139**) inhibited the growth of bacteria (*Bacillus subtilis* and *S. aureus*), showed antiviral activity with IC_{50} values in the range of 0.25–1.0 µg/mL (against *Vesicular stomatitis* virus and *Herpes simplex* virus type-1), and showed cytotoxicity with IC_{50} values ranging from 0.5–1.0 µg/mL (against P388, A549, and HT-29 cell lines) [111]. Mycaperoxide A (**138**) has also displayed cytotoxicity with an IC_{50} value of 0.45 µM (against six tumour cell lines in an MTT assay), which was in contrast to the inactivity (IC_{50} value of 10 µM) of euplectellodiol (**145**), a norterpenoid (discussed in the next section) that is thought to be an oxidative degradation product of mycaperoxide A (**138**) [114]. This highlights the importance of the presence of a 1,2-dioxane ring for biological activity [114]. Mycaperoxide H (**143**) has also displayed activity as a cytotoxic agent with an IC_{50} value of 0.8 µg/mL against HeLa cells [113].

Norterpenes and norterpenoids

Bicyclic norterpenes and norterpenoids (**145**–**152**, ▶ **Fig. 12**) are biogenetically related to cyclic peroxides, either as oxidative degradation products or through related biosynthetic pathways yielding similar structures. Six compounds were reported from an Australian *Mycale* sp., these are comprised of the three C_{16} bicyclic norterpenes **146, 147**, and **148** as well as three C_{18} bicyclic norterpenoids, one containing a hydroxyl group (**149**) and two containing ketones (**150** and **151**) [106]. A third C_{18} bicyclic norterpenoid ketone (**152**) was reported in another specimen of an Australian *Mycale* sp. [112] and a C_{16} dihydroxy bicyclic norterpenoid, euplectellodiol (**145**), was isolated from an Indonesian specimen of *M. (Arenochalina) euplectellioides* [114].

The C_{18} norterpenoids **149**–**151**, co-isolated with *enantio*-sigmosceptrellin A (**132**) and cyclic peroxide **134**, share the same bicyclic moiety [106]. The C_{18} norterpenoid ketone **152** shares a common bicyclic moiety with mycaperoxide F (**137**) [112], and the C_{16} norterpenoid euplectellodiol (**145**) reflects the same bicyclic system as mycaperoxide A (**138**) [114]. The only comparative study to assess the biological activity of cyclic peroxides and their norterpene equivalents was that of euplectellodiol (**145**), which showed no cytotoxicity in contrast to its related cyclic peroxide mycaperoxide A (**138**), which displayed potent cytotoxicity. This provides evidence that the cyclic peroxy functionality is essential for bioactivity [114].

Lipids

Ceramides

The new ceramide **153** (▶ **Fig. 13**) was reported in an Indian specimen of *M. (Carmia) mytilorum* [26]. The known C_{22}-ceramide **154** was reported in a Chinese specimen of *Mycale* sp. [30] and was originally isolated from the marine sponge *Haliclona koremella* [120]. Ceramides have displayed a range of bioactivities, including antiviral, cytotoxic, antifungal, antifouling, antitumour, immunostimulatory, and anti-inflammatory activities (documented in review [121]). In the original isolation, ceramide **154** displayed antifouling activity through inhibiting the rate of attachment and germination of macroalgae (*Ulva conglobata*) spores [120].

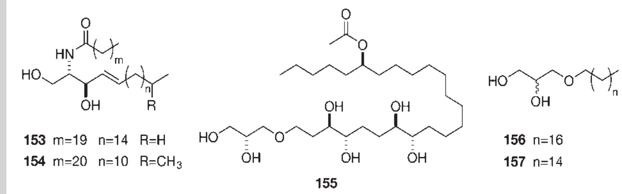

Fig. 13 Chemical structures of ceramides and ether lipids.

Ether lipids

A new polyoxygenated monoalkyl glyceryl ether, mycalol (**155**, ▶ **Fig. 13**), was isolated and characterised from the species *M. (Oxymycale) acerata* collected from Antarctica [122]. The original structure was revised through total synthesis [123]. Two known alkyl glycerols have been reported in two Mycalid specimens. Batyl alcohol (**156**) was reported in an *M. (Carmia) mytilorum* specimen from India [26], and chimyl alcohol (**157**) was reported in a Chinese specimen of *Mycale* sp. [30]. Mycalol (**155**) is a unique ether lipid, however, the related batyl alcohol (**156**) and chimyl alcohol (**157**) have been widely reported since they were the first isolated in the 1920 s (see reference [124] for review of ether lipids).

