Does the Chemical Diversity of the Order Haplosclerida (Phylum Porifera: Class Demospongia) Fit with Current Taxonomic Classification?

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Abstract
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Sponges and their associated microbiota are well known to produce a large diversity of natural products, also called specialized metabolites. In addition to their potential use in the pharmaceutical industry, these rather species-specific compounds may help in the classification of some particular sponge groups. We review herein compounds isolated from haplosclerid sponges (Class Demospongia, Order Haplosclerida) in order to help in the revision of this large group of marine invertebrates. We focus only on 3-alkylpyridine derivatives and polyacetylenic compounds, as these two groups of natural products are characteristic of haplosclerid species and are highly diverse. A close collaboration between chemists and biologists is required in order to fully apply chemotaxonomical approaches, and whenever possible biological data should include morphological and molecular data and some insight into their microbial abundance.

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Introduction
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Sponges (Phylum Porifera) are sessile invertebrates distributed in most aquatic ecosystems. In marine areas like the Caribbean Sea, they may represent the largest substrate cover and/or the largest organic biomass of living organisms, thus contributing significantly to several nutrient cycles due to their outstanding filtering capabilities [1,2]. In addition, during their long evolutionary history, most, if not all, of the diverse species of this group (> 8000 described species to date) together with their associated microbiota have developed unique metabolic pathways leading to a huge diversity of natural products, also called specialized metabolites [3]. Taxonomic classification in this particular group of marine invertebrates is still highly challenging due to a paucity of morphological characters and a discrepancy between molecular and morphological data in many cases. For this reason, biochemical information has been recently used as a complementary tool (particularly within the framework of targeted or untargeted metabolomic approaches), leading to the recent concept of integrative systematics [4].
Within the Class Demospongiae, sponges belonging to the Order Haplosclerida are considered among the most prolific sources of bioactive marine natural products, including alkaloids, polyacetylenes, or terpene derivatives. This group is also one of the most diverse of the sponge groups in terms of numbers of species and habitats, and its members also have few distinguishing morphologial characteristics. The current classification of the order as outlined in Systema Porifera, based primarily on morphology, is comprised of three suborders [two marine (Haplosclerina and Petrosina) and one freshwater (Spongillina)]. The marine suborders together comprise six families; Callyspongiidae, Chalinidae, Niphatidae, Petrosiidae, Phloeodictyidae, and Calcifibrospongiidae [5]. Analysis of sterol chemistry had indicated possible difficulties with their classification [6], suggesting patterns of relatedness that did not agree with morphological data, while in contrast, a review of 3-alkylpiperidine alkaloids appeared to agree with the current classification [7]. Subsequent molecular phylogenetic studies reveal an evolutionary history that is not completely compatible with Systema Porifera, indicating that the freshwater sponges belong elsewhere in the Demospongiae, and that while the marine Haplosclerida do form a clade, the suborders and the families (where there is enough data) are polyphyletic [8]. For this reason, a reassessment of the Order Haplosclerida is underway by multiple research groups, as an assessment of chemical

diversity may help in the development of a robust integrative classification of the group and, in return, current systematic studies in this group may also direct the search for related compounds of interest.

This review will focus on two major classes of specialized metabolites found in the Order Haplosclerida (3-alkylpyridine derivatives and polyacetylene derivatives) and will discuss them in view of the currently accepted classification for five of the six families described in Systema Porifera [5], with no compound being reported so far from sponges of the sixth family Calcifibrospongiidae [9]. Sterols and fatty acids have been reported for some members of this group in 1994 [6], and the large chemical diversity produced by this prolific sponge group was last collated in 1996 for 3-alkylpiperidine derivatives [7]. This review is not aimed to be exhaustive but discusses representatives of 3-alkylpyridine derivatives and polyacetylene derivatives. Given that they are both widely distributed amongst haplosclerid species, are largely restricted to this group, and are rather unique in the field of natural products, we consider that focusing our review on these two chemical families provides ample information to help identify discrepancies in the classification, areas for focus in the construction of a revised integrative classification and valuable avenues for future research focus.

Major issues with publishing descriptions of compounds from species that have not been fully identified will become apparent. This issue is relevant not only for the group of marine sponges included here, but for any organism of interest for bioprospecting. Accompanying morphological identification with a DNA sequence is a highly recommended way forward (in addition to deposition of a specimen voucher in a respected institute/museum). We intend this review to encourage better connections between chemists and biologists in an effort to identify novel compounds of interest while also striving to understand the origins and evolution of the same. A solid taxonomic description and classification will help in the rational collection of closely related species that will produce a large diversity of analogues of a targeted natural product family. Greater collaborative efforts will therefore increase avenues for identification of bioactive compounds, increase the likelihood of finding exploitable sources and perhaps even a biotechnological route for production. Knowledge of the complex comparative chemistry will assist in unravelling the controversial systematics specifically within the Order Haplosclerida, but will also lead to fruitful considerations in terms of chemotaxonomy within the phylum itself (Porifera, the sponges).

