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 (Anonymycale), Mycale (Arenochalina), Mycale (Carmia), Mycale (Grapelia), Mycale (Naviculina), Mycale (Oxymycale), Mycale (Paresperella), Mycale (Rhaphidotheca), and Mycale (Zygomycale) [4].

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

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

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

Chemical Constituents of the Family Mycalidae

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

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

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

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

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

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

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

Many of these pyrrole derivatives have displayed various biological activities. Mycalazal 2 (20) and the mycalazols 1–12 (21–32) showed cytotoxicity against a panel of cell lines (P388, SCHABEL, A549, HT29, and MEL28) with ED50 values of less than 10 µg/mL, and many of these compounds displaying ED50 values of less than 2.5 µg/mL. Of these, mycalazol 6 (26) was the most active with an ED50 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 LD50 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 GI50 values). The authors...
compared the LN-caP cell line inhibition with the structures of the compounds and found that activity was associated with the presence of a single double bond, activity decreased with three double bonds, and was lost completely with two double bonds or saturated alkyl chains [27]. As a mixture, the pyrroles 16 and 46 inhibited the growth of mouse lymphoma cells (L5178Y) with an IC_{50} value of 1.8 µg/mL [28]. Mycalenitriles showed inhibition of hypoxia-induced factor (HIF-1) activation. Mycalenitriles 6 (67) and 7 (68) were the most active with IC_{50} values of 7.8 and 8.6 µM, respectively. Mycalenitriles 1 (60), 5 (66), 8 (69), and 13 (74) were moderately active with IC_{50} values ranging from 10–20 µM [29].

Other alkaloids
Mirabilins A–F (84–89, Fig. 5) were reported from the sponge *M. (Arenochalina) mirabilis* (originally reported as *Arenochalina mirabilis*) [33]. This is the only report of guanidine tricyclic alkaloids from a member of the family Mycalidae. Several of these mirabilins have since been reported in other sponge species including mirabilins A (84), C (86), and F (89) from Bienna laboutei [34], a *Clathria (Issociella)* sp. [35], a *Batella* 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], *Batella* [34, 36, 41], *Clathria (Issociella)* [35, 42], *Monanchora* [37, 38, 43, 44], and *Ptilocaulis* [45].

Some of these mirabilins have been reported to possess moderate biological activities. Mirabilin A (84) has displayed antimalarial activity against *Plasmodium falciparum* (IC_{50} value of 20.7 µM) [34], and mirabilin B (85) has been reported to have antifungal activity against the strain *Cryptococcus neoformans* (IC_{50} value of 7.0 µg/mL) as well as antiprotozoal activity against *Leishmania donovani* (IC_{50} value of 17 µg/mL) [38]. Other members of this structure class have also displayed antimalarial activity [34] and several have displayed cytotoxicity to tumour cells [34, 37, 41]. A new cyclic amine 1,5-diazacyclohenicosane (90, Fig. 5) was isolated from a *Mycale* sp. collected from Kenya [46]. Moderate cytotoxic activity was reported against human lung, colon, and breast tumour cell lines (A549, HT29, MDA-MB-231) with GI_{50} values in the micromolar range (ranging from 5.07–5.74 µM) [46].