Mycalol (**155**) has shown specific cytotoxicity against anaplastic thyroid carcinoma (ATC) with IC_{50} values ranging from 3.8–15.7 µM for a range of human ATC-derived cell lines (FRO, FRO-asHMGA1, ACT1, 8505c) [122]. Mycalol (**155**) was also tested against other solid tumour lines showing cytotoxicity in the micromolar range to HCT116 (IC_{50} value of 10.9 µM), but was inactive to the other cell lines tested (GEO, GEO + HMGA1, OVCAR8, and MCF7) [122].

Sterols

In total, 11 common sterols, one epidioxy sterol, and one steroidal lactone (**158**–**170**, ▶ **Fig. 14**) have been reported in members of the family Mycalidae. The first two cholesterol derivatives **158** and **159** were reported from the Indian sponge *M. (Carmia) mytilorum* [22]. The compound **158** was also isolated together with cholesterol (**160**) and seven other sterols (**161**–**167**) in the free sterol fraction of a specimen of *M. (Arenochalina) laxissima* from Cuba [125]. Cholesterol (**160**) was also reported from a Chinese *Mycale* sp. with an epidioxy sterol (**168**) [30] after which **168** was isolated from a second Chinese *Mycale* sp. [126]. Another common sterol (**169**) was isolated from *M. (Arenochalina) euplectellioides* from Egypt [127]. An unidentified Australian *Mycale* sp. yielded the steroidal lactone mycalone (**170**), which possess an unusual side chain containing a six-membered lactone [128]. All of the 11 common sterols reported in the family Mycalidae have been reported in many other sponges. Most sponges contain a mixture of common sterols with a dominance of C_{27}, C_{28}, and C_{29} sterols.

The 5α,8α-epidioxy **168** reported from *Mycale* sp. was originally reported from a sea pen (*Virgularia* sp.) and a mollusc (*Adalaria* sp.) [129], and since its first report it has been isolated from other marine invertebrates including a sea anemone (*Metridium senile* [130]), a tunicate (*Dendrodoa grossularia* [131]), and a sponge (*Homaxinella* sp. [132]). Epidioxy sterols have shown biological activities with **168** showing toxicity against brine shrimp larvae (LD_{50} value of 4.7 µg/mL [30]) and inhibitory effects against Foxo3 a (IC_{50} value of 32.8 µg/mL), HMGCR-GFP (IC_{50} value of 6.8 µg/mL), and NF-*κ*B-luciferase (IC_{50} value of 16.3 µg/mL) assays [126]. Mycalone (**170**) is a novel steroidal lactone, an unusual side chain that contains a 6-membered lactone ring has also been observed in other sterols such as **171** isolated from the root of the plant *Trichodesma indicum*. This compound showed antimicrobial activity against gram-positive and gram-negative bacteria and fungi (MICs ranging from 4.8–19.2 µg/mL) [133].

Steroid glycosides

Eleven new steroid oligoglycosides, mycalosides A–K (**172**–**182**, ▶ **Fig. 15**), have been characterised from a Cuban *M. (Arenochalina) laxissima* [125, 134, 135]. The aglycones of mycalosides A–H (**172**–**179**) consist of a polyhydroxylated Δ^5 steroid, and mycaloside I (**180**) consists of a polyhydroxylated Δ^7 steroid [125]. Additionally, mycalosides F, G, and H (**177**–**179**) possess a ketone group at position C-15 on the sterol nucleus [125]. Steroidal and tetracyclic triterpenoid glycosides have been isolated from several sponge orders including Tetractinellida, Poecilosclerida, Axinellida, and Haplosclerida. In addition to those isolated from the family Mycalidae, glycosides have been reported in other genera of the order Poecilosclerida, including the *Ulosa* [136], *Pandaros* [137], and *Ectyoplasia* [138]. Mycalosides A–I (**172**–**180**) have displayed activity as spermostatics, inhibiting the fertilisation of sea urchin (*Strongylocentrotus nudus*) eggs, with individual glycosides showing EC_{50} values of 32 µg/mL [125]. Sponge glycosides have shown biological activities leading to the conclusion that they can serve multiple ecological roles such as feeding deterrents, prevention of biofilm formation, chemical signalling, and allelopathy (see [139] for a review of activities).

