

# Chemical and Biological Aspects of Marine Sponges from the Family Mycalidae

## Authors

Leesa J. Habener<sup>1</sup>, John N. A. Hooper<sup>2</sup>, Anthony R. Carroll<sup>1</sup>

## Affiliations

<sup>1</sup> Environmental Futures Research Institute, School of Environment, Griffith University, Gold Coast, Australia

<sup>2</sup> Biodiscovery and Geosciences Program, Queensland Museum, Brisbane, Australia

## Key words

- *Mycale*
- Mycalidae
- sponges
- Porifera
- bioactivity
- alkaloids
- polyketides
- chemical diversity

## 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>

received Sep. 3, 2015  
revised January 29, 2016  
accepted February 6, 2016

## Bibliography

DOI <http://dx.doi.org/10.1055/s-0042-103245>  
Published online March 22, 2016  
Planta Med 2016; 82: 816–831  
© Georg Thieme Verlag KG  
Stuttgart · New York ·  
ISSN 0032-0943

## Correspondence

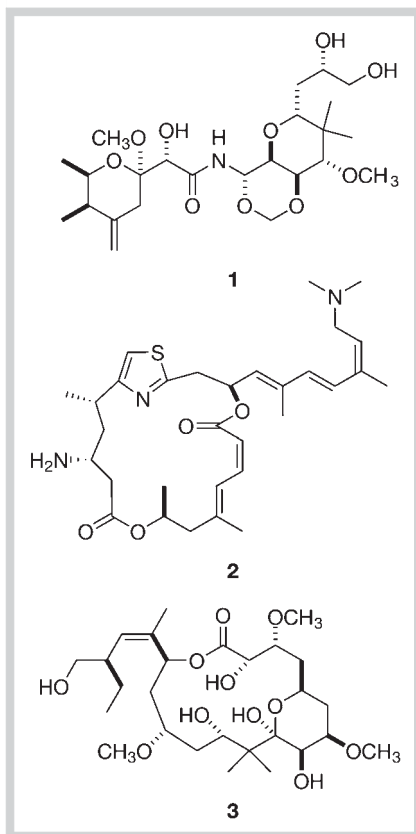
**Prof. Anthony R. Carroll**  
Environmental Futures  
Research Institute  
Griffith University  
Gold Coast, QLD 4222  
Australia  
Phone: + 61 7 55 52 91 87  
Fax: + 61 7 55 52 77 85  
[a.carroll@griffith.edu.au](mailto:a.carroll@griffith.edu.au)

## Introduction

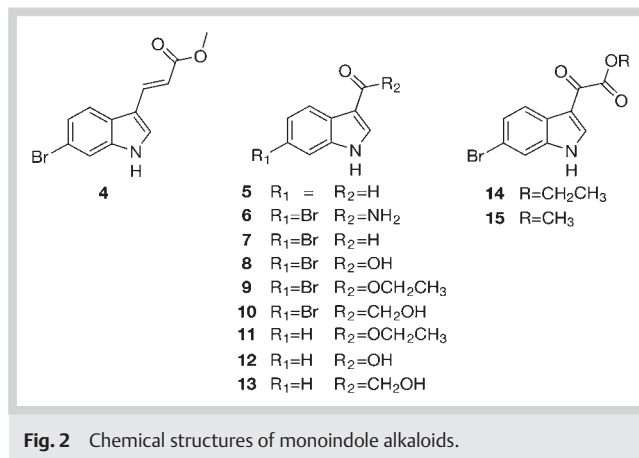
▼  
The Porifera is one of the most studied marine phyla for the discovery of novel bioactive natural products [1]. This is not surprising considering the diversity associated with marine sponges, with the phylum comprising over 8500 described species [2,3]. Knowledge of species diversity within the 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 re-

search 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 *Spongisorites* [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. (Mycala) monanchorata* (originally reported as *Mycalacarmia 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 *Mycala* 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<sub>50</sub> values of less than 10 µg/mL, and many of these compounds displaying ED<sub>50</sub> values of less than 2.5 µg/mL. Of these, mycalazol **6** (**26**) was the most active with an

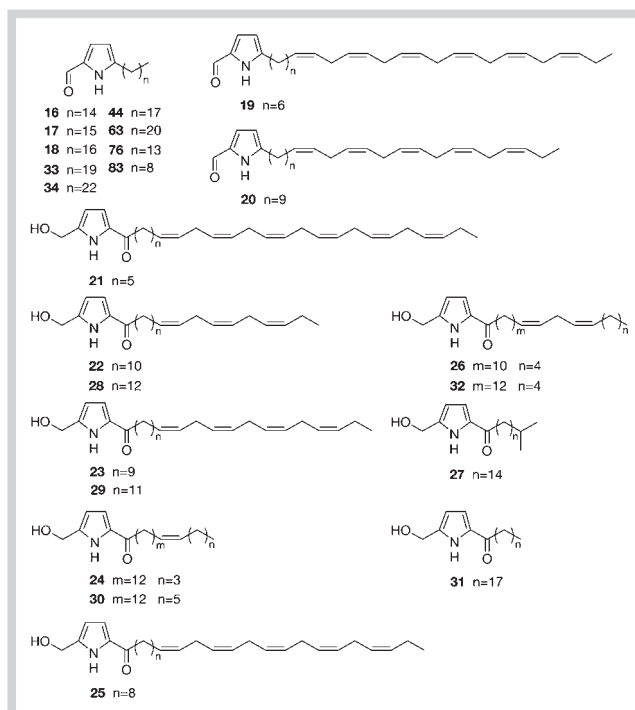


Fig. 3 Chemical structures of 2,5-disubstituted pyrrole derivatives.

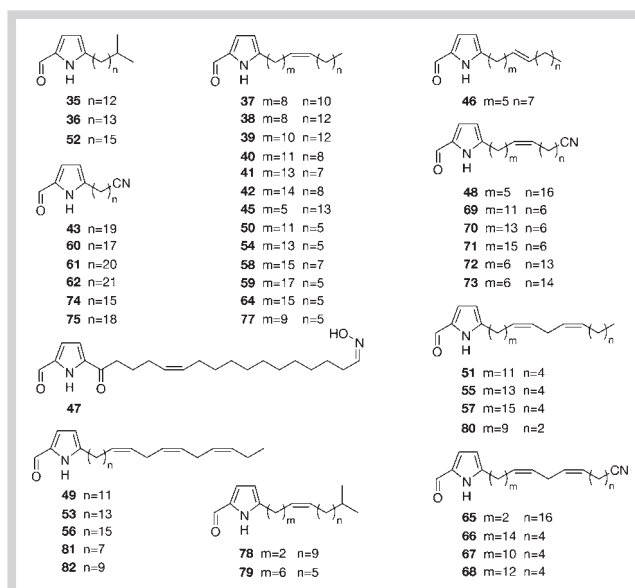
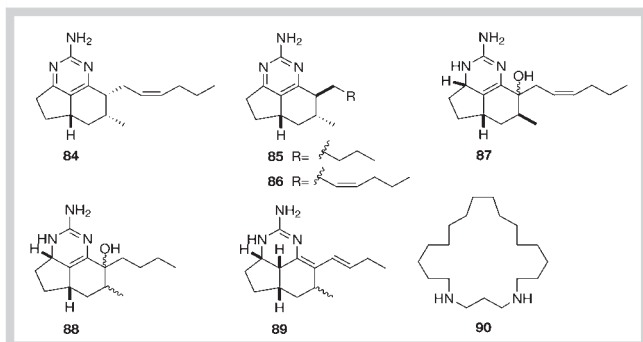


Fig. 4 Chemical structures of 2,5-disubstituted pyrrole derivatives.

ED<sub>50</sub> 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<sub>50</sub> 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<sub>50</sub> 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  $\mu\text{g}/\text{mL}$  [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  $\mu\text{M}$ , respectively. Mycalenitriles **1** (**60**), **5** (**66**), **8** (**69**), and **13** (**74**) were moderately active with  $IC_{50}$  values ranging from 10–20  $\mu\text{M}$  [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  $\mu\text{M}$ ) [34], and mirabilin B (**85**) has been reported to have antifungal activity against the strain *Cryptococcus neoformans* ( $IC_{50}$  value of 7.0  $\mu\text{g}/\text{mL}$ ) as well as antiprotozoal activity against *Leishmania donovani* ( $IC_{50}$  value of 17  $\mu\text{g}/\text{mL}$ ) [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  $\mu\text{M}$ ) [46].