Distribution of Simple 3-Alkylpyridine Derivatives in the Haplosclerida
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Several 3-alkylpyridine derivatives have been isolated from the Haplosclerida, including in some cases the coupling of one or more similar moieties. This group of compounds is differentially distributed across Niphatidae, Callyspongiidae, Chalinidae, and Petrosiidae, but they are not yet reported from confirmed members of the Phloeodictyidae. The presence/absence of these classes of compounds in haplosclerid sponges are summarized in ⊙ **Table 1**.

Family Niphatidae

Within the family Niphatidae, an outstanding diversity of alkaloids has been isolated from members of the genus *Amphimedon*. Monomers of 3-alkylpyridines named hachijodines E–G as well as glycosylated monomers named amphimedosides A–E were isolated from *Amphimedon* sp. collected off Hachijo-Jima Island (Japan; ⊙ **Fig. 1**) [10,11]. Additional mono- and dimers, pyrinodemins B–I, were reported from *Amphimedon* sp. found in the same area (Nakijin, Okinawa) along with a high number of dimers bearing a hydroxylamine moiety, starting with the *bis*-3-alkylpyridine derivative pyrinodemin A and nakinadines A–F (with a *β*-aminoacid) [12–16]. All of the compounds mentioned were found to exhibit cytotoxicity. *Niphates* sp. yielded some mono-3-alkylpyridine derivatives named niphatynes A–B, again from the Northwestern Pacific (Fiji; ⊙ **Fig. 2**) [17], and Kobayashi's group more recently described some very close analogues named niphatesines A–H from a Japanese sponge of the same genus (⊙ **Fig. 2**) [18,19]. Pyrinadines A–G have been isolated from *Cribrochalina* sp., also from the Japanese coast (⊙ **Fig. 2**) [20,21]. It is not known if the two *Amphimedons* or *Niphates* sp. mentioned here are the same species or two separate species in each case given that the specimens were collected in the same geographical area. Comparison of the specimen vouchers from the various studies will have to be performed to confirm if this is the case and preferably also comparison of DNA sequences.

It would appear that simple mono- and bis-3-alkylpyridine derivatives are restricted to species belonging to the genera *Amphimedon, Cribrochalina*, and *Niphates*, all belonging to the family Niphatidae (⊙ **Table 1**). While molecular data confirms that certain *Niphates* and *Amphimedon* species are related to each other, the position of *Cribrochalina* and *Pachychalina* in relation to other members of the Niphatidae family remains unresolved [22]. As more focus is placed on resolving haplosclerid taxonomy, and compounds are isolated from more fully described species, it will be interesting to confirm if this pattern remains.

Also, within the family Niphatidae, a dimeric cyclostellettamine (3 alkylpyridiniums) was isolated from the Northwestern Pacific sponge *Amphimedon compressa* [23]. Complex mixtures of polymeric halitoxins were isolated from several species present in the Northern Caribbean (*Haliclona. rubens, H. viridis* and *H. erina*) that later were classified as *A. compressa, Amphimedon viridis*, and *Amphimedon erina* (⊙ **Fig. 3**) [24]. Later, analogous and bioactive polymers named amphitoxins were isolated as major constituents of *A. compressa* from the Caribbean [25,26]. Some trimeric 3-alkylpyridinium salts named niphatoxins A–B were isolated from *Niphates* sp. collected in the Red Sea by Talpir et al. (⊙ **Fig. 3**) [27]. No DNA sequence has been generated yet for *A. erina*, and while molecular data does not cluster *A. compressa* and *A. viridis* directly together, they are both placed in the same subgroup (Clade C), and are thus related to each other and with *Niphates* species [8,22]. The chemical content of the Southwestern Atlantic (Brazil) sponge *Pachychalina alcaloidifera* also includes the presence of antimicrobial and antimycobacterial cyclostellettamines A–K (⊙ **Fig. 3**) [28,29]. In addition, C-C and C–N bis- and tris-3-alkylpyridinium derivatives named pachychalines A–C were isolated from *Pachychalina* sp. collected in the Northwestern Atlantic (Caribbean; ⊙ **Fig. 3**) [30]. Relationships of these *Pachychalina* species to each other and to other Haplosclerida have not yet been resolved using morphological and molecular data.

Table 1 Distribution of 3-alkylpyridine derivatives and polyacetylenic compounds within Haplosclerida sponges.