Peptides

Five new cyclic tetrapeptides, azumamides A–E (**183**–**187**, ▶ **Fig. 16**), were reported from the Japanese species *M. izuensis* [140]. These structures are comprised of three *α*-amino acids (Phe, Ala, Val, or Tyr) and the final residue is a *β*-amino acid residue with either a terminal amide or carboxylic acid [140]. Marine sponges are a source of diverse peptides having been reported widely throughout the phylum with a range of biological activities (see [141] for a review of bioactive sponge peptides). Cyclic peptides are commonly observed as fungal metabolites [142–144]. Sponges often form associations with fungi and it has been speculated that the azumamides could originate from a sponge-associated fungal source rather than the sponge itself [145].

The azumamides, and other cyclic tetrapeptides, have received interest due to their bioactivities [146]. Of particular interest is the potent inhibitory action against the enzyme HDAC reported to be a good target for cancer treatment. Azumamides A–D (**183**–**186**) showed inhibitory activity in the nanomolar range (IC_{50} values of 0.045, 0.11, 0.11, and 0.064 µM, respectively) and azumamide E (**187**) was slightly less potent (IC_{50} value of 1.3 µM) [140].

Nucleosides and nucleobases

Two new nucleosides (▶ **Fig. 16**), mycalisines A (**188**) and B (**189**), were characterised in a *Mycale* sp. collected from Japan [147]. These compounds inhibited cell division of fertilised starfish (*Asterina pectinifera*) eggs [147]. The mycalisines belong to a class of nucleosides containing a pyrrolopyrimidine ring structure that have been widely reported [147–149]. Aside from the genus

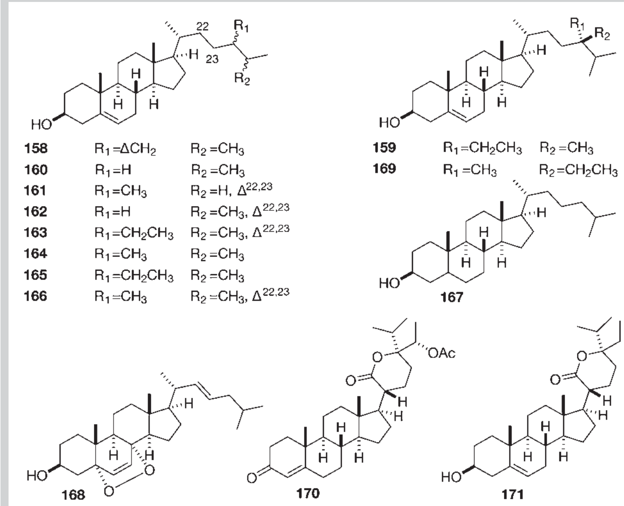

Fig. 14 Chemical structures of sterols.

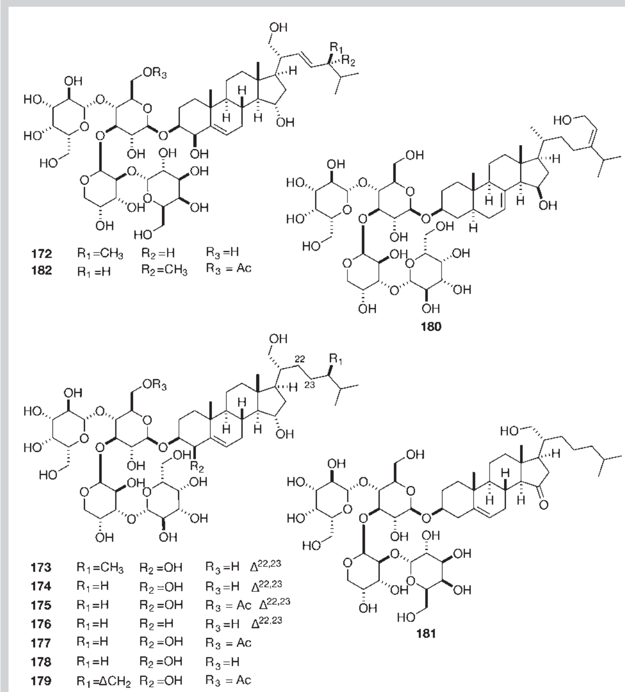

Fig. 15 Chemical structures of steroid glycosides.