**Polyketides Macrolides**

The trisoxazole family of macrolides (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 reisolation of mycalolides A (91) and B (92) from *M. (Aegogropila) adhaerens* of Japanese origin [9]. Mycalolide A (91) has been reported in other Japanese Mycalid specimens including *M. (Aegogropila) magellanica* [47], *M. izuensis* [50], and an unidentified *Mycale* sp. [51] and was reported together with mycalolide C (93) in the non-Mycalid sponge *Sarcotragus* sp. [52]. Mycalolide C (93) has also been reported from the coral *Tubastrea faulkneri* together with the first characterisations of mycalolides D (94) and E (95) [53], which to date have not been reported from *Mycale* (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 halichondrimide (96) and ulapaulide 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 (*Pachaustrissa nut* [55] and *Jaspis* sp. [56]), *Suberitida* (*Halichondria* sp. [57–59]), *Chondrosiida* (*Chondrosia corticata* [60]), *Poecilosclerida* (*Hydroides* sp.), and *Dictyoceratida* (*Sarcastegia* sp. [52]). Additionally, trisoxazole macrolides have also been reported from other non-sponge sources such as the egg masses of the nudibranch *Hexabranchus* sp. [58, 61–63]. Trisoxazole macrolides have displayed a range of biological activities, including cytotoxic, proteasome inhibiting, actin-depolymerising, antimarial, and antifungal activities. Mycalolides A–C (91–93) have reported cytotoxic activity against B-16 melanoma cells (IC_{50} values ranging from 0.5–1.0 ng/mL) [49], mycalolide B (92) has displayed activity against HeLa cells (IC_{50} value of 0.0035 µg/mL) [64], and mycalolides C (93) and D (94) have shown moderate activity (average IC_{50} values of 2.5 and 0.6 µM, respectively) against the National Cancer Institute’s 60-human tumour cell line panel [53]. The sulphated and hydroxylated mycalolides have also shown considerable cytotoxicity. Thiomycalolides A (98) and B (99) are both active (IC_{50} value of 18 ng/mL for both compounds) against P388 cells [54]. The hydroxylated mycalolides 30-hydroxymycalolide A, 32-hydroxymycalolide A, and 38-hydroxymycalolide B (100–102) have shown activity against L1210 cells (with IC_{50} values of 0.019, 0.013, and 0.015 µg/mL, respectively) [47] and 30,32-dihydroxymycalolide A (103) has shown activity against HeLa cells (IC_{50} value of 2.6 ng/mL) [50]. The mycalolides secomycalolide A (104), mycalolide A (91), and 30-hydroxymycalolide A (100) have also displayed proteasome

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**Fig. 5** Chemical structures of mirabilin alkaloids and 1,5-diazacyclohenicosane.
inhibitory activity in an assay using a chymotrypsin-like substrate with IC₅₀ values of 11, 30, and 45 µg/mL, respectively [51]. Additionally, the activity of mycalolide B (92) has been further explored in an effort to characterise both the actin depolymerising activity [65] and actomyosin inhibitory activity [66]. Through the exploration of an analogue of mycalolide B (92), Suenaga et al. [64] documented that the side chain portion of the compound is responsible for actin-depolymerisation activity and that the macrocyclic ring is essential to cytotoxicity.

Six other unrelated macrolides with various biological activities have been isolated from the family Mycalidae (Figs. 1 and 8). The Japanese specimen of M. (Aegogropila) adhaerens afforded a 13-deoxytedanolide (105) [9], which is related to the original compound tedanolide (106) first isolated from the sponge Teda-nia 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 IC₅₀ value of 94 pg/mL [9] and protein synthesis inhibition [70]. Tedanolide (106) is known for possessing potent cytotoxicity when tested against cell cultures of human carcinoma of nasopharynx (ED₅₀ value of 0.25 ng/mL) and in vitro lymphotytic leukaemia (ED₅₀ value of 16 pg/mL) and can cause S-phase arrest at a concentration of 0.01 µg/mL [67].

The 19-membered thiazole-containing dilactone macrolide pateamine (2, Fig. 1) was isolated from two specimens of Mycale sp. and a specimen of M. (Carmia) hentscheli from New Zealand [6, 7, 71]. Pateamine (2) has attracted considerable interest due to its potent biological activities (see [72] for summary of progress of 2 as a drug target). Pateamine (2) has displayed potent cytotoxicity against P388 murine leukaemia (IC₅₀ value of 0.15 ng/mL) and antifungal activity against Candida albicans, Trichophyton mentagrophytes, and Cladosporium resinae (MIC of 1 µg/disk, 20 ng/disk, and 0.4 µg/disk, respectively) [6]. Pateamine (2) also showed promise as an immunosuppressive agent with an IC₅₀ value of 0.46 nM in an interleukin-2 reporter gene assay [73]. Peloruside A (3, Fig. 1), a polyoxygenated 16-member macro-lide, 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 macrocyclic ring of pateamine (2), however, they are not bi-chemically related [7].