	3-Alkyl-pyridine	3-Alkyl-pyridiniums	Simple C4–C5′ bis-3-alkylpiperidine	Complex C4–C5′ bis-3-alkylpiperidine	Manzamines	Polyacetylenes
Callyspongiidae						
Arenosclera brasiliensis			X			
Callyspongia fistularis						X
Callyspongia pseudoreticulata						X
Callyspongia ridleyi		X				
Callyspongia siphonella						X
Callyspongia truncata						X
Callyspongia sp.		X				X
Siphonochalina sp.						X
Chalinidae						
Haliclona densaspicula				X		
Haliclona fulva						X
Haliclona osiris						X
Haliclona sarai				X		
Haliclona viscosa		X	X			
Haliclona (Haliclona)						X
Haliclona sp.	X	X	X		X	X
Haliclona (Reniera)		X		X		
Niphatidae						
Amphimedon sp.	X	X	X		X	
Cribrochalina dura						X
Cribrochalina vasculum						X
Cribrochalina sp.	X					
Niphates lunisimisis						X
Niphates sp.	X	X				X
Pachychalina alcaloidifera		X	X	X		
Pachychalina sp.		X				
Petrosiidae						
Acanthostrongylophora ingens			X		X	
Acanthostrongylophora sp.					X	
Neopetrosia exigua			X			
Neopetrosia proxima			X			
Neopetrosia seriata			X			
Petrosia corticata						X
Petrosia ficiformis						X
Petrosia solida						X
Petrosia strongylata						X
Petrosia volcano						X
Petrosia (Strongylophora)						X
Petrosia sp.						X
Xestospongia muta						X
Xestospongia testudinaria						X
Xestospongia sp.					X	X
Phloeodictyidae						
Oceanapia triangulata						X
Oceanapia sp.						X

Family Callyspongiidae

Alkylation at the nucleophilic nitrogen N-1 of the pyridine leading to 3-alkylpyridinium salts is observed in some species of this family. A tris-3-alkylpyridine derivative called niphatoxin C was found in *Callyspongia* sp. from the Western Pacific (Northwestern Australia), while Buchanan et al. showed the presence of 3-alkyl-pyridinium polymeric salts from *Callyspongia (Toxochalina) ridleyi* also collected in the Western Pacific (Papua New Guinea; ◐ **Fig. 4**) [31]. These compounds with MW between 5 and 6 kDa cause an irreversible membrane potential depolarization.

In some particular cases, 3-alkylpyridiniums are functionalized through reduction of the aromatic ring leading to highly reactive iminium/enamines intermediates that most commonly lead to the coupling of two units through a C-4/C-5′ bond. This function

to connect the two chemical moieties is highly specific and the capability is present only in Haplosclerida and within this group in only a small number of species. The presence of this enzymatic capacity is likely to have phylogenetic significance and thus represents a link between chemistry and taxonomy. Within the family Callyspongiidae, Torres et al. [32] described the arenosclerins A, B, and C but also haliclonacyclamine E, macrocylic bis-3-alkyl-piperidine derivatives from the Southwestern Pacific sponge *Arenosclera brasiliensis* (◐ **Fig. 5**) [32]. Inversion of configurations at several asymmetric centers is intriguing and suggests a non-specificity of the enzymes involved. Later, the same authors reported some antibacterial activities of arenosclerins but also some cytotoxic activities against tumoral cell lines [33]. *Arenosclera* as a member of the family Callyspongidae is a genus well
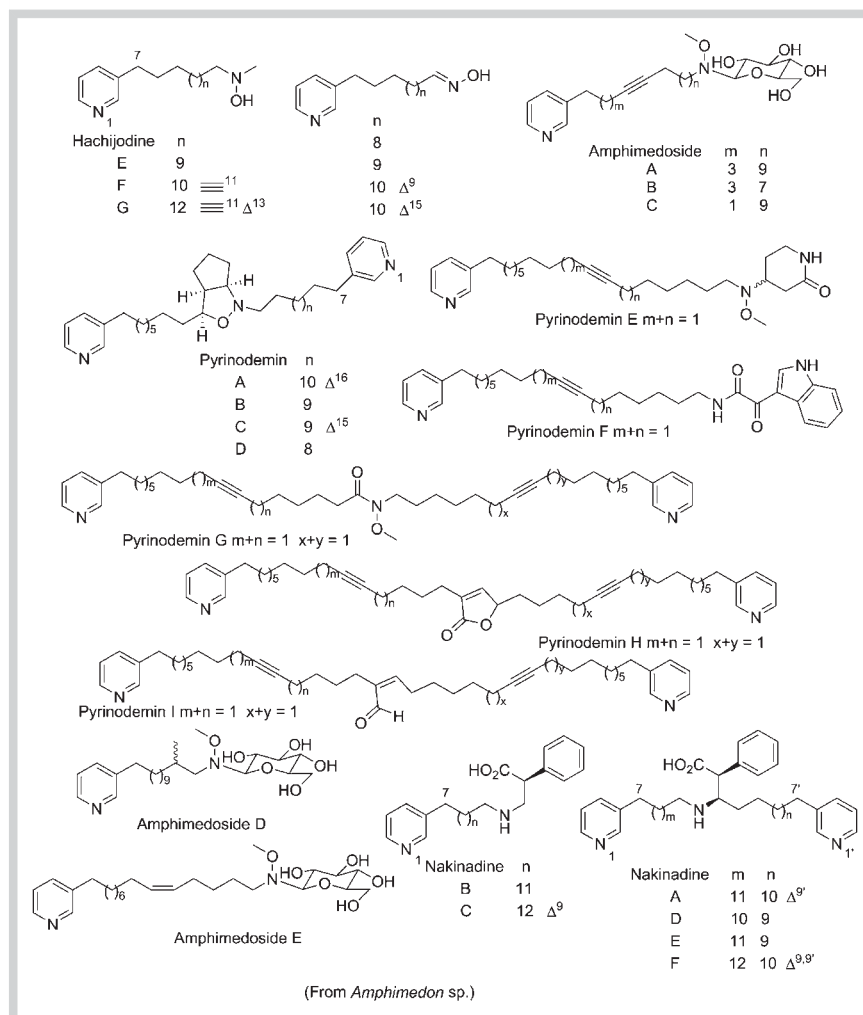
Fig. 1   3-Alkylpyridine derivatives isolated from the species *Amphimedon* sp. (Niphatidae)
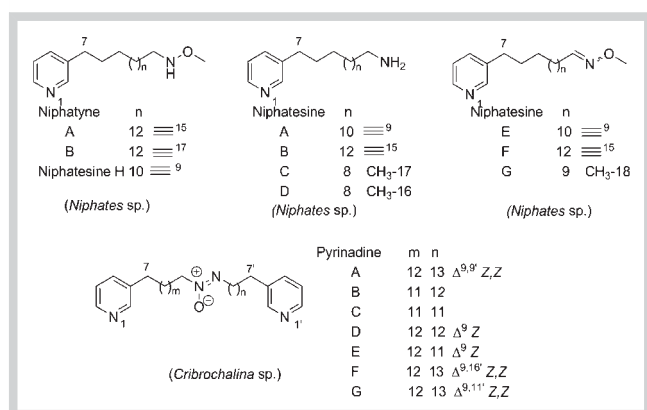