Mycale, nucleosides have been reported from two other sponge genera, *Echinodictyum* (order Axinellida) and *Jaspis* (order Tetractinellida) [149]. The known deoxynucleoside thymidine (**190**) was reported in an Indian specimen of *M. (Carmia) tenuispiculata* [8], and thymine (**191**) and uracil (**192**) were reported in a *Mycale* sp. collected from China [30].

Others

The remaining compounds isolated from Mycalid sponges are small known organic molecules (**193**–**201**, ▶ **Fig. 16**). A fatty acid methyl ester, methyl henicosanoate (**193**), benzoic acid (**194**), and 4-hydroxybenzoic acid (**195**) as well as dibutyl phthalate (**196**) (dibutyl phthalate is a plasticiser and most likely an artefact from the isolation procedure) were reported from a Chinese specimen of *Mycale* sp. [30]. In addition to this, *p*-hydroxyphenylacetic acid (**197**) was reported in an Indian specimen of *M. (Carmia) mytilorum* in combination with a known tetrahydrophan derivative (**198**) [26]. Finally, three fatty acids (**199**–**201**) have been reported from the Red Sea sponge *M. (Arenochalina) euplectellioides* [127].

Chemical Diversity of Sponges of the Family Mycalidae ▼

In 2007, a computational method, ChemGPS-NP, to explore the biologically relevant chemical space of natural products using 35 calculated molecular descriptors from SMILES codes was reported [150, 151]. The online tool allows one to evaluate biologically relevant chemical properties such as size, lipophilicity, polarity, and hydrogen bond capacity. Through principal components analysis (PCA), the tool produces score predictions that can be used to map chemical properties in multidimensional space. Each principal component (PC) corresponds to particular physicochemical properties, for example, the second principal component (PC2) comprises aromatic- and conjugation-related properties, while the third principal component (PC3) comprises lipophilicity, polarity, and hydrogen bonding capacity [150, 151]. The SMILES codes for the published Mycalid compounds were submitted to ChemGPS-NP for analysis and their chemical diversity was plotted using the PC2 and PC3 descriptors (**Fig. 17**) to map these compounds in chemical space. The physicochemical properties of Mycalid compounds are largely overlapping between different structural classes. A large portion of these compounds has lipophilic properties (positive values on PC3) with low aromatic properties (negative values on PC2). The compounds with low aromatic properties paired with low lipophilic properties can be viewed (negative values on both PC2 and PC3). Finally of interest are those with high aromatic properties (positive values on PC2), most of which also correspond to low lipophilic characteristics (negative values on PC3).

The 190 compounds reported to date from members of the family Mycalidae consist of a chemically diverse group of structures (**Fig. 18** and **Table 1**). Almost half of these (86 compounds) are alkaloids mainly comprised of 2,5-disubstituted pyrrole derivatives and monoindoles. The 2,5-disubstituted pyrrole derivatives are the largest group of compounds isolated from the family with 67 structures reported, most of which differ by the length, branching, and saturation of the 5-alkyl substituents. The majority of the non-alkaloids are either polyketides, terpenoids, or lipids. Polyketides (30 compounds) are mostly dominated by macrolides (16 compounds), in particular the trisoxazole mycalolides. Within the terpenoids (26 compounds), the majority are either cyclic peroxides known as mycaperoxides or the related norterpenoid oxidative degradation products (19 compounds). The lipids are mainly comprised of sterols or steroid-containing compounds (steroidal glycosides). The remaining 19 compounds include some peptides, nucleosides, and nucleobases, among others. Compounds were identified from members of seven subgenera of the genus *Mycale*, but no compounds were reported from the smaller genus *Phlyctaenopora*. Almost half (91 compounds) of the compounds reported in the family Mycalidae are from species in the subgenus *Mycale (Carmia)* (**Fig. 19** and **Table 1S**, Supporting Information). The majority of these compounds are alkaloids, in particular 2,5-disubstituted pyrrole derivatives. This indicates that members of this subgenus are a good source of pyrrole-2-carboxaldehydes and related compounds. The remaining compound classes were found spread throughout the subgenera. It might appear that the subgenus *Mycale (Arenochalina)* contains a large proportion of lipids, but this is the result of the efforts of one research group isolating the mycalosides and associated ster-