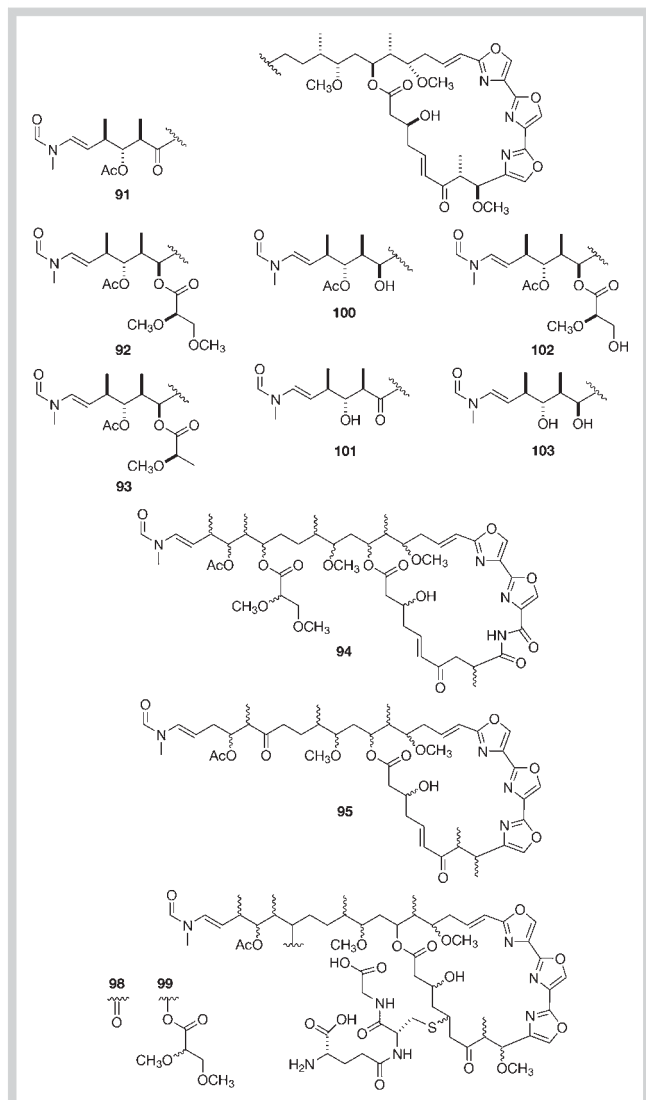
## Polyketides

### Macrolides

The trisoxazole family of macrolides (**Fig. 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 re-isolation 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 *Hexabranhus* 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  $\text{ng}/\text{mL}$ ) [49], mycalolide B (**92**) has displayed activity against HeLa cells ( $IC_{50}$  value of 0.0035  $\mu\text{g}/\text{mL}$ ) [64], and mycalolides C (**93**) and D (**94**) have shown moderate activity (average  $LC_{50}$  values of 2.5 and 0.6  $\mu\text{M}$ , 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  $\text{ng}/\text{mL}$  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  $\mu\text{g}/\text{mL}$  respectively) [47] and 30,32-dihydroxymycalide A (**103**) has shown activity against HeLa cells ( $IC_{50}$  value of 2.6  $\text{ng}/\text{mL}$ ) [50].

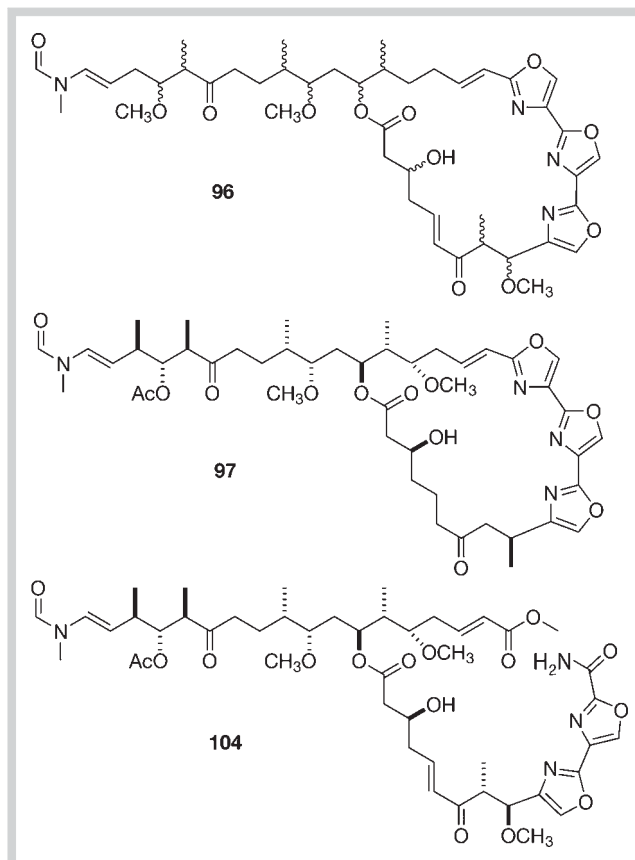
The mycalolides secomycalolide A (**104**), mycalolide A (**91**), and 30-hydroxymycalolide A (**100**) have also displayed proteasome



**Fig. 6** Chemical structures of macrolide polyketides.

inhibitory activity in an assay using a chymotrypsin-like substrate with  $IC_{50}$  values of 11, 30, and 45  $\mu\text{g}/\text{mL}$ , 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  $\mu\text{g}/\text{mL}$  [9] and protein synthesis inhibition [70]. Tedanolide (**106**) is known for possessing potent cytotoxicity when tested against cell cultures of human carcinoma of naso-



**Fig. 7** Chemical structures of macrolide polyketides.

pharynx ( $ED_{50}$  value of 0.25  $\text{ng}/\text{mL}$ ) and *in vitro* lymphocytic leukaemia ( $ED_{50}$  value of 16  $\mu\text{g}/\text{mL}$ ) and can cause S-phase arrest at a concentration of 0.01  $\mu\text{g}/\text{mL}$  [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  $\text{ng}/\text{mL}$ ) and antifungal activity against *Candida albicans*, *Trichophyton mentagrophytes*, and *Cladosporium resinae* (MIC of 1  $\mu\text{g}/\text{disk}$ , 20  $\text{ng}/\text{disk}$ , and 0.4  $\mu\text{g}/\text{disk}$ , 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  $\mu$ M, 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].

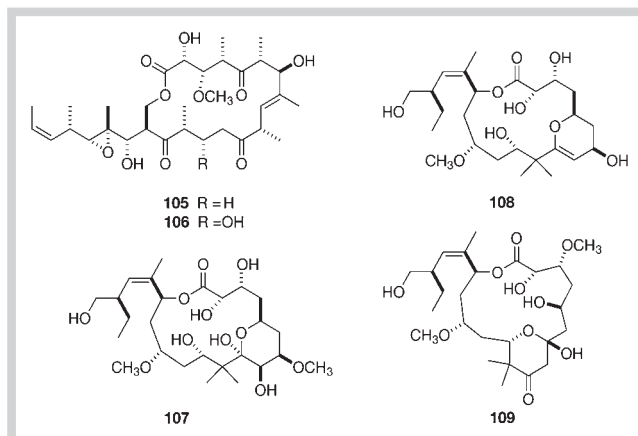
### Nitrogen-containing polyketides

During the search for antiviral compounds, mycalamides A and B (**1** and **110**, **Fig. 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].

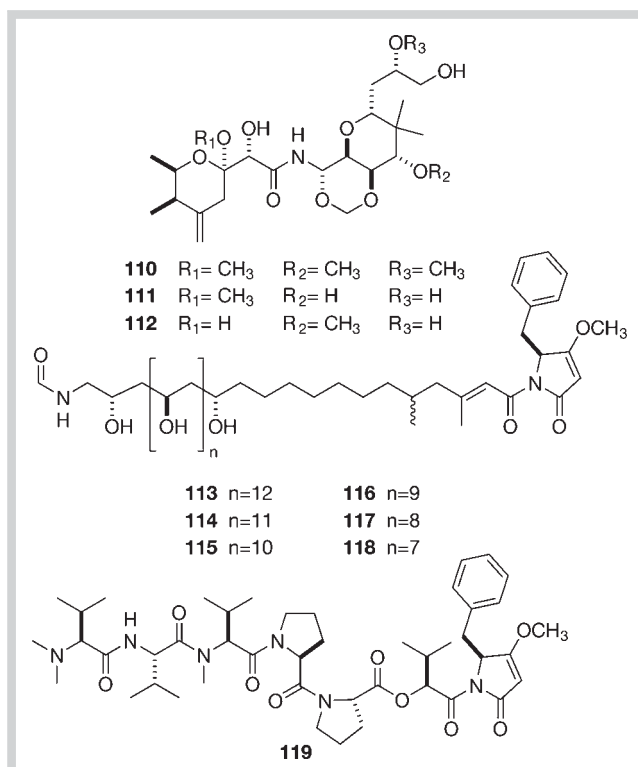
The six mycapolyols A–F (**113–118**, **Fig. 9**), metabolites of PKS-NRPS, were isolated from a Japanese specimen of *M. izuensis* [84]. Several other compounds have been reported in the literature that contain the dolapyrrolidone unit; a good example of this is dolastatin 15 (**119**) isolated from 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  $\mu$ g/mL) [84], and the related dolastatin 15 (**119**) is known for its potent cytotoxicity ( $ED_{50}$  value of 0.0024  $\mu$ g/mL against P388 cells [85]).

### Other polyketides

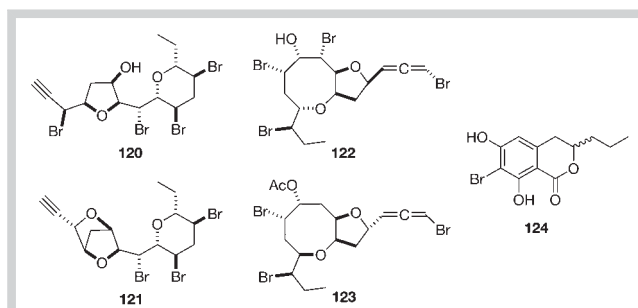
Three acetogenins (**120–122**, **Fig. 10**) have been reported from the species *M. (Aegogropila) rotalis* [89, 90]. Since then, **120** and **121** have been reisolated from the red alga *Laurencia paniculata* [91] and other structures similar to **122**, such as **123**, have been reported from *Laurencia intricate* [92]. The brominated dihydroisocoumarin hiburipyrone (**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  $\mu$ g/mL [9].



**Fig. 8** Chemical structures of macrolide polyketides.



**Fig. 9** Chemical structure of mycalamides and mycapolyols.



**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<sub>50</sub> 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<sub>50</sub> 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<sub>50</sub> 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].

### Diterpenes

The first Mycalid diterpenes, rotilin A (**129**) and B (**130**) (● Fig. 11), were characterised from a Sicilian specimen of the species *M. (Aegogropila) rotalis* [99]. Rotilin A (**129**) resembles the labdane family of plant-derived diterpenoids containing a rearranged labdane skeleton [99], while rotilin 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* cf. *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.