Peloruside A (3) was active against P388 murine leukaemia cells at approximately 18 nM [7] and peloruside B (107) was active (IC₅₀ value of 71 nM) against human ovarian carcinoma (1A9...
Pelorusides A–D (3, 107–109) were active against human myeloid leukaemia (HL-60 cells) with IC50 values of 10 nM, 33 nM, 221 nM, and 2 µM, respectively [71, 74]. Pelorusides have also been shown to arrest cells in the G2/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, Figs. 1 and 9) were discovered after the extract of a New Zealand Mycale sp. displayed in vitro antiviral activity [5, 77]. Since then, mycalamide A (1) has been reisolated from several other New Zealand specimens of Mycale sp. [7, 78] and M. (Carmia) hentscheli [71, 74, 79] together with additional mycalamides. These include mycalamide D (111) from a Mycale sp. [78] and mycalamide E (112) from M. (Carmia) hentscheli [79]. Mycalamides have also been isolated in other taxa such as the sponge Stylinos n. sp. (mycalamides A and D (1 and 112) [80]) and the ascidian Polysyncraton sp. (mycalamide A (1) [81]).

Mycalamides have displayed antiviral activity against Herpes simplex type-1 and Polio type-1 viruses active at 3.5–5.0 ng/disk for mycalamide A (1) and 1.0–2.0 ng/disk for mycalamide B (110) [77]. Several mycalamides have shown cytotoxicity against various cell lines with most IC50 values at sub-5 nM [78, 79, 82, 83]. Notably, mycalamide A (1) was active in the sub-nanomolar range (IC50 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 (IC50 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 auriculata [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 (IC50 values from 0.06–0.90 µg/mL) [84], and the related dolastatin 15 (119) is known for its potent cytotoxicity (ED50 value of 0.0024 µg/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 hiburipyranone (124) was isolated from the Japanese M. (Aegogropila) adhaerens and has exhibited cytotoxicity against P388 murine leukaemia cells with an IC50 value of 0.19 µg/mL [9].
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., 127) and 3,4’-didehydrocurcudiol (128), were reported from sponge sources including *Discus flavus* [95] and *Myrmekidderma styx* [96]. The new compounds 127 and 128 were later reported together with (+)-curcuphenol and several other aromatic bisabolones 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 F388 murine leukaemia (IC₅₀ 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 (IC₅₀ 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* (IC₅₀ 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, rotalin A (129) and B (130) (© Fig. 11), were characterised from a Sicilian specimen of the species *M. (Aegogropila) rotalis* [99]. Rotalin A (129) resembles the labdane family of plant-derived diterpenoids containing a re-arranged labdane skeleton [99], while rotalin B (130) is a brominated diterpene. The new diterpene mycgranol (131), with an isocopalane skeleton, was reported in the species *M. (Arenochalina) aff. gravelleyi* collected from Kenya [100]. The isocopalanes are a class of diterpenoids that exist in two enantiomeric forms and are restricted to the marine environment [101]. These compounds have been reported from organisms such as nudibranchs (e.g., *Anisodoris fontaini* [102]) and sponges (e.g., *Coelocarteria cfr. singaporensis* [101] and *Spongia zimocca* [103]). No activity has been reported for these Mycalid diterpenes and little activity has been reported for the related compounds.