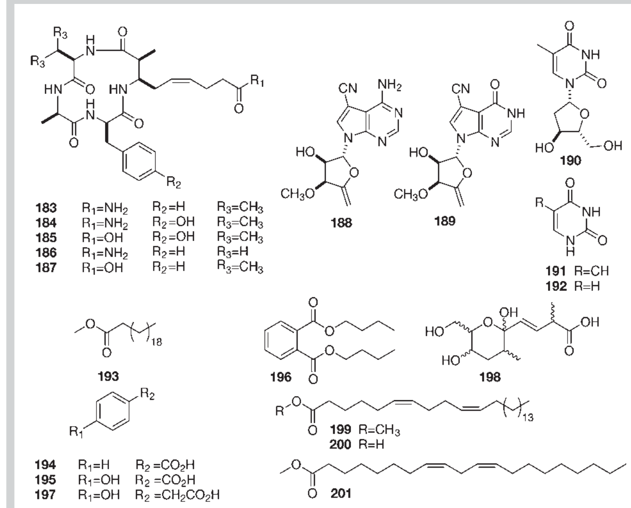

Fig. 16 Chemical structures of cyclic tetrapeptides, nucleosides, nucleobases, and other compounds.

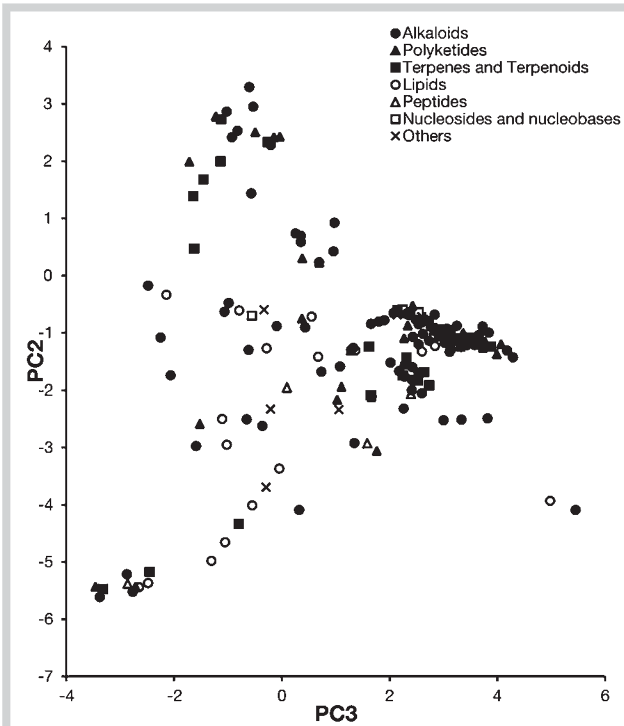

Fig. 17 Plot of principal components (PC2 versus PC3) generated from submitting the SMILES codes to ChemGPS-NP, mapping the compounds in chemical space. PC2 comprises aromatic- and conjugation-related properties with aromatic properties increasing in positive values, and PC3 comprises lipophilicity, polarity, and hydrogen bonding capacity with lipophilic properties increasing in the positive values.

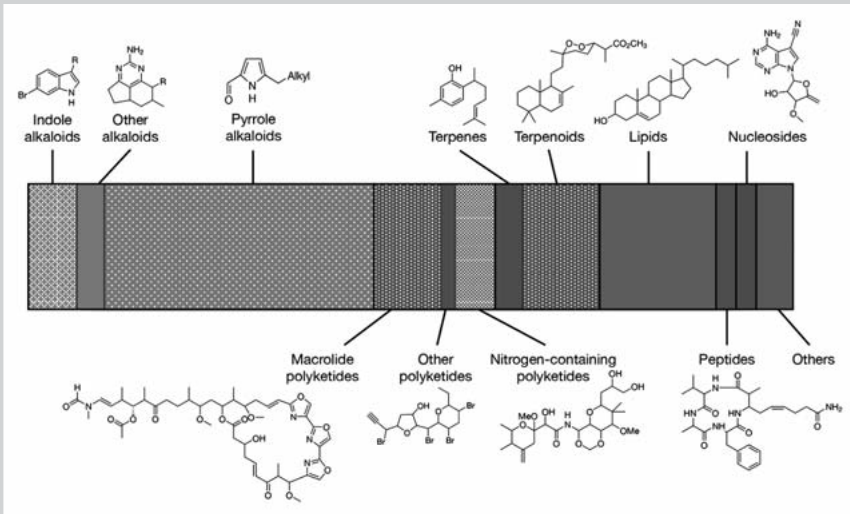

Fig. 18 Structural diversity of Mycalid compounds across compound classes. Shaded regions are proportionate to the number of compounds within each class and structures presented are representative of the compounds observed for each class.