### 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*-sigmosceptrillin A (**132**) isolated from an Australian *M. (Aegogropila)* cf. *ancorina* [107]. This is the enantiomer of sigmosceptrillin A (**133**), which was originally isolated from the sponge *Diacarnus laevis* (originally reported as *Sigmosceptrilla 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

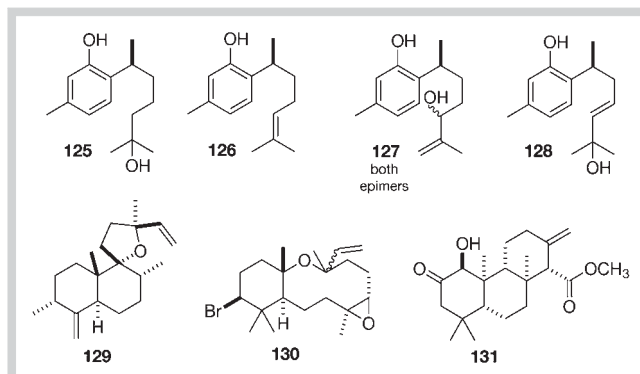


Fig. 11 Chemical structures of aromatic sesquiterpenes and diterpenes.

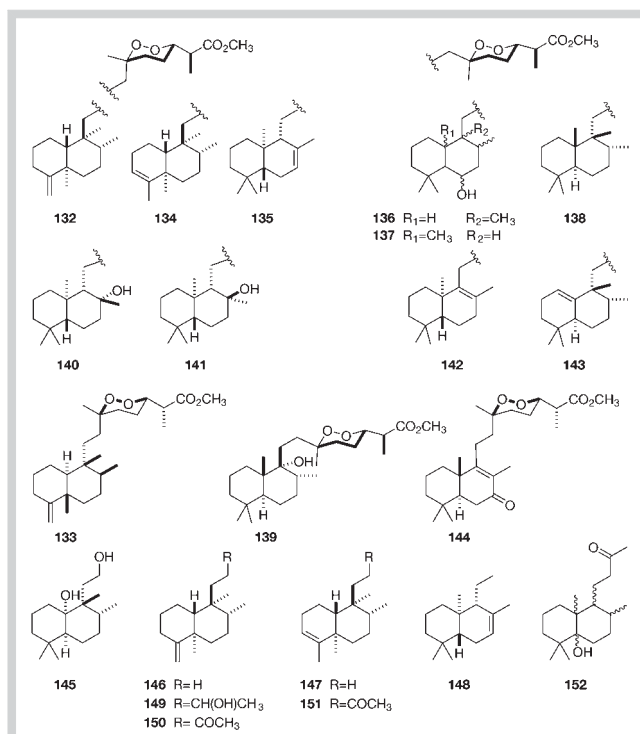


Fig. 12 Chemical structures of cyclic peroxides and related norterpene and norterpenoids.

isomeric with *enantio*-sigmosceptrillin 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*-sigmosceptrillin 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 sigmosceptrrellins (e.g., sigmosceptrrellin A **133**) isolated from the sponge *Diacarnus laevis* [108, 109] and diacarpoxides (e.g., diacarpoxide F **144**) from the sponge *Diacarnus megaspinothabdoma* [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  $\mu\text{g}/\text{mL}$  (against *Vesicular stomatitis* virus and *Herpes simplex* virus type-1), and showed cytotoxicity with  $IC_{50}$  values ranging from 0.5–1.0  $\mu\text{g}/\text{mL}$  (against P388, A549, and HT-29 cell lines) [111]. Mycaperoxide A (**138**) has also displayed cytotoxicity with an  $IC_{50}$  value of 0.45  $\mu\text{M}$  (against six tumour cell lines in an MTT assay), which was in contrast to the inactivity ( $IC_{50}$  value of 10  $\mu\text{M}$ ) 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  $\mu\text{g}/\text{mL}$  against HeLa cells [113].

### Norterpenes and norterpenoids

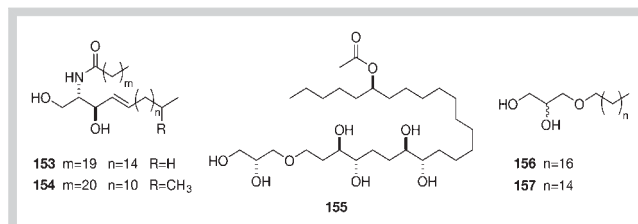
Bicyclic norterpenes and norterpenoids (**145**–**152**, **Fig. 12**) are biogenetically related to cyclic peroxides, either as oxidative degradation products or through related biosynthetic pathways yielding similar structures. Six compounds were reported from an Australian *Mycale* sp., these are comprised 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*-sigmosceptrrellin 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 norterpenoid 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, anti-tumour, immunostimulatory, and anti-inflammatory activities (documented in review [121]). In the original isolation, ceramide **154** displayed antifouling activity through inhibiting the rate of



**Fig. 13** Chemical structures of ceramides and ether lipids.

attachment and germination of macroalgae (*Ulva conglobata*) spores [120].

### 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 1920s (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  $\mu\text{M}$  for a range of human ATC-derived cell lines (FRO, FRO-asHMG1, 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  $\mu\text{M}$ ), 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  $5\alpha,8\alpha$ -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<sub>50</sub> value of 4.7 µg/mL [30]) and inhibitory effects against Foxo3a (IC<sub>50</sub> value of 32.8 µg/mL), HMGR-GFP (IC<sub>50</sub> value of 6.8 µg/mL), and NF-κB-luciferase (IC<sub>50</sub> 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

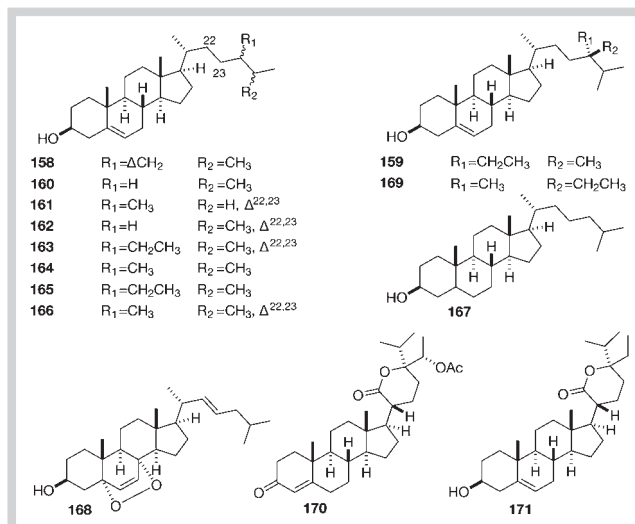
Eleven new steroid oligoglycosides, mycalosides A–K (**172–182**, **Fig. 15**), have been characterised from a Cuban *M. (Arenochalina) laxissima* [125, 134, 135]. The aglycones of mycalosides A–H (**172–179**) consist of a polyhydroxylated  $\Delta^5$  steroid, and mycaloside I (**180**) consists of a polyhydroxylated  $\Delta^7$  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 spermatostatics, inhibiting the fertilisation of sea urchin (*Strongylocentrotus nudus*) eggs, with individual glycosides showing EC<sub>50</sub> 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

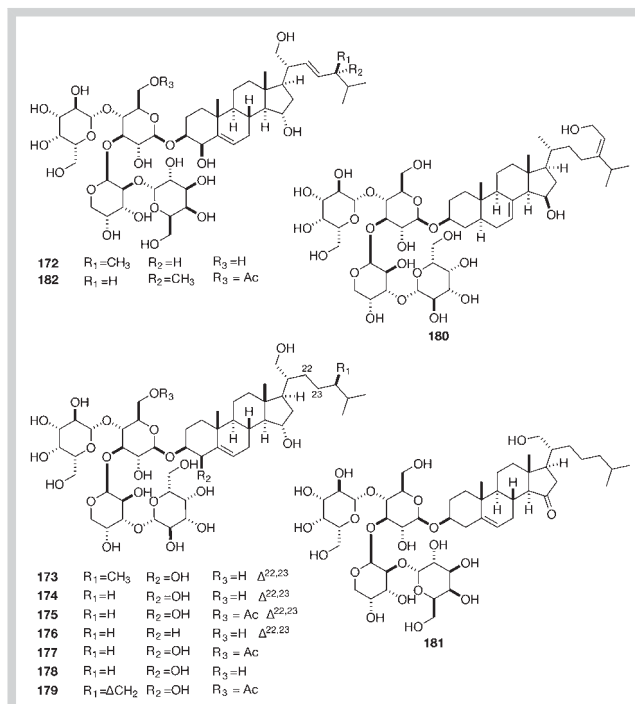
Five new cyclic tetrapeptides, azumamides A–E (**183–187**, **Fig. 16**), were reported from the Japanese species *M. izuensis* [140]. These structures are comprised of three  $\alpha$ -amino acids (Phe, Ala, Val, or Tyr) and the final residue is a  $\beta$ -amino acid residue with either a terminal 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<sub>50</sub> values of 0.045, 0.11, 0.11, and 0.064 µM, respectively) and azumamide E (**187**) was slightly less potent (IC<sub>50</sub> 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 hencosanoate (**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 norterpene 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 *Phylactenopora*. Almost half (91 compounds) of the compounds reported in the family Mycalidae are from species in the subgenus *Mycale (Carmia)* (● Fig. 19 and Table 15, 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-

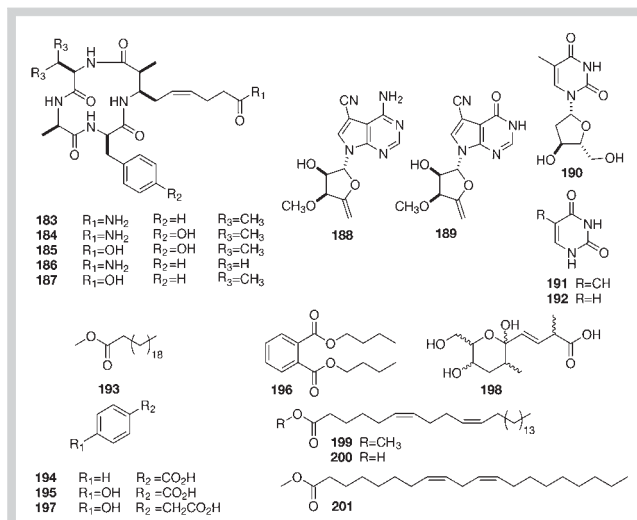


Fig. 16 Chemical structures of cyclic tetrapeptides, nucleosides, nucleobases, and other compounds.