Fig. 2   3-Alkylpyridine derivatives isolated from the species *Cribrochalina* sp. and *Niphates* sp. (Niphatidae).

separated from *Haliclona* (Chalinidae) where bis-3-alkylpiperidines are more commonly found. However, recent molecular studies suggest that members of the Callyspongidae family are closely related to the type species of *Haliclona* including the only *Arenosclera* species so far sequenced (*Arenosclera heroni*) [8,22, 34].
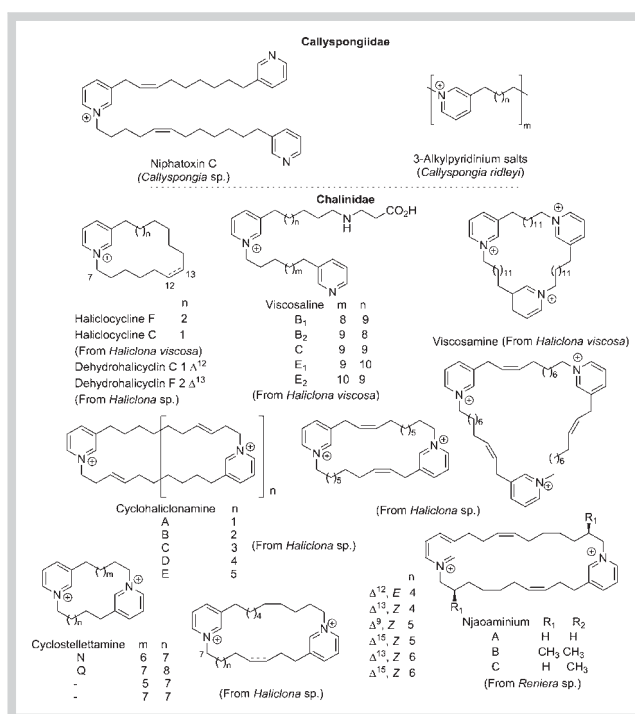

Fig. 3   3-Alkylpyridinium salts isolated from Niphatidae sponges.

Family Chalinidae

Within this family, the genus *Haliclona* is the most represented and diverse, and it has led to an outstanding diversity of natural products, most of them being alkaloids. It is worth underlining, however, that the classification of *Haliclona* urgently needs revisiting. Molecular data indicates that many very distantly related species have been placed in this genus and will eventually be placed in other families of the Haplosclerida [8]. An impressive diversity of 3-alkylpyridinium natural products has been isolated from the Arctic (Svalbard, Norway) sponge *Haliclona (Rhizoniera) viscosa*, including monomers like haliclocycline C and F [35, 36], dimers like the viscosalines [37], and trimers like viscosamine [38] (○ **Fig. 3**). It will be very interesting to determine if related compounds exist in the closely related species *H. indistincta* (currently being investigated by the authors).

Many additional compounds have been isolated from unidentified *Haliclona* species (listed all together as *Haliclona* sp. in ○ **Table 1**). The compounds so far isolated include cyclohaliclonamines A–E, which are cyclic and polymeric 3-alkylpyridinium salts isolated from a Okinawan species [39]; dimeric and trimeric unsaturated cyclized 3-alkylpyridiniums from a Guatemalan species [40]; a large diversity of bis-3-alkylpyridiniums of the cyclostellettamine type from a Korean species [41]; cyclic monomers called dehydrohalicyclins C and F from a Southeastern Pacific (New Zealand) *Haliclona* sp. [42] (○ **Fig. 4**), and finally methyl-substituted cyclostellettamines called njaoaminiums A–C isolated from *Reniera* sp. (*Reniera* has been reclassified as a subgenus of *Haliclona*) collected in the Western Indian ocean [43] (○ **Fig. 4**). All of these results strongly illustrate the high propensity of the Haplosclerida (and perhaps a subgroup within it) to produce 3-alkylpyridinium derivatives and therefore to connect at least two 3-alkylpyridines through the nucleophilic nitrogen atom of at least one pyridine.