Table 1 Number of compounds of each compound class reported in the family Mycalidae.

Compound class	Number of compounds
Alkaloids – Indoles	12
Alkaloids – Other	7
Alkaloids – Pyrrole derivatives	67
Polyketides – Macrolides	16
Polyketides – Others	4
Polyketides – Containing Nitrogen	10
Terpenes	7
Terpenoids	19
Lipids	29
Peptides	5
Nucleosides and Nucleobases	5
Others	9
Total	190

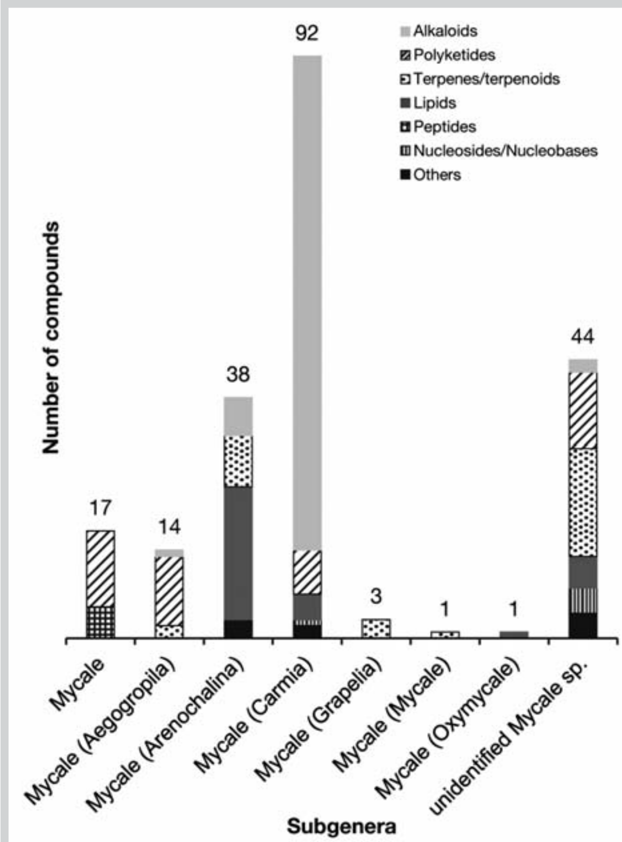

Fig. 19 Number of compounds and division across compound classes for each of the subgenera of the family Mycalidae.

ols from a single specimen of *M. (Arenochalina) laxissima* [125, 134, 135].

Analysis of the geographic distribution of the different compound classes found within the Mycalidae provides no obvious pattern (**Fig. 20** and **Table 2S**, Supporting Information). This suggests that the production of compounds across the family is not (at least not obviously) affected by geographic location and climatic conditions. It can be seen that some of the oceans are under sampled, with no samples from the South Atlantic Ocean, and only a single specimen from the Southern Ocean that yielded a single lipid. The majority of compounds (n = 90) were isolated from the North Pacific Ocean, which is not surprising considering the efforts of research groups located in China and Japan.

Taxonomic Considerations

Some of the compound classes including the pyrrole alkaloids, polyketide macrolides, and cyclic peroxides isolated from Mycalid sponges hold potential to aid in sponge taxonomy. Brominated indole alkaloids have been suggested as potentially useful chemotaxonomic indicators for the family Mycalidae [10]. However, their potential might be limited by the distribution of brominated monoindole alkaloids across the sponge class Demospongiae as well as across other marine taxa. The 2,5-disubstituted pyrrole derivatives, however, appear to be distinctly sponge compounds that may have a possible restriction to the family Mycalidae (and closely related sponges). A large diversity of structures has been reported, and there are limited reports of related compounds in non-Mycalid sponge taxa, and no reports in other non-sponge taxa (with the exception of the coral-sponge association [31]). This provides evidence that Mycalid sponges could be targeted

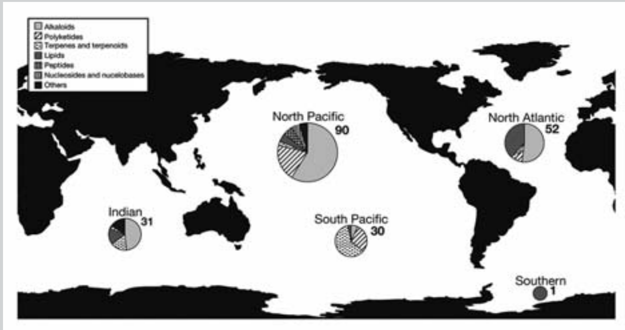

Fig. 20 Geographic distribution of isolated Mycalid compounds across the world oceans, categorised by compound class.