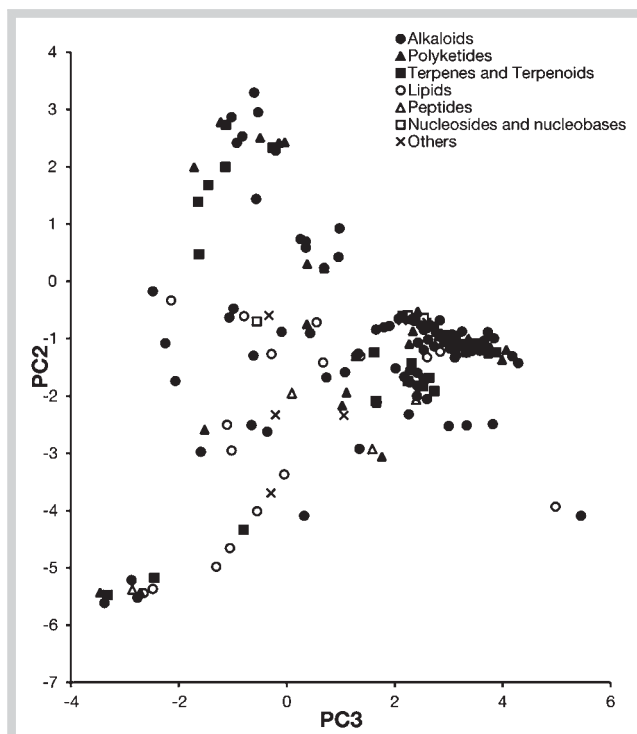
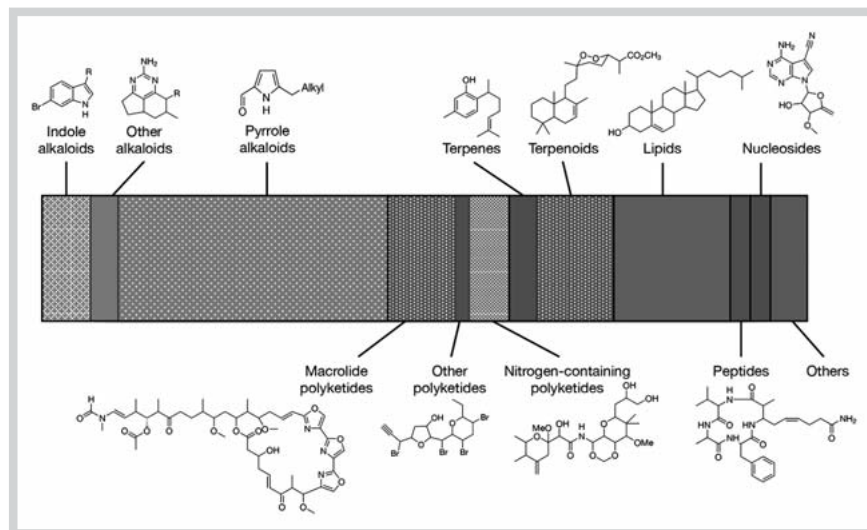


Fig. 17 Plot of principal components (PC2 versus PC3) generated from submitting the SMILES codes to ChemGPS-NP, mapping the compounds in chemical space. PC2 comprises aromatic- and conjugation-related properties with aromatic properties increasing in positive values, and PC3 comprises lipophilicity,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

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. 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.

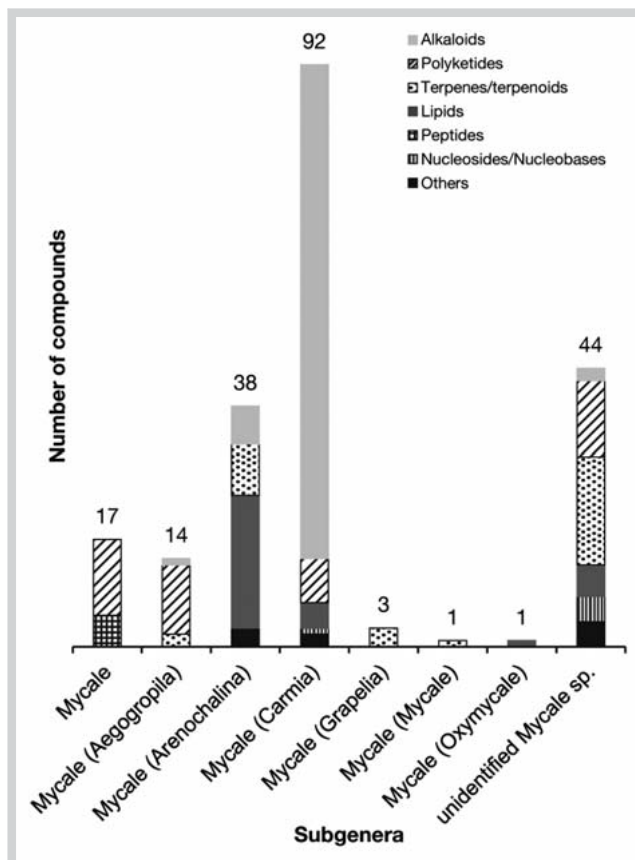
Compound class	Number of compounds
Alkaloids – Indoles	12
Alkaloids – Other	7
Alkaloids – Pyrrole derivatives	67
Polyketides – Macrolides	16
Polyketides – Others	4
Polyketides – Containing Nitrogen	10
Terpenes	7
Terpenoids	19
Lipids	29
Peptides	5
Nucleosides and Nucleobases	5
Others	9
Total	190

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.

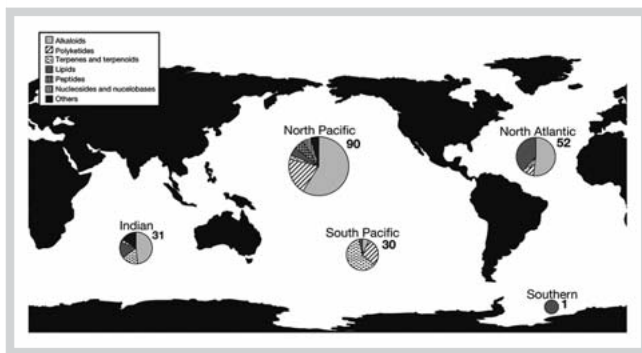
### Taxonomic Considerations

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



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

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 (Sociella)*] 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 trioxazole 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 re-isolation 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.

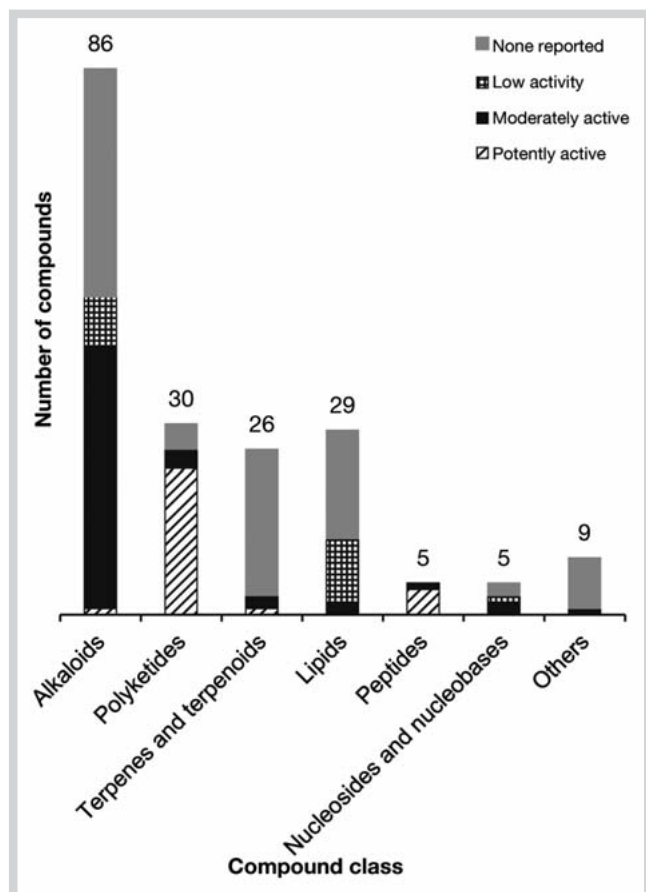
One last taxonomic consideration is that of appropriate species identification. Sponge taxonomy is notoriously difficult for a non-taxonomist, and requires microscopic and histological analysis for correct identification (and even then it is often challenging). It is common for many sponges to only be 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  $< 1 \mu M$ ), 27% ( $n = 52$ ) exhibited moderate activities in the low micromolar range ( $IC_{50}$  values of  $1-20 \mu M$ ), and 10% ( $n = 19$ ) exhibited low activities (with  $IC_{50}$  values  $> 20 \mu M$ ) (Fig. 21 and Table 4S, Supporting Information). The polyketides accounted for the largest proportion of the potentially 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 ( $< 1 \mu\text{M}$ ), moderately active ( $1\text{--}20 \mu\text{M}$ ), low activity ( $> 20 \mu\text{M}$ ), 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).

## Acknowledgements

We thank L. Robertson (Griffith University) for reading a draft manuscript. L.J.H. is grateful to be the recipient of an Australian Postgraduate Award from the Australian Government.

## Conflict of Interest

The authors declare no conflict of interest.