While the biosynthesis of the huge polyamine family of sponge alkaloids remains unknown due to the lack of experimental data, we can hypothesize a key role of the polyamine pathway in the construction of bis-3-alkylpyridinium intermediates [44]. Indeed some other alkaloids produced by Chalinidae sponges exhibit a key N-C$_3$-N moiety, e.g., papuamine and haliclonadiamine, epimers isolated from possibly two specimens of the same *Haliclona* sp. from the Western Pacific (Papua New Guinea and Palau; ○ **Fig. 6**) [45, 46]. Halitulins are macrocyclic tertiary amines linked to aromatic components. These cytotoxic compounds were identified by Kashman et al. [47] from *Haliclona tulearensis* in the Southwestern Indian Ocean (Madagascar). Later, isomer and macrocyclic amines named haliclorensins were isolated from the same species, suggesting their implication in the biosynthesis of these bioactive alkaloids (○ **Fig. 6**) [47–50].

The family Chalinidae has led to the largest diversity of bis-3-alkylpiperidine derivatives. Rather simple macrocyclic bis-3-alkylpiperidines named haliclamines A and B, a reduced form of the previous 3-alkylpyridinium cyclostellettamines, were isolated from *Haliclona* sp. growing in the Northwestern Pacific (Japan; ○ **Fig. 5**) [51]. Additional haliclamines C–H were isolated from the Arctic sponge *H. viscosa*, thus linking bis-3-alkylpyridiniums with their reduced forms [52–54]. These simple cyclic dimers have led to more complex products after connection of both piperidine cycles through the C-4/C-5′ carbons. Halicyclamine A is a C-4/C-5′ connected bis-3-alkylpiperidine, isolated from *Haliclona* sp. collected in the Western Pacific (Indonesia; ○ **Fig. 5**) [55]. This compound has mainly displayed antimycobacterial activities [56, 57]. Close analogues named haliclonacycl-
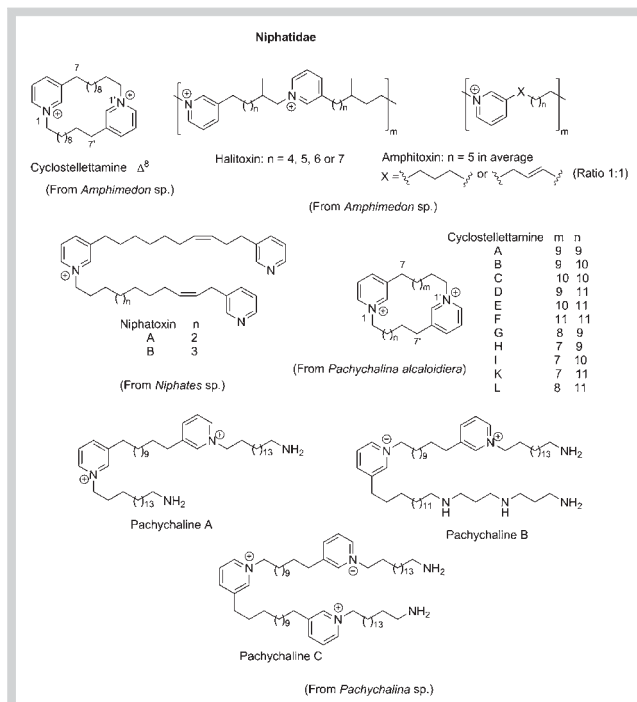

Fig. 4 3-Alkylpyridinium salts isolated from Callyspongiidae and Chalinidae sponges.
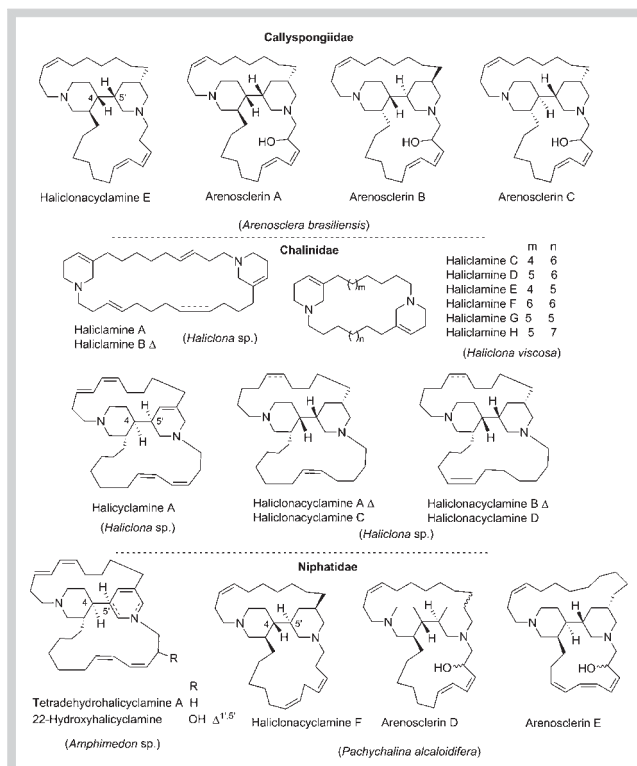

Fig. 5 Simple 3-alkylpiperidines isolated from Callyspongiidae, Chalinidae, and Niphatidae sponges.

amines A–D were isolated from another *Haliclona* sp. in the Western Pacific (Australia; ○ **Fig. 5**) [58,59]. These compounds were found to be cytotoxic, but also displayed antibacterial and antifungal properties [54].