Cyclic peroxides

Cyclic peroxides are norsesquiterpenes containing a 1,2-dioxane ring (© Fig. 12) that usually exist as carboxylic acids, but are more easily isolated as their methyl esters and have displayed various bioactivities [104–106]. The first cyclic peroxide isolated from a Mycalid source was *enantio*-sigmosceptrellin A (132) isolated from an Australian *M. (Aegogropila)* cf. *ancorina* [107]. This is the enantiomer of sigmosceptrellin A (133), which was originally isolated from the sponge *Diacarnus laevis* (originally configured as *Simgosceptrella laevis*) [108, 109] but where the absolute configuration was later corrected by Capon and MacLeod [107]. Later, 132 was again isolated from an Australian *M. (Grapelia) ancorina* together with the two new cyclic peroxides 134 and 135 that are isomeric with *enantio*-sigmosceptrellin A (132) [110]. The Australian sponge *M. (Carmia)* cf. *spongiosa* was the source of two new cyclic peroxides that were later named mycaperoxide E (136) and F (137) [104]. A Thai *Mycale* sp. yielded the two cyclic peroxides mycaperoxide A (138) and B (139) [111] and two further mycaperoxides, C (140) and D (141), were isolated from an Australian *Mycale* sp. in addition to the known compounds *enantio*-sigmosceptrellin A (132), 134, and 135 [106]. The known mycaperoxide F (137) was reisolated from an Australian *Mycale* sp., and the new mycaperoxide G (142) was characterised from another individual of unidentified *Mycale* sp. [112]. Mycaperoxide H (143), isolated together with mycaperoxide B (139), was characterised from another Thai *Mycale* sp. [113], and mycaperoxide A (138) was reisolated from an Indonesian *M. (Arenochalina) euptectellioides* [114].
Cyclic peroxides have also been reported in other sponge genera, mainly Diacarnus [108, 109, 115, 116], Latrunculia [107, 117], Nematobrachia [118] and Sigmoseptrella [119], which are all from the order Poecilosclerida. Bicyclic peroxides that share similar structural characteristics to the mycaperoxides include the sigmoscetrellins (e.g., sigmoscetrellin A [133]) isolated from the sponge Diacarnus laevis [108, 109] and diacarperoxides (e.g., diacarperoxide F [144]) from the sponge Diacarnus megaspinorhabdosa [116]. Mycaperoxides A (138) and B (139) inhibited the growth of bacteria (Bacillus subtilis and S. aureus), showed antiviral activity with IC50 values in the range of 0.25–1.0 µg/mL (against Vesicular stomatitis virus and Herpes simplex virus type-1), and showed cytotoxicity with IC50 values ranging from 0.5–1.0 µg/mL (against P388, A549, and HT-29 cell lines) [111]. Mycaperoxide A (138) has also displayed cytotoxicity with an IC50 value of 0.45 µM (against six tumour cell lines in an MTT assay), which was in contrast to the inactivity (IC50 value of 10 µM) of euplectellodiol (145), a norterpenoid (discussed in the next section) that is thought to be an oxidative degradation product of mycaperoxide A (138) [114]. This highlights the importance of the presence of a 1,2-dioxane ring for biological activity [114]. Mycaperoxide H (143) has also displayed activity as a cytotoxic agent with an IC50 value of 0.8 µg/mL against HeLa cells [113].

Norterpenes and norterpenoids

Bicyclic norterpenes and norterpenoids (145–152, Fig. 12) are biogenetically related to cyclic peroxides, either as oxidative degradation products or through related biosynthetic pathways yielding similar structures. Six compounds were reported from an Australian Mycale sp., these are comprised of the three C16 bicyclic norterpenes 146, 147, and 148 as well as three C18 bicyclic norterpenoids, one containing a hydroxyl group (149) and two containing ketones (150 and 151) [106]. A third C18 bicyclic norterpenoid ketone (152) was reported in another specimen of an Australian Mycale sp. [112] and a C16 dihydroxy bicyclic norterpenoid, euplectellodiol (145), was isolated from an Indonesian specimen of M. (Arenochalina) euplectelloides [114].