## References

- Munro MHG, Blunt JW, Dumdei EJ, Hickford SJH, Lill RE, Li S, Battershill CN, Duckworth AR. The discovery and development of marine compounds with pharmaceutical potential. *J Biotechnol* 1999; 35: 15–25
- van Soest RWM, Boury-Esnault N, Hooper JNA, Rützler K, de Voogd NJ, Alvarez de Glasby B, Hajdu E, Pisera AB, Manconi R, Schönberg C, Janussen D, Tabachnick KR, Klautau M, Picton B, Kelly M, Vacelet J, Dohrmann M, Díaz MC, Cardenas P. World Porifera Database, 2015. Available at <http://www.marinespecies.org/porifera>. Accessed May 25, 2015
- van Soest RWM, Boury-Esnault N, Vacelet J, Dohrmann M, Erpenbeck D, De Voogd NJ, Santodomingo N, Vanhoorne B, Kelly M, Hooper JNA. Global diversity of sponges (Porifera). *PLoS One* 2012; 7: e35105
- van Soest RWM, Hajdu E. Family Mycalidae Lundbeck, 1905. In: Hooper JNA, van Soest RWM, editors. *Systema Porifera: a guide to the classification of sponges*. New York, USA: Kluwer Academic/Plenum Publishers; 2002: 669–690
- Perry NB, Blunt JW, Munro MH, Pannell LK. Mycalamide A, an antiviral compound from a New Zealand sponge of the genus *Mycale*. *J Am Chem Soc* 1988; 110: 4850–4851
- Northcote PT, Blunt JW, Munro MHG. Pateamine: a potent cytotoxin from the New Zealand marine sponge, *Mycale* sp. *Tetrahedron Lett* 1991; 32: 6411–6414
- West LM, Northcote PT, Battershill CN. Peloruside A: a potent cytotoxic macrolide isolated from the New Zealand marine sponge *Mycale* sp. *J Org Chem* 2000; 65: 445–449
- Venkatesham U, Rama Rao M, Venkateswarlu Y. New 5-alkylpyrrole-2-carboxaldehyde derivatives from the sponge *Mycale tenuispiculata*. *J Nat Prod* 2000; 63: 1318–1320
- Fusetani N, Sugawara T, Matsunaga S, Hirota H. Cytotoxic metabolites of the marine sponge *Mycale adhaerens* Lambe. *J Org Chem* 1991; 56: 4971–4974
- Wang RP, Lin HW, Li LZ, Gao PY, Xu Y, Song SJ. Monoindole alkaloids from a marine sponge *Mycale fibrexilis*. *Biochem Syst Ecol* 2012; 43: 210–213
- Cardellina JH, Nigh D, VanWagenen BC. Plant growth regulatory indoles from the sponges *Dysidea etheria* and *Ulosa ruetzleri*. *J Nat Prod* 1986; 49: 1065–1067
- Dellar G, Djura P, Sargent MV. Structure and synthesis of a new bromoindole from a marine sponge. *J Chem Soc Perkin Trans 1* 1981: 1679–1680
- Li L, Deng Z, Fu H, Li J, Proksch P, Lin W. Chemical constituents from the marine sponge *Iotrochoto birotulata*. *Pharmazie* 2003; 58: 680–681
- Dillman RL, Cardellina JH. Aromatic secondary metabolites from the sponge *Tedania ignis*. *J Nat Prod* 1991; 54: 1056–1061
- Guerriero A, D'Ambrosio M, Pietra F, Debitus C, Ribes O. Pteridines, sterols, and indole derivatives from the Lithistid sponge *Corallistes undulatus* of the Coral sea. *J Nat Prod* 1993; 56: 1962–1970
- Guella G, Mancini I, Duhet D, Richer de Forges B, Pietra F. Ethyl 6-bromo-3-indolcarboxylate and 3-hydroxyacetal-6-bromoindole, novel bromoindoles from the sponge *Pleroma menoui* of the Coral sea. *Z Naturforsch C* 1989; 44: 914–916
- Capon RJ, Skene C, Vuong D, Lacey E, Gill JH, Heiland K, Friedel T. Equilibrating isomers: bromoindoles and a seco-xanthine encountered during a study of nematocides from the Southern Australian marine sponge *Hymeniacion* sp. *J Nat Prod* 2002; 65: 368–370