There are some taxonomic connections between the families Chalinidae and Niphatidae that are currently under investigation, but are relevant to the organization of this review. Very few C-4/C-5′ connected bis-3-alkylpiperidine derivatives have been isolated from the Niphatidae family, but include oxidized analogues of halicyclamines identified in *Amphimedon* sp. from the Northwestern Pacific (Japan; ○ **Fig. 5**) [60] and some bis-3-alkylpiperidine alkaloids identified from *Pachychalina alcaloidifera*, namely haliclonacyclamine F and arenosclerins D and E (○ **Fig. 5**) [61]. However, *H. viscosa* mentioned above is more related via molecular data to species of *Niphates* than it is to the type species of *Haliclona* (Stephens, unpublished PhD thesis, National University of Ireland, Galway). Some of the Australian *Haliclona* also cluster with *Niphates* species rather than the type *Haliclona* species, meaning that this group of compounds may end up being more characteristic of Niphatidae than the Chalinidae in time, and make better sense of the distribution of these specific derivatives.

Family Petrosiidae

A large diversity of alkaloids has been described from sponges of the genus *Acanthostrongylophora*, but only a small number of simple bis-3-alkylpiperidines. Garson's group isolated a derivative named acanthocyclamine A from *Acanthostrongylophora ingens* collected from the Western Pacific (Indonesia; ○ **Fig. 7**) [62]. Nakagawa et al. [63] first isolated Xestospongins A–D from the Northwestern Pacific (Japan) sponge *Xestospongia exigua* that was subsequently renamed *Neopetrosia exigua* (○ **Fig. 7**). Araguspongines A–H are stereoisomers of these compounds isolated from *Xestospongia* sp. collected in the same area [64]. An additional xestospongin analogue was further isolated from *Xestospongia* sp. collected in the Southwestern Pacific (New Caledonia) [65]. Some macrocyclic bis-3-alkylpiperidine named araguspongines C and D, but also xestospongin D, were also isolated from *N. exigua* collected in the Northeastern Indian Ocean (India; ○ **Fig. 7**), while Araguspongin M was isolated from this species collected in Palau and a dimethyl analogue of xestospongin C was also isolated from this species from the Northwestern Pacific [66–68]. Wei et al. [69] isolated the C-4/C-5′ connected neopetrosiamine A from a related species from the Caribbean, i.e., *Neopetrosia proxima* (○ **Fig. 7**). This compound was shown to exhibit cytotoxic bioactivities, and the relatedness of the two *Neopetrosia* species is evident also from molecular data [22]. Later, xestoproxamines were described from the same Caribbean sponge (*N. proxima*) [70]. Petrosins A and B isolated from *Petrosia seriata* collected in the Western Pacific (Indonesia) are unique reports of 3-alkylpiperidine derivatives from this genus (○ **Fig. 7**) [71,72]. This sponge has been renamed as *Neopetrosia seriata* and two separate pieces of DNA evidence (a short piece of the 28 S ribosomal RNA gene and a region of the mitochondrial cytochrome oxidase 1 gene) place this species with another but unnamed *Petrosia* species [8]. The relationships of both species to other *Petrosia* or *Neopetrosia* or indeed any other Haplosclerida currently remain unresolved.
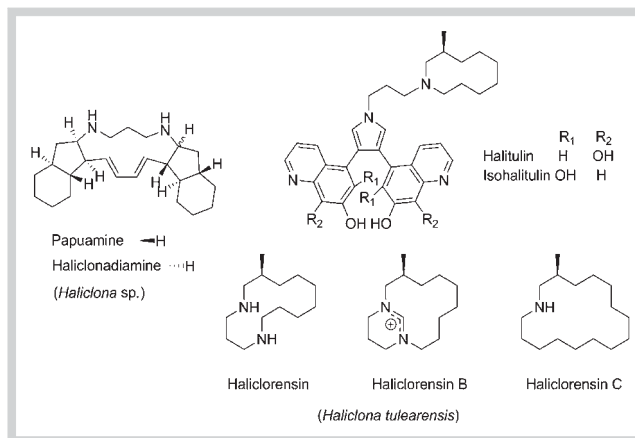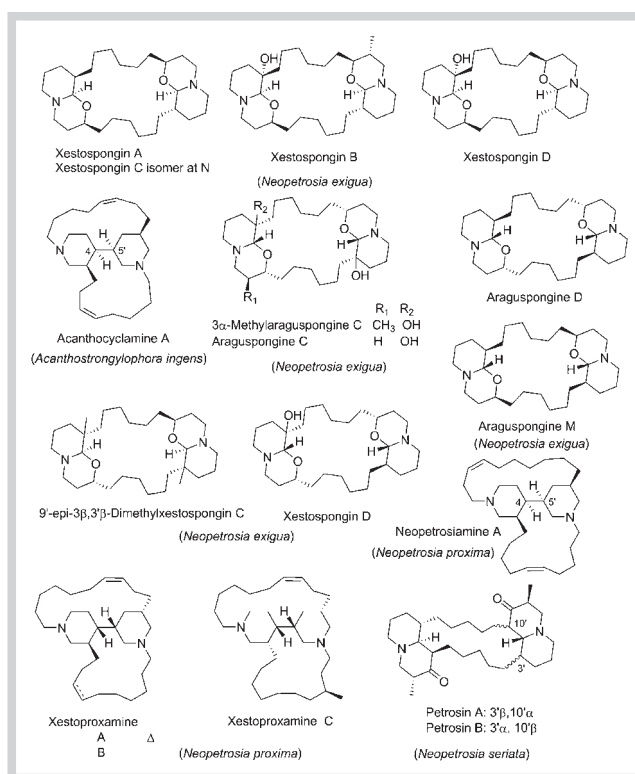