as a good source of 2,5-disubstituted pyrrole derivatives. The mirabilins and related guanidine tricyclic alkaloids appear to be distinctly sponge derived. They have been characterised mainly from the order Poecilosclerida [from the genera *Batzella, Monanchora,* and *Clathria (Isociella)*] as well as the orders Biemnida (*Biemna*) and Axinellida (*Acanthella*). Despite the uncertainty of mirabilins as true Mycalidae compounds due to questionable specimen identification, guanidine tricyclic alkaloids might still hold potential as taxonomic indicators for this group of Poecilosclerids.

The current survey has shown that researchers are very likely to encounter polyketides (in particular macrolides) in the family Mycalidae, with these compounds widespread throughout the family. Many polyketides are thought to be microbial in origin, which can limit their potential usefulness in sponge taxonomy. There is evidence of cases where sponge-associated microbial communities have displayed species specificity [152, 153] and therefore it is possible the resulting co-metabolites might be of taxonomic usefulness. For this to occur the nature of the sponge-microbe association needs to be assessed on a case-by-case basis. Additionally, if these compounds are produced by symbionts this could provide insight into the microbial diversity present within Mycalid sponges and the subsequent uniqueness of their biosynthetic pathways. In some cases it is also thought that sponges possess the ability to further elaborate products of microbial polyketide synthesis, resulting in compounds of mixed biogenetic origin (e.g., [154, 155]). The mycalolides and other trisoxazole macrolides are so far found in sponges among five orders (Chondrosiida, Dictyoceratida, Poecilosclerida, Suberitida, and Tetractinellida) as well being sequestered by nudibranch predators.

To assess the suitability of the species *M. (Carmia) hentscheli* for aquaculture, the spatial and temporal variation of three bioactive macrolides, mycalamide A (**1**), pateamine (**2**), and peloruside A (**3**) has been assessed. Variation in the concentration and production of these compounds was observed at different locations indicating the presence of different chemotypes [156, 157]. However, the reisolation of these compounds from several different specimens confirms their consistent presence in this sponge species and further suggests that the sponge's macrolide-producing microbial flora may be obligate symbionts.

The 1,2-dioxane ring containing norsesterterpene cyclic peroxides are distinctly sponge metabolites that could be a potential marker for the order Poecilosclerida. Acyclic, monocyclic, and bicyclic structures have been isolated from the genera *Diacarnus, Latrunculia, Negombata*, and *Sigmosceptrella* in addition to *Mycale*. Their presence suggests this family, in addition to other Poecilosclerid families, would be a good source to target the isolation of peroxy natural products. Peptides are perhaps underrepresented in the family Mycalidae considering the diversity of peptides isolated from sponges as a whole. This might provide some indication of the microbial symbionts of this family with peptides commonly of fungal or cyanobacterial origin.

One last taxonomic consideration is that of appropriate species identification. Sponge taxonomy is notoriously difficult for a non-taxonomist, and requires microscopic and histological analysis for correct identification (and even then it is often challenging). It is common for many sponges to only be identified to genus and remain unidentified at the species level. In terms of this review, it is then possible some of these specimens reported here might be incorrectly identified as Mycalids, and that other true Mycalids might have been misidentified as other sponge taxa. For example, the specimen of *M. (Arenochalina) mirabilis* (reported as *Arenochalina mirabilis*), after reexamination of the voucher material, appears to possess characters of a *Monanchora* sp. [43]. As this is the only source of mirabilins in the family Mycalidae, the questionable identification of the specimen makes the presence of these compounds in the family uncertain. It is important to consider the possibility of erroneous species identifications when interpreting the distribution of compounds and relationships among different sponge taxa.

Biologically Active Compounds from the Family Mycalidae

Of the 190 Mycalid compounds, over half (n = 99) have some type of biological activity reported, and the remaining (n = 91) have no reported activity (**Fig. 1S** and **Table 3S**, Supporting Information). Cytotoxic activities were reported for 90% (n = 89) of the active compounds, with the remaining showing a variety of other types of activity including anti-infective properties (antibacterial, antifungal, antiviral, antimalarial, and nematocidal), protein synthesis and enzyme inhibitions, and immunosuppressive activity. In a few cases, compounds were reported to possess more than one type of bioactivity.