- 18 Rasmussen T, Jensen J, Anthoni U, Christophersen C, Nielsen PH. Structure and synthesis of bromoindoles from the marine sponge *Pseudosuberites hyalinus*. J Nat Prod 1993; 56: 1553–1558
- 19 Bao B, Zhang P, Lee Y, Hong J, Lee CO, Jung JH. Monoindole alkaloids from a marine sponge *Spongosorites* sp. Mar Drugs 2007; 5: 31–39
- 20 Rudolph KE, Liberio MS, Davis RA, Carroll AR. Pteridine-, thymidine-, choline- and imidazole-derived alkaloids from the Australian ascidian, *Leptoclinides durus*. Org Biomol Chem 2013; 11: 261–270
- 21 Fu X, Schmitz FJ, Tanner RS. Chemical constituents of halophilic facultatively anaerobic bacteria. J Nat Prod 1995; 58: 1950–1954
- 22 Venkateswarlu Y, Rama Rao M, Farooq Biabani M. 5-Alkylpyrrole-2-carboxaldehydes from the sponges *Mycalecarmia monanchrorata* and *Mycale mytilorum*. Indian J Chem B 1996; 35: 876–877
- 23 Stierle DB, Faulkner DJ. Metabolites of the marine sponge *Laxosuberites* species. J Org Chem 1980; 45: 4980–4982
- 24 Ortega MJ, Zubía E, Carballo JL, Salvá J. New cytotoxic metabolites from the sponge *Mycale micracanthoxea*. Tetrahedron 1997; 53: 331–340
- 25 Compagnone RS, Oliveri MC, Piña IC, Marques S, Rangel HR, Daggar F, Suárez AI, Gómez M. 5-Alkylpyrrole-2-carboxaldehydes from the Caribbean sponges *Mycale microsigmatosa* and *Desmapsamma anchorata*. Nat Prod Lett 1999; 13: 203–211
- 26 Reddy GB, Dhananjaya N. Chemical investigation of *Mycale mytilorum* and a study on toxicity and antidiabetic activity of 5-octadecylpyrrole-2-carboxaldehyde. Bioorg Med Chem 2000; 8: 27–36
- 27 Ortega MJ, Zubía E, Sánchez MC, Salvá J, Carballo JL. Structure and cytotoxicity of new metabolites from the sponge *Mycale cecilia*. Tetrahedron 2004; 60: 2517–2524
- 28 Hertiani T, Edrada RA, van Soest RWM, Sudarsono, Muller WEG, Proksch P. Chemical investigation on Indonesian marine sponge *Mycale phyllophila*. Maj Farm Indones 2009; 20: 104–111
- 29 Mao SC, Liu Y, Morgan JB, Jekabsons MB, Zhou YD, Nagle DG. Lipophilic 2, 5-disubstituted pyrroles from the marine sponge *Mycale* sp. inhibit mitochondrial respiration and HIF-1 activation. J Nat Prod 2009; 72: 1927–1936
- 30 Zhou X, Lin X, Guo X, Yang B, Yang XW, Liu Y. Chemical constituents of the sponge *Mycale* species from South China sea. Rec Nat Prod 2013; 7: 119–123
- 31 Bowden BF, Clezy PS, Coll JC, Ravi BN, Tapiolas DM. Studies of Australian soft corals. XXXIV. A new substituted pyrrole from a soft coral-sponge association. Aust J Chem 1984; 37: 227–230
- 32 Loukaci A, Muricy G, Brouard JP, Guyot M, Vacelet J, Boury-Esnault N. Chemical divergence between two sibling species of *Oscarella* (Porifera) from the Mediterranean Sea. Biochem Syst Ecol 2004; 32: 893–899
- 33 Barrow RA, Murray LM, Lim TK, Capon RJ. Mirabilins (A–F): New alkaloids from a Southern Australian marine sponge, *Arenochalina mirabilis*. Aust J Chem 1996; 49: 767–773
- 34 Gros E, Al-Mourabit A, Martin MT, Sorres J, Vacelet J, Frederich M, Aknin M, Kashman Y, Gauvin-Bialecki A. Netamines H–N, tricyclic alkaloids from the marine sponge *Biemna laboutei* and their antimalarial activity. J Nat Prod 2014; 77: 818–823
- 35 El-Naggar M, Conte M, Capon RJ. Mirabilins revisited: polyketide alkaloids from a Southern Australian marine sponge, *Clathria* sp. Org Biomol Chem 2010; 8: 407–412
- 36 Patil AD, Freyer AJ, Offen P, Bean MF, Johnson RK. Three new tricyclic guanidine alkaloids from the sponge *Batzella* sp. J Nat Prod 1997; 60: 704–707
- 37 Ferreira EG, Wilke DV, Jimenez PC, de Oliveira JR, Pessoa ODL, Silveira ER, Viana FA, Pessoa C, de Moraes MO, Hajdu E, Costa-Lotufo LV. Guanidine alkaloids from *Monanchora arbuscula*: Chemistry and antitumor potential. Chem Biodivers 2011; 8: 1433–1445
- 38 Hua HM, Peng J, Fronczek FR, Kelly M, Hamann MT. Crystallographic and NMR studies of anti-infective tricyclic guanidine alkaloids from the sponge *Monanchora unguifera*. Bioorg Med Chem 2004; 12: 6461–6464
- 39 Berlinck RG, Trindade-Silva AE, Santos MF. The chemistry and biology of organic guanidine derivatives. Nat Prod Rep 2012; 29: 1382–1406
- 40 Grkovic T, Bles JS, Bayer MM, Colburn NH, Thomas CL, Henrich CJ, Peach ML, McMahon JB, Schmid T, Gustafson KR. Tricyclic guanidine alkaloids from the marine sponge *Acanthella cavernosa* that stabilize the tumor suppressor PDCD4. Mar Drugs 2014; 12: 4593–4601
- 41 Sorek H, Rudi A, Gueta S, Reyes F, Martin MJ, Aknin M, Gaydou E, Vacelet J, Kashman Y. Netamines A–G: seven new tricyclic guanidine alkaloids from the marine sponge *Biemna laboutei*. Tetrahedron 2006; 62: 8838–8843
- 42 Capon RJ, Miller M, Rooney F. Mirabilin G: a new alkaloid from a Southern Australian marine sponge, *Clathria* species. J Nat Prod 2001; 64: 643–644
- 43 Santos MF, Harper PM, Williams DE, Mesquita JT, Pinto EG, da Costa-Silva TA, Hajdu E, Ferreira AG, Santos RA, Murphy PJ, Andersen RJ, Tempone AG, Berlinck RG. Anti-parasitic guanidine and pyrimidine alkaloids from the marine sponge *Monanchora arbuscula*. J Nat Prod 2015; 78: 1101–1112
- 44 Tavares R, Daloze D, Braekman JC, Hajdu E, Van Soest RWM. 8β-Hydroxyptilocalin, a new guanidine alkaloid from the sponge *Monanchora arbuscula*. J Nat Prod 1995; 58: 1139–1142
- 45 Harbour GC, Tymiak AA, Rinehart jr. KL, Shaw PD, Hughes jr. R, Mizsak SA, Coats JH, Zurenko GE, Li LH, Kuentzel SL. Ptilocalin and isoptilocalin, antimicrobial and cytotoxic cyclic guanidines from the Caribbean sponge *Ptilocalis* aff. *P. spiculifer* (Lamarck, 1814). J Am Chem Soc 1981; 103: 5604–5606
- 46 Coello L, Martín MJ, Reyes F. 1, 5-Diazacycloheicosane, a new cytotoxic metabolite from the marine sponge *Mycale* sp. Mar Drugs 2009; 7: 445–450
- 47 Matsunaga S, Sugawara T, Fusetani N. New mycalolides from the marine sponge *Mycale magellanica* and their interconversion. J Nat Prod 1998; 61: 1164–1167
- 48 Riego E, Hernández D, Albericio F, Álvarez M. Directly Linked Polyazoles: Important Moieties in Natural Products. Synthesis (Mass) 2005; 12: 1907–1922
- 49 Fusetani N, Yasumuro K, Matsunaga S, Hashimoto K. Mycalolides A–C, hybrid macrolides of ulapualides and halichondramide, from a sponge of the genus *Mycale*. Tetrahedron Lett 1989; 30: 2809–2812
- 50 Phuwapraisirisan P, Matsunaga S, van Soest RW, Fusetani N. Isolation of a new mycalolide from the marine sponge *Mycale izuensis*. J Nat Prod 2002; 65: 942–943
- 51 Tsukamoto S, Koimaru K, Ohta T. Secomycalolide A: A New Proteasome Inhibitor Isolated from a Marine Sponge of the Genus *Mycale*. Mar Drugs 2005; 3: 29–35
- 52 Liu Y, Ji H, Zhang S, Jung JH, Xu T. Trisoxazole macrolides from the sponge *Sarcotragus* species. Chem Nat Compd 2008; 44: 140–141
- 53 Rashid MA, Gustafson KR, Cardeilina JH, Boyd MR. Mycalolides D and E, new cytotoxic macrolides from a collection of the stony coral *Tubastrea faulkneri*. J Nat Prod 1995; 58: 1120–1125
- 54 Matsunaga S, Nogata Y, Fusetani N. Thiomycalolides: new cytotoxic trisoxazole-containing macrolides isolated from a marine sponge *Mycale* sp. J Nat Prod 1998; 61: 663–666
- 55 Sirirak T, Kittiwisut S, Janma C, Yuenyongsawad S, Suwanborirux K, Plubrukarn A. Kabiramides J and K, trisoxazole macrolides from the sponge *Pachastrissa nux*. J Nat Prod 2011; 74: 1288–1292
- 56 Kobayashi J, Murata O, Shigemori H, Sasaki T. Jaspisamides A–C, new cytotoxic macrolides from the Okinawan sponge *Jaspis* sp. J Nat Prod 1993; 56: 787–791
- 57 Kernan MR, Faulkner DJ. Halichondramide, an antifungal macrolide from the sponge *Halichondria* sp. Tetrahedron Lett 1987; 28: 2809–2812
- 58 Kernan MR, Molinski TF, Faulkner DJ. Macrocyclic antifungal metabolites from the Spanish dancer nudibranch *Hexabranchnus sanguineus* and sponges of the genus *Halichondria*. J Org Chem 1988; 53: 5014–5020
- 59 Kobayashi J, Tsuda M, Fuse H, Sasaki T, Mikami Y. Halishigamides A–D, new cytotoxic oxazole-containing metabolites from Okinawan sponge *Halichondria* sp. J Nat Prod 1997; 60: 150–154
- 60 Shin J, Lee HS, Kim JY, Shin HJ, Ahn JW, Paul VJ. New macrolides from the sponge *Chondrosia corticata*. J Nat Prod 2004; 67: 1889–1892
- 61 Matsunaga S, Fusetani N, Hashimoto K, Koseki K, Noma M. Bioactive marine metabolites. Part 13. Kabiramide C, a novel antifungal macrolide from nudibranch egg masses. J Am Chem Soc 1986; 108: 847–849
- 62 Matsunaga S, Fusetani N, Hashimoto K, Koseki K, Noma M, Noguchi H, Sankawa U. Further kabiramides and halichondramides, cytotoxic macrolides embracing trisoxazole, from the *Hexabranchnus* egg masses. J Org Chem 1989; 54: 1360–1363
- 63 Roesener JA, Scheuer PJ. Ulapualide A and B, extraordinary antitumor macrolides from nudibranch egg masses. J Am Chem Soc 1986; 108: 846–847
- 64 Suenaga K, Kimura T, Kuroda T, Matsui K, Miya S, Kuribayashi S, Sakakura A, Kigoshi H. Synthesis and biological activity of mycalolide analogs. Tetrahedron 2006; 62: 8278–8290
- 65 Saito S, Watabe S, Ozaki H, Fusetani N, Karaki H. Mycalolide B, a novel actin depolymerizing agent. J Biol Chem 1994; 269: 29710–29714