Fig. 6   Polyamines from Chalinidae sponges.

Fig. 7   Simple 3-alkylpiperidines isolated from Petrosiidae sponges.

Distribution of Complex 3-Alkylpiperidine Derivatives in the Haplosclerida

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The complexity of 3-alkylpiperidine derivatives culminates with the biosynthesis of outstanding complex molecules, most of them including the C-4/C-5′ but also additional C-C connections and then becoming real cage compounds. Many such compounds are present in members of Chalinidae and Niphatidae families, which, as mentioned above, require reassessment, e.g., some *Haliclona* should be renamed and are more closely related to members of the Niphatidae family. Hence, they are treated here in a separate section. Saraines 1–3 and A–C were isolated from the Northern Mediterranean sponge *Haliclona (Rhizoniera) sarai*

(○ **Fig. 5**) [73, 74]. Both piperidine cycles are also connected through the C-4/C-5′ bond, but in the case of saraines A–C, other connections were established between both cycles. A large array of biological activities have been described for these compounds [75]. Finally a bis-3-alkylpiperidine derivative called haliclonin A was isolated from *Haliclona* sp. in the Northwestern Pacific (Korea) [76]. Just like saraines A–C, this compound exhibits a C-2/C-3′ bond and one of the piperidines has been opened, maybe after oxidation/hydrolysis processes.

An unusual connection with a quinoline aromatic ring on one alkyl chain is characteristic of the njaoamines A–H isolated from the same *Reniera* sp. as the njaoaminiums in the Western Indian Ocean (○ **Fig. 8**) [77, 78]. In these compounds, both piperidine cycles are connected through C-4/C-5′ as before but also through a second C-3/C-2′ connection. Densanins were isolated from *Haliclona densaspicula* in the shallow waters of the Northwestern Pacific (Japan) [79]. They are highly complex pyrrole alkaloids, but their biosynthesis may originate from a common bis-3-alkyl-piperidine group through contraction of a piperidine. We still observe the usual C-4/C-5′ connection between both cycles. Complex bis-3-alkylpiperidine alkaloids ingenamine G and madangamine F have been isolated from the Southwestern Atlantic sponge *Pachychalina alcaloidifera,* a species currently placed in the family Niphatidae via morphology (○ **Fig. 8**) [28, 61, 80]. Preliminary molecular data suggest that *H. sarai* is actually more closely related to species of *Niphates* than to the *Haliclona* species (*H. oculata*). Much more work relating to morphology, DNA, and chemical evidence is again needed to understand the origin and development of such compounds. Despite the complexity of the chemistry in *P. alcaloidifera*, the authors were not able to isolate more advanced derivatives belonging to the manzamine alkaloids from this sponge.

In some cases, the opening of one piperidine ring can lead to condensation of aromatic rings through Pictet-Spengler condensation. This is the case for the well-known manzamines A and B that maintain the C-4/C-5′ connection and which were first isolated from *Haliclona* sp. in the Northwestern Pacific (Japan; ○ **Fig. 9**) [81, 82]. Manzamine C, isolated in the same study, lacks the 3-alkylpiperidine parts but keeps the *β*-carboline. These compounds are among the most promising natural antiparasitic and antitumoral compounds to date [83]. A close analogue called manzamine Y was isolated later from a similar sponge (○ **Fig. 9**) [84]. At the same time, similar compounds named keramamimes A and B were isolated from *Pellina* sp. [85]. However, its taxonomic status has not been clearly confirmed and it may be the same *Haliclona* species mentioned above. The structure of keramamime B has subsequently been revised and corresponds to manzamine F, a structure much more consistent with biosynthetic hypotheses (○ **Fig. 9**) [86].