The C18 norterpenoids 149–151, co-isolated with enantio-sigmoscetrellin A (132) and cyclic peroxide 134, share the same bicyclic moiety [106]. The C18 norterpenoid ketone 152 shares a common bicyclic moiety with mycaperoxide F (137) [112], and the C18 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 norterpen equivalent 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 peroxide 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 C22-ceramide 154 was reported in a Chinese specimen of Mycale sp. [30] and was originally isolated from the marine sponge Haliclo na koremella [120]. Ceramides have displayed a range of bioactivities, including antiviral, cytotoxic, antifungal, antifouling, antitumour, immunostimulatory, and anti-inflammatory activities (documented in review [121]). In the original isolation, ceramide 154 displayed antifouling activity through inhibiting the rate of attachment and germination of macroalgae (Ulva conglobata) spores [120].

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 chymyl 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 chymyl alcohol (157) have been widely reported since they were the first isolated in the 1920 s (see reference [124] for review of ether lipids).

Mycalol (155) has shown specific cytotoxicity against anaplastic thyroid carcinoma (ATC) with IC50 values ranging from 3.8–15.7 µM for a range of human ATC-derived cell lines (FRO, FRO-asHMGA1, ACT1, 8505c) [122]. Mycalol (155) was also tested against other solid tumour lines showing cytotoxicity in the micromolar range to HCT116 (IC50 value of 10.9 µM), but was inactive to the other cell lines tested (GEO, GEO + HMGA1, OVCAR8, and MCF7) [122].

Sterols

In total, 11 common sterols, one epoxydiol steroid, 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 steroid fraction of a specimen of M. (Arenochalina) laxissima from Cuba [125]. Cholesterol (160) was also reported from a Chinese Mycale sp. with an epoxydiol steroid (168) [30] after which 168 was isolated from a second Chinese Mycale sp. [126]. Another common sterol (169) was isolated from M. (Arenochalina) euplectelloi des 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 C27, C28, and C29 sterols.

The 5α,8α-epoxydiol 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]). Epoxydiol sterols have shown biological...
activities with 168 showing toxicity against brine shrimp larvae (LD$_{50}$ value of 4.7 µg/mL [30]) and inhibitory effects against Fxo3a (IC$_{50}$ value of 32.8 µg/mL), HMGCR-GFP (IC$_{50}$ value of 6.8 µg/mL), and NF-κB-luciferase (IC$_{50}$ value of 16.3 µg/mL) assays [126]. Mycalone (170) is a novel steroidal lactone, an unusual side chain that contains a 6-membered lactone ring has also been observed in other sterols such as 171 isolated from the root of the plant *Trichodesma indicum*. This compound showed antimicrobial activity against gram-positive and gram-negative bacteria and fungi (MICs ranging from 4.8–19.2 µg/mL) [133].

Steroid glycosides

Eleven new steroid oligoglycosides, mycalosides A–K (172–182, Fig. 15), have been characterised from a Cuban M. (*Arenochalinia*) laxissima [125, 134, 135]. The aglycons of mycalosides A–H (172–179) consist of a polyhydroxylated Δ5 steroid, and mycaloside I (180) consists of a polyhydroxylated Δ7 steroid [125]. Additionally, mycalosides F, G, and H (177–179) possess a ketone group at position C-15 on the sterol nucleus [125]. Steroidal and tetracyclic triterpenoid glycosides have been isolated from several sponge orders including Tetractinellida, Poecilosclerida, Axinellida, and Haplosclerida. In addition to those isolated from the family Mycalidae, glycosides have been reported in other genera of the order Poecilosclerida, including the *Ulosa* [136], Pandaros [137], and *Ectyoplasia* [138]. Mycalosides A–I (172–180) have displayed activity as spermostatics, inhibiting the fertilisation of sea urchin (Strongylocentrotus nudus) eggs, with individual glycosides showing EC$_{50}$ values of 32 µg/mL [125]. Sponge glycosides have shown biological activities leading to the conclusion that they can serve multiple ecological roles such as feeding deterrents, prevention of biofilm formation, chemical signalling, and allelopathy (see [139] for a review of activities).