- 66 Hori M, Saito S, Shin YZ, Ozaki H, Fusetani N, Karaki H. Mycalolide-B, a novel and specific inhibitor of actomyosin ATPase isolated from marine sponge. *FEBS Lett* 1993; 322: 151–154
- 67 Schmitz FJ, Gunasekera SP, Yalamanchili G, Hossain MB, van der Helm D. Tedanolide: a potent cytotoxic macrolide from the Caribbean sponge *Tedania ignis*. *J Am Chem Soc* 1984; 106: 7251–7252
- 68 Chevallier C, Bugni TS, Feng X, Harper MK, Orendt AM, Ireland CM. Tedanolide C: a potent new 18-membered-ring cytotoxic macrolide isolated from the Papua New Guinea marine sponge *Ircinia* sp. *J Org Chem* 2006; 71: 2510–2513
- 69 Whitson EL, Pluchino KM, Hall MD, McMahon JB, McKee TC. New candidaspongolides, tedanolide analogues that selectively inhibit melanoma cell growth. *Org Lett* 2011; 13: 3518–3521
- 70 Nishimura S, Matsunaga S, Yoshida M, Hirota H, Yokoyama S, Fusetani N. 13-Deoxytedanolide, a marine sponge-derived antitumor macrolide, binds to the 60 S large ribosomal subunit. *Bioorg Med Chem* 2005; 13: 449–454
- 71 Singh AJ, Razzak M, Teesdale-Spittle P, Gaitanos TN, Wilmes A, Paterson I, Goodman JM, Miller JH, Northcote PT. Structure-activity studies of the pelorusides: new congeners and semi-synthetic analogues. *Org Biomol Chem* 2011; 9: 4456–4466
- 72 Clardy J. Stopping trouble before it starts. *ACS Chem Biol* 2006; 1: 17–19
- 73 Romo D, Rzaa RM, Shea HA, Park K, Langenhan JM, Sun L, Akhiezer A, Liu JO. Total synthesis and immunosuppressive activity of (–)-pateamine A and related compounds: Implementation of a  $\beta$ -lactam-based macrocyclization. *J Am Chem Soc* 1998; 120: 12237–12254
- 74 Singh AJ, Xu CX, Xu X, West LM, Wilmes A, Chan A, Hamel E, Miller JH, Northcote PT, Ghosh AK. Peloruside B, a potent antitumor macrolide from the New Zealand marine sponge *Mycale hentscheli*: isolation, structure, total synthesis, and bioactivity. *J Org Chem* 2009; 75: 2–10
- 75 Hood KA, West LM, Rouwé B, Northcote PT, Berridge MV, Wakefield SJ, Miller JH. Peloruside A, a novel antimetabolic agent with paclitaxel-like microtubule-stabilizing activity. *Cancer Res* 2002; 62: 3356–3360
- 76 Miller JH, Singh AJ, Northcote PT. Microtubule-stabilizing drugs from marine sponges: focus on peloruside A and zampanolide. *Mar Drugs* 2010; 8: 1059–1079
- 77 Perry NB, Blunt JW, Munro MH, Thompson AM. Antiviral and antitumor agents from a New Zealand sponge, *Mycale* sp. 2. Structures and solution conformations of mycalamides A and B. *J Org Chem* 1990; 55: 223–227
- 78 West LM, Northcote PT, Hood KA, Miller JH, Page MJ. Mycalamide D, a new cytotoxic amide from the New Zealand marine sponge *Mycale* species. *J Nat Prod* 2000; 63: 707–709
- 79 Venturi V, Davies C, Singh AJ, Matthews JH, Bellows DS, Northcote PT, Keyzers RA, Teesdale-Spittle PH. The protein synthesis inhibitors mycalamides A and E have limited susceptibility toward the drug efflux network. *J Biochem Mol Toxicol* 2012; 26: 94–100
- 80 Simpson JS, Garson MJ, Blunt JW, Munro MHG, Hooper JNA. Mycalamides C and D, cytotoxic compounds from the marine sponge *Stylinos* n. species. *J Nat Prod* 2000; 63: 704–706
- 81 Dyshlovoy SA, Fedorov SN, Kalinovsky AI, Shubina LK, Bokemeyer C, Stonik VA, Honecker F. Mycalamide A shows cytotoxic properties and prevents EGF-induced neoplastic transformation through inhibition of nuclear factors. *Mar Drugs* 2012; 10: 1212–1224
- 82 Burrens NS, Clement JJ. Antitumor activity and mechanism of action of the novel marine natural products mycalamide-A and-B and onnamide. *Cancer Res* 1989; 49: 2935–2940
- 83 Hood K, West L, Northcote P, Berridge M, Miller J. Induction of apoptosis by the marine sponge (*Mycale*) metabolites, mycalamide A and pateamine. *Apoptosis* 2001; 6: 207–219
- 84 Phuwapraisrisan P, Matsunaga S, Fusetani N. Mycopolys A–F, new cytotoxic metabolites of mixed biogenesis from the marine sponge *Mycale izuensis*. *Org Lett* 2005; 7: 2233–2236
- 85 Pettit GR, Kamano Y, Dufresne C, Cerny RL, Herald CL, Schmidt JM. Isolation and structure of the cytostatic linear depsipeptide dolastatin 15. *J Org Chem* 1989; 54: 6005–6006
- 86 Cardellina JH, Marner FJ, Moore RE. Malyngamide A, a novel chlorinated metabolite of the marine cyanophyte *Lyngbya majuscula*. *J Am Chem Soc* 1979; 101: 240–242
- 87 Simmons TL, McPhail KL, Ortega-Barría E, Mooberry SL, Gerwick WH. Belamide A, a new antimitotic tetrapeptide from a Panamanian marine cyanobacterium. *Tetrahedron Lett* 2006; 47: 3387–3390
- 88 Teta R, Irollo E, Della Sala G, Pirozzi G, Mangoni A, Costantino V. Smenamides A and B, chlorinated peptide/polyketide hybrids containing a dolapyrrolidinone unit from the Caribbean sponge *Smeno-spongia aurea*. Evaluation of their role as leads in antitumor drug research. *Mar Drugs* 2013; 11: 4451–4463
- 89 Giordano F, Mayol L, Notaro G, Piccialli V, Sica D. Structure and absolute configuration of two new polybrominated C15 acetogenins from the sponge *Mycale rotalis*. *J Chem Soc Chem Commun* 1990; 1990: 1559–1561
- 90 Notaro G, Piccialli V, Sica D, Mayol L, Giordano F. A further C15 nonterpenoid polybromoether from the encrusting sponge *Mycale rotalis*. *J Nat Prod* 1992; 55: 626–632
- 91 Imre S, Aydogmus Z, Guner H, Lotter H, Wagner H. Polybrominated non-terpenoid C15 compounds from *Laurencia paniculata* and *Laurencia obtusa*. *Z Naturforsch C* 1995; 50: 743–747
- 92 Suzuki M, Sasage Y, Ikura M, Hikichi K, Kurosawa E. Structure revision of okamurallene and structure elucidation of further C15 non-terpenoid bromoallenes from *Laurencia intricata*. *Phytochemistry* 1989; 28: 2145–2148
- 93 Butler M, Capon R, Nadeson R, Beveridge A. Aromatic bisabolens from an Australian marine sponge, *Arenochalina* sp. *J Nat Prod* 1991; 54: 619–623
- 94 McEnroe FJ, Fenical W. Structures and synthesis of some new antibacterial sesquiterpenoids from the gorgonian coral *Pseudopterogorgia rigida*. *Tetrahedron* 1978; 34: 1661–1664
- 95 Wright AE, Pomponi SA, McConnell OJ, Kohmoto S, McCarthy PJ. (+)-Curcuphenol and (+)-curcudiol, sesquiterpene phenols from shallow and deep water collections of the marine sponge *Didiscus flavus*. *J Nat Prod* 1987; 50: 976–978
- 96 Peng J, Franzblau SG, Zhang F, Hamann MT. Novel sesquiterpenes and a lactone from the Jamaican sponge *Myrmekioderma styx*. *Tetrahedron Lett* 2002; 43: 9699–9702
- 97 Georgantea P, Ioannou E, Vagias C, Roussis V. Bisabolane and chamigrane sesquiterpenes from the soft coral *Pseudopterogorgia rigida*. *Phytochem Lett* 2014; 8: 86–91
- 98 Gaspar H, Feio SS, Rodrigues AI, Van Soest RWM. Antifungal activity of (+)-curcuphenol, a metabolite from the marine sponge *Didiscus oxeata*. *Mar Drugs* 2004; 2: 8–13
- 99 Corriero G, Madaio A, Mayol L, Piccialli V, Sica D. Rotalin A and B, two novel diterpene metabolites from the encrusting Mediterranean sponge *Mycale rotalis* (Bowerbank). *Tetrahedron* 1989; 45: 277–288
- 100 Rudi A, Benayahu Y, Kashman Y. Mycgranol, a new diterpene from the marine sponge *Mycale* aff. *graveleyi*. *J Nat Prod* 2005; 68: 280–281
- 101 Fattorusso E, Romano A, Tagliatalata-Scafati O, Bavestrello G, Bonelli P, Calcinaï B. Coelodiol and coeloidic acid, ent-isocopalane diterpenes from the Indonesian sponge *Coelocartheria* cfr. *singaporensis*. *Tetrahedron Lett* 2006; 47: 2197–2200
- 102 Gavagnin M, Ungur N, Castelluccio F, Muniain C, Cimino G. New minor diterpenoid diacylglycerols from the skin of the nudibranch *Anisodoris fontaini*. *J Nat Prod* 1999; 62: 269–274
- 103 Zubía E, Gavagnin M, Scognamiglio G, Cimino G, Giusto GB. Spongiane and ent-isocopalane diterpenoids from the Mediterranean sponge *Spongia zimocca*. *J Nat Prod* 1994; 57: 725–731
- 104 Capon RJ. Two new norsesterterpene cyclic peroxides from a marine sponge, *Mycale* (*Carmia*) cf. *spongiosa*. *J Nat Prod* 1991; 54: 190–195
- 105 Higa T, Kuniyoshi M. Biologically active terpenoids from sponges. In: Fingerman M, Nagabhushan R, editors. *Biomaterials from aquatic and terrestrial organisms*. Enfield, NH, USA: Science Publishers; 2006: 393–450
- 106 Capon RJ, Rochfort SJ, Ovenden SP. Cyclic peroxides and related norterpenes from a southern Australian marine sponge, *Mycale* sp. *J Nat Prod* 1997; 60: 1261–1264
- 107 Capon RJ, Macleod JK. Structural and stereochemical studies on marine norterpenes cyclic peroxides. *Tetrahedron* 1985; 41: 3391–3404
- 108 Albericci M, Braekman JC, Daloz D, Tursch B. Chemical studies of marine invertebrates–XLV: The chemistry of three norterpenes peroxides from the sponge *Sigmosceptrella laevis*. *Tetrahedron* 1982; 38: 1881–1890
- 109 Albericci M, Collart-Lempereur M, Braekman JC, Dalcze D, Tursch B, Declercq J, Germain G, Van Meerssche M. Chemical studies of marine invertebrates. XLI. Sigmosceptrellin-A methyl ester a nor-sesterterpene peroxide from the sponge *Sigmosceptrella laevis*. *Tetrahedron Lett* 1979; 29: 2687–2690
- 110 Capon RJ, MacLeod JK. Structural and stereochemical studies on marine norterpenes cyclic peroxides, Part 2. *J Nat Prod* 1987; 50: 225–229