A large diversity of manzamine alkaloids has also been isolated from the family Niphatidae and especially from one *Amphimedon* species. First, 6-hydroxymanzamine and 3,4-dihydromanzamine were isolated from *Amphimedon* sp. in the Northwestern Pacific (Japan) (○ **Fig. 9**) [87]. Keramaphidin B is a plausible biogenetic precursor of the bis-3-alkylpiperidine parts of manzamine [88], while keramaphidin C and keramamine C [89] are precursors of manzamine C (○ **Fig. 9**), and ircinols are antipode of the putative biosynthetic precursor of the manzamines [90]. Tetrahydro-*β*-carbolines manzamines H and L were isolated from the same species of *Amphimedon* (○ **Fig. 9**) [91] and additional manzamines were isolated later: 3,4-dihydromanzamine J, 3,4-dihydro-6-hydroxymanzamine A and manzamine M [92]. Finally, manz-
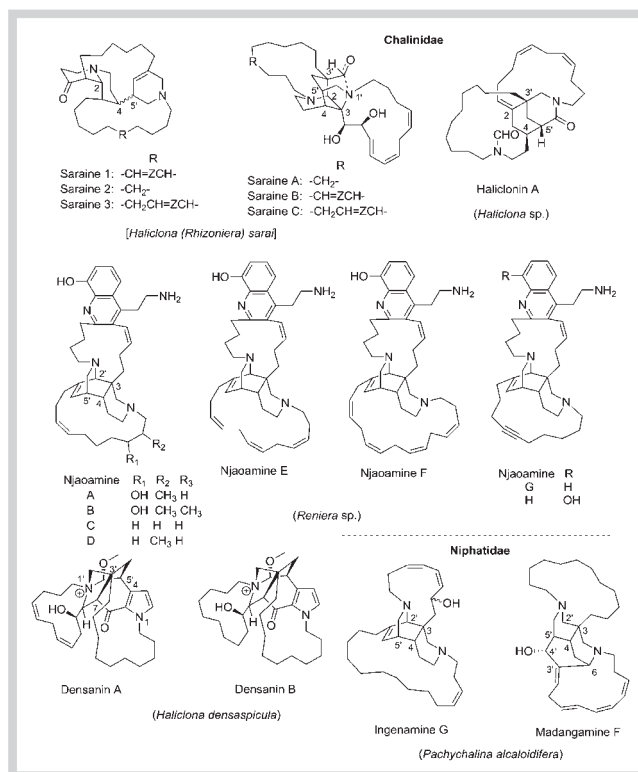

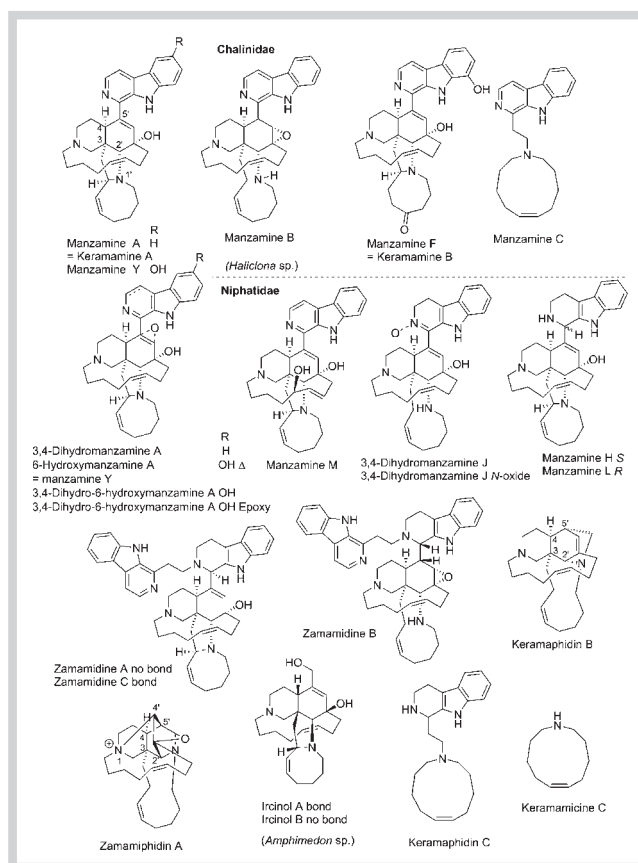**Fig. 8** Complex bis-3-alkylpiperidines from Chalinidae sponges.

Fig. 9 Manzamine alkaloids isolated from Chalinidae and Niphatidae sponges.

amine derivatives condensed with a second β-carboline unit gave a name to the zamamidines, but also 3,4-dihydromanzamine J *N*-oxide and 3,4-dhydro-6-hydroxymanzamine A [93]. Finally a derivative of keramaphidin B named zamamiphidin A was isolated from the same *Amphimedon* sp. (○ **Fig. 9**) [94].

Isolated from *Acanthostrongylophora* sp., a sponge currently placed in the family Petrosiidae and collected in the Northwestern Pacific, are quite a number of manzamines, i.e., ircinol A, ircinal A, 12,28-oxaircinal A, manzamine A, manzamine A *N*-oxide, 3,4-dihydromanzamine A *N*-oxide, and 8-hydroxymanzamine A as well as manzamine