Peptides

Five new cyclic tetrapeptides, azumamides A–E (183–187, Fig. 16), were reported from the Japanese species *M. izuensis* [140]. These structures are comprised of three α-amino acids (Phe, Ala, Val, or Tyr) and the final residue is a β-amino acid residue with either a terminal amide or carboxylic acid [140]. Marine sponges are a source of diverse peptides having been reported widely throughout the phylum with a range of biological activities (see [141] for a review of bioactive sponge peptides). Cyclic peptides are commonly observed as fungal metabolites [142–144]. Sponges often form associations with fungi and it has been speculated that the azumamides could originate from a sponge-associated fungal source rather than the sponge itself [145]. The azumamides, and other cyclic tetrapeptides, have received interest due to their bioactivities [146]. Of particular interest is the potent inhibitory action against the enzyme HDAC reported to be a good target for cancer treatment. Azumamides A–D (183–186) showed inhibitory activity in the nanomolar range (IC$_{50}$ values of 0.045, 0.11, 0.11, and 0.064 µM, respectively) and azumamide E (187) was slightly less potent (IC$_{50}$ value of 1.3 µM) [140].

Nucleosides and nucleobases

Two new nucleosides (Fig. 16), mycalisines A (188) and B (189), were characterised in a *Mycale* sp. collected from Japan [147]. These compounds inhibited cell division of fertilised starfish (Asterina pectinifera) eggs [147]. The mycalisines belong to a class of nucleosides containing a pyrrolypyrimidine ring structure that have been widely reported [147–149]. Aside from the genus *Mycale*, nucleosides have been reported from two other sponge genera, *Echinodictyum* (order Axinellida) and *Jaspis* (order Tetractinellida) [149]. The known deoxynucleoside thymidine (190) was reported in an Indian specimen of *M. (Carmia) tenuispiculata* [8], and thymine (191) and uracil (192) were reported in a *Mycale* sp. collected from China [30].

Others

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

Chemical Diversity of Sponges of the Family Mycalidae

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

The 190 compounds reported to date from members of the family Mycalidae consist of a chemically diverse group of structures (Fig. 18 and Table 1). Almost half of these (86 compounds) are alkaloids mainly comprised of 2,5-disubstituted pyrrole derivatives and monoindoles. The 2,5-disubstituted pyrrole derivatives are the largest group of compounds isolated from the family with 67 structures reported, most of which differ by the length, branching, and saturation of the 5-alkyl substituents. The majority of the non-alkaloids are either polyketides, terpenoids, or lipids. Polyketides (30 compounds) are mostly dominated by macrolides (16 compounds), in particular the trisoxazole mycalolides. Within the terpenoids (26 compounds), the majority are either cyclic peroxides known as mycaperoxides or the related norterpenoid oxidative degradation products (19 compounds). The lipids are mainly comprised of sterols or steroid-containing compounds (steroidal glycosides). The remaining 19 compounds include some peptides, nucleosides, and nucleobases, among others. Compounds were identified from members of seven subgenera of the genus Mycale, but no compounds were reported from the smaller genus Phlyctaenopora. Almost half (91 compounds) of the compounds reported in the family Mycalidae are from species in the subgenus Mycale (Carmia) (Fig. 19 and Table 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-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-
ols from a single specimen of *M. (Arenochalina) laxissima* [125, 134, 135].