- 111 Tanaka J, Higa T, Suwanborirux K, Kokpol U, Bernardinelli G, Jefford CW. Bioactive norsesterterpene 1, 2-dioxanes from a Thai sponge, *Mycale* sp. *J Org Chem* 1993; 58: 2999–3002
- 112 Capon RJ, Rochfort SJ, Ovenden SP, Metzger RP. Mycaperoxides F and G and a related norterpene ketone from southern Australian marine sponges, *Mycale* species. *J Nat Prod* 1998; 61: 525–528
- 113 Phuwapraisirisan P, Matsunaga S, Fusetani N, Chaitanawisuti N, Kritsanapuntu S, Menasveta P. Mycaperoxide H, a new cytotoxic norsesterterpene peroxide from a Thai marine sponge *Mycale* sp. *J Nat Prod* 2003; 66: 289–291
- 114 Salmoun M, Braekman JC, Dewelle J, Darro F, Kiss R, De Voogd NJ, Van Soest RWM. New terpenoids from two Indonesian marine sponges. *Nat Prod Res* 2007; 21: 149–155
- 115 Youssef DTA. Tasnemoxides A–C, new cytotoxic cyclic norsesterterpene peroxides from the Red Sea sponge *Diacarnus erythraenus*. *J Nat Prod* 2004; 67: 112–114
- 116 Ibrahim SR, Ebel R, Wray V, Müller WE, Edrada-Ebel R, Proksch P. Diacarperoxides, norterpene cyclic peroxides from the sponge *Diacarnus megaspinothabdosus*. *J Nat Prod* 2008; 71: 1358–1364
- 117 Capon RJ, MacLeod JK, Willis AC. Trunculins A and B, norsesterterpene cyclic peroxides from a marine sponge, *Latrunculia brevis*. *J Org Chem* 1987; 52: 339–342
- 118 Chao CH, Chou KJ, Wang GH, Wu YC, Wang LH, Chen JP, Sheu JH, Sung PJ. Norterpenoids and related peroxides from the Formosan marine sponge *Negombata corticata*. *J Nat Prod* 2010; 73: 1538–1543
- 119 Ovenden SP, Capon RJ. Nuapapuins A and sigmosceptrellins D and E: new norterpene cyclic peroxides from a Southern Australian marine sponge, *Sigmosceptrella* sp. *J Nat Prod* 1999; 62: 214–218
- 120 Hattori T, Adachi K, Shizuri Y. New ceramide from marine sponge *Haliclona koremella* and related compounds as antifouling substances against macroalgae. *J Nat Prod* 1998; 61: 823–826
- 121 Muralidhar P, Radhika P, Krishna N, Rao DV, Rao CB. Sphingolipids from marine organisms: a review. *Nat Prod Sci* 2003; 9: 117–142
- 122 Cutignano A, Nuzzo G, D'Angelo D, Borbone E, Fusco A, Fontana A. Mycalol: a natural lipid with promising cytotoxic properties against human anaplastic thyroid carcinoma cells. *Angew Chem Int Ed Engl* 2013; 125: 9426–9430
- 123 Seetharamsingh B, Rajamohan P, Reddy DS. Total Synthesis and structural revision of mycalol, an anticancer natural product from the marine source. *Org Lett* 2015; 17: 1652–1655
- 124 Magnusson CD, Haraldsson GG. Ether lipids. *Chem Phys Lipids* 2011; 164: 315–340
- 125 Antonov AS, Afiyatullova SS, Kalinovsky AI, Ponomarenko LP, Dmitrenok PS, Aminin DL, Agafonova IG, Stonik VA. Mycalosides B–I, eight new spermostatic steroid oligoglycosides from the sponge *Mycale laxissima*. *J Nat Prod* 2003; 66: 1082–1088
- 126 Zhou X, Sun J, Ma W, Fang W, Chen Z, Yang B, Liu Y. Bioactivities of six sterols isolated from marine invertebrates. *Pharm Biol* 2014; 52: 187–190
- 127 Mohamed GA, Abd-Elrazek AE, Hassanean HA, Alahdal AM, Almohammadi A, Youssef DT. New fatty acids from the Red Sea sponge *Mycale euplectelloides*. *Nat Prod Res* 2014; 28: 1082–1090
- 128 Rochfort SJ, Gable RW, Capon RJ. Mycalone: a new steroidal lactone from a Southern Australian marine sponge, *Mycale* sp. *Aust J Chem* 1996; 49: 715–718
- 129 Stonard RJ, Petrovich JC, Andersen RJ. A new C26 sterol peroxide from the opisthobranch mollusk *Adalaria* sp. and the sea pen *Virgularia* sp. *Steroids* 1980; 36: 81–86
- 130 Findlay JA, Patil AD. A novel sterol peroxide from the sea anemone *Metridium senile*. *Steroids* 1984; 44: 261–265
- 131 Jiménez C, Quiñó E, Castedo L, Riguera R. Epidioxy sterols from the tunicates *Dendrodoa grossularia* and *Asciodiella dispersa* and the Gastropoda *Aplysia depilans* and *Aplysia punctata*. *J Nat Prod* 1986; 49: 905–909
- 132 Mansoor TA, Hong J, Lee CO, Bae SJ, Im KS, Jung JH. Cytotoxic sterol derivatives from a marine sponge *Homaxinella* sp. *J Nat Prod* 2005; 68: 331–336
- 133 Perianayagam JB, Sharma S, Pillai K, Pandurangan A, Kesavan D. Evaluation of antimicrobial activity of ethanol extract and compounds isolated from *Trichodesma indicum* (Linn.) R. Br. root. *J Ethnopharmacol* 2012; 142: 283–286
- 134 Afiyatullova SS, Antonov AS, Kalinovsky AI, Dmitrenok PS. Two new steroid oligoglycosides from the Caribbean sponge *Mycale laxissima*. *Nat Prod Commun* 2008; 3: 1581–1586
- 135 Kalinovsky AI, Antonov AS, Afiyatullova SS, Dmitrenok PS, Evtuschenko EV, Stonik VA. Mycaloside A, a new steroid oligoglycoside with an unprecedented structure from the Caribbean sponge *Mycale laxissima*. *Tetrahedron Lett* 2002; 43: 523–525
- 136 Antonov AS, Kalinovsky AI, Stonik VA. Ulososide B, a new unusual norlanostane-triterpene glycoside and its genuine aglycone from the Madagascar sponge *Ulosa* sp. *Tetrahedron Lett* 1998; 39: 3807–3808
- 137 Cachet N, Regalado EL, Genta-Jouve G, Mehiri M, Amade P, Thomas OP. Steroidal glycosides from the marine sponge *Pandaros acanthifolium*. *Steroids* 2009; 74: 746–750
- 138 Campagnuolo C, Fattorusso E, Tagliatela-Scafati O. Feroxosides A–B, two norlanostane tetraglycosides from the Caribbean sponge *Ectyoplasia ferox*. *Tetrahedron* 2001; 57: 4049–4055
- 139 Kalinin VI, Ivanchina NV, Krasokhin VB, Makarieva TN, Stonik VA. Glycosides from marine sponges (Porifera, Demospongiae): structures, taxonomical distribution, biological activities and biological roles. *Mar Drugs* 2012; 10: 1671–1710
- 140 Nakao Y, Yoshida S, Matsunaga S, Shindoh N, Terada Y, Nagai K, Yamashita JK, Ganesan A, van Soest RWM, Fusetani N. Azumamides A–E: histone deacetylase inhibitory cyclic tetrapeptides from the marine sponge *Mycale izuensis*. *Angew Chem Int Ed Engl* 2006; 118: 7715–7719
- 141 Fusetani N, Matsunaga S. Bioactive sponge peptides. *Chem Rev* 1993; 93: 1793–1806
- 142 Itazaki H, Nagashima K, Sugita K, Yoshida H, Kawamura Y, Yasuda Y, Matsumoto K, Ishii K, Uotani N, Nakai H, Terui A, Yoshimatsu S, Ikenishi Y, Nakagawa Y. Isolation and structural elucidation of new cyclotetra-peptides, trapoxins A and B, having detransformation activities as antitumor agents. *J Antibiot (Tokyo)* 1990; 43: 1524–1532
- 143 Singh SB, Zink DL, Polishook JD, Dombrowski AW, Darkin-Rattray SJ, Schmatz DM, Goetz MA. Apicidins: Novel cyclic tetrapeptides as coccidiostats and antimicrobial agents from *Fusarium pallidroseum*. *Tetrahedron Lett* 1996; 37: 8077–8080
- 144 Gu W, Cueto M, Jensen PR, Fenical W, Silverman RB. Microsporins A and B: new histone deacetylase inhibitors from the marine-derived fungus *Microsporium cf. gypseum* and the solid-phase synthesis of microsporin A. *Tetrahedron* 2007; 63: 6535–6541
- 145 Degenkolb T, Gams W, Brückner H. Natural cyclopeptaibiotics and related cyclic tetrapeptides: structural diversity and future prospects. *Chem Biodivers* 2008; 5: 693–706
- 146 Newman DJ, Cragg GM. Bioactive macrocycles from nature. In: Levin J, editor. *Macrocycles in drug discovery*. Cambridge, UK: RSC Publishing; 2014
- 147 Kato Y, Fusetani N, Matsunaga S, Hashimoto K. Bioactive marine metabolites IX. Mycalisines A and B, novel nucleosides which inhibit cell division of fertilized starfish eggs, from the marine sponge *Mycale* sp. *Tetrahedron Lett* 1985; 26: 3483–3486
- 148 Isono K. Nucleoside antibiotics: structure, biological activity, and biosynthesis. *J Antibiot (Tokyo)* 1988; 41: 1711–1739
- 149 McCarty RM, Bandarian V. Biosynthesis of pyrrolopyrimidines. *Bioorg Chem* 2012; 43: 15–25
- 150 Larsson J, Gottfries J, Muresan S, Backlund A. ChemGPS-NP: tuned for navigation in biologically relevant chemical space. *J Nat Prod* 2007; 70: 789–794
- 151 Rosén J, Lövgren A, Kogej T, Muresan S, Gottfries J, Backlund A. ChemGPS-NPWeb: chemical space navigation online. *J Comput Aided Mol Des* 2009; 23: 253–259
- 152 Lee OO, Wang Y, Yang J, Lafi FF, Al-Suwailam A, Qian PY. Pyrosequencing reveals highly diverse and species-specific microbial communities in sponges from the Red Sea. *ISME J* 2011; 5: 650–664
- 153 Reveillaud J, Maignien L, Eren AM, Huber JA, Apprill A, Sogin ML, Vanreusel A. Host-specificity among abundant and rare taxa in the sponge microbiome. *ISME J* 2014; 8: 1198–1209
- 154 Guella G, Pietra F. Rogiolenyne A, B, and C: the first branched marine C15 acetogenins. Isolation from the red seaweed *Laurencia microcladia* or the sponge *Spongia zimocca* of Il Rogiolo. *Helv Chim Acta* 1991; 74: 47–54
- 155 Taylor RE. Tedanolide and the evolution of polyketide inhibitors of eukaryotic protein synthesis. *Nat Prod Rep* 2008; 25: 854–861
- 156 Page M, West L, Northcote P, Battershill C, Kelly M. Spatial and temporal variability of cytotoxic metabolites in populations of the New Zealand sponge *Mycale hentscheli*. *J Chem Ecol* 2005; 31: 1161–1174
- 157 Page MJ, Northcote PT, Webb VL, Mackey S, Handley SJ. Aquaculture trials for the production of biologically active metabolites in the New Zealand sponge *Mycale hentscheli* (Demospongiae: Poecilosclerida). *Aquaculture* 2005; 250: 256–269