Of the reported activities, 15% (n = 29) exhibited potent activities in the nanomolar range (IC_{50} values < 1 µM), 27% (n = 52) exhibited moderate activities in the low micromolar range (IC_{50} values of 1–20 µM), and 10% (n = 19) exhibited low activities (with IC_{50} values > 20 µM) (**Fig. 21** and **Table 4S**, Supporting Information). The polyketides accounted for the largest proportion of the potently biologically active compounds (79%, n = 23). The alkaloids also contained a large number of active compounds with 82% (n = 41) of the moderately active compounds found within this class. Despite the peptides being underrepresented with only five compounds reported, all displayed HDAC inhibitory activity. Only three of the reported terpenes have displayed biological activity, however, considering the biological activity reported for other related endoperoxides, this number could probably be higher since many of the cyclic peroxides remain untested rather than inactive.

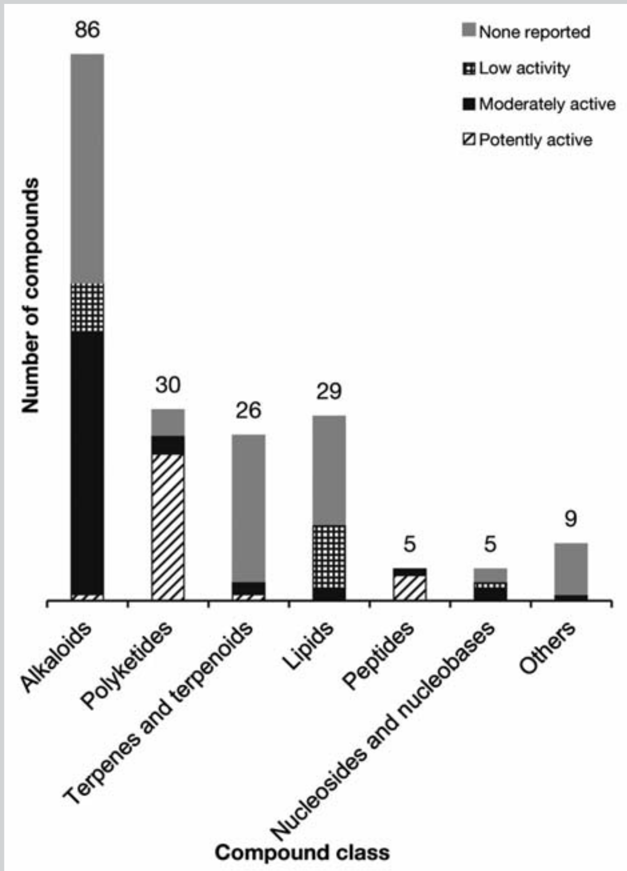

Fig. 21 The distribution of the potency of reported biological activity in each of the compound classes of the family Mycalidae categorised as: potently active (< 1 µM), moderately active (1–20 µM), low activity (> 20 µM), or no reported activity (none reported).

Conclusions

The chemical diversity documented above demonstrates that the family Mycalidae provides a good source of diverse and biologically active natural products. Biodiscovery researchers would do well to consider obtaining collections of Mycalid sponges since they are likely to provide a potential valuable new source of macrocyclic polyketides, many of which are likely to exhibit potent cytotoxicity. Targeted collection of Mycalidae are also likely to provide a lucrative source of pyrrole derivatives, as well as the bicyclic peroxides with unique structures and the potential to exhibit biological activity. Finally, the trisoxazole macrolides, cyclic peroxides, and 2,5-disubstituted pyrrole derivatives might prove useful to assess the higher relationships of the family Mycalidae to other sponge taxa and as chemotaxonomic markers within the family.

Supporting information

Tabulated data of the number of compounds within each compound class for subgenera, world oceans, biological activity type, and biological potency, and a figure of bioactivity types can be found in Supporting Information (**Tables 1S–4S** and **Fig. 1S**). Also provided is the number of publications reporting the isolation of natural products from the family Mycalidae for each country over the time period 1985–2014 to illustrate the distribution of research efforts (**Table 5S** and **Fig. 2S**).

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Conflict of Interest

The authors declare no conflict of interest.

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