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

### Taxonomic Considerations

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

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

<table>
<thead>
<tr>
<th>Compound class</th>
<th>Number of compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaloids – Indoles</td>
<td>12</td>
</tr>
<tr>
<td>Alkaloids – Other</td>
<td>7</td>
</tr>
<tr>
<td>Alkaloids – Pyrrole derivatives</td>
<td>67</td>
</tr>
<tr>
<td>Polyketides – Macrolides</td>
<td>16</td>
</tr>
<tr>
<td>Polyketides – Others</td>
<td>4</td>
</tr>
<tr>
<td>Polyketides – Containing Nitrogen</td>
<td>10</td>
</tr>
<tr>
<td>Terpenes</td>
<td>7</td>
</tr>
<tr>
<td>Terpenoids</td>
<td>19</td>
</tr>
<tr>
<td>Lipids</td>
<td>29</td>
</tr>
<tr>
<td>Peptides</td>
<td>5</td>
</tr>
<tr>
<td>Nucleosides and Nucleobases</td>
<td>5</td>
</tr>
<tr>
<td>Others</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>190</td>
</tr>
</tbody>
</table>

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**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.

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

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from the order Poecilosclerida [from the genera distinctly sponge derived. They have been characterised mainly mirabilins and related guanidine tricyclic alkaloids appear to be as a good source of 2,5-disubstituted pyrrole derivatives. The chora, (macrolides, mycalamide A (aquaculture, the spatial and temporal variation of three bioactive To assess the suitability of the species predators. (Chondrosiida, Dictyoceratida, Poecilosclerida, Suberitida, soxazole macrolides are so far found in sponges among five or-biogenetic origin (e.g., [154, 155]). The mycalolides and other tri-microbial polyketide synthesis, resulting in compounds of mixed that sponges possess the ability to further elaborate products of 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 tri-soxazole macrolides are so far found in sponges among five or orders (Chondrosiida, Dictyoceratida, Poecilosclerida, Suberitida, and Tetractinellida) as well being sequestered by nudibranch predators. To assess the suitability of the species M. (Carmia) hentscheli for aquaculture, the spatial and temporal variation of three bioactive macrolides, mycalamide A (1), pateamine (2), and peloruside A (3) has been assessed. Variation in the concentration and production of these compounds was observed at different locations indicating the presence of different chemotypes [156,157]. However, the reisolation of these compounds from several different specimens confirms their consistent presence in this sponge species and further suggests that the sponge’s macrolide-producing microbial flora may be obligate symbionts. The 1,2-dioxane ring containing norsesterterpene cyclic peroxides are distinctly sponge metabolites that could be a potential marker for the order Poecilosclerida. Acyclic, monocyclic, and bi-cyclic structures have been isolated from the genera Diacarnus, Latrunculia, Negombata, and Sigmosceptrella in addition to Mycal. Their presence suggests this family, in addition to other Poecilosclerid families, would be a good source to target the isolation of peroxyl natural products. Peptides are perhaps under-represented 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. 15 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, anti-fungal, antiviral, antimarial, and nematicidal), protein synthesis and enzyme inhibitions, and immunosuppressive activity. In a few cases, compounds were reported to possess more than one type of bioactivity. Of the reported activities, 15% (n = 29) exhibited potent activities in the nanomolar range (IC_{50} values < 1 µM), 27% (n = 52) exhibited moderate activities in the low micromolar range (IC_{50} values of 1–20 µM), and 10% (n = 19) exhibited low activities (with IC_{50} values > 20 µM) (Fig. 21 and Table 4S, Supporting Information). The polyketides accounted for the largest proportion of the potently biologically active compounds (79%, n = 23). The alkaloids also contained a large number of active compounds with 82% (n = 41) of the moderately active compounds found within this class. Despite the peptides being underrepresented with only five compounds reported, all displayed HDAC inhibitory activity. Only three of the reported terpenes have displayed biological activity, however, considering the biological activity reported for other related endoperoxides, this number could probably be higher since many of the cyclic peroxides remain untested rather than inactive.
natural products from the family Mycalidae for each country over the time period 1985–2014 to illustrate the distribution of research efforts (Table 5S and Fig. 2S).

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Conflict of Interest

The authors declare no conflict of interest.

References


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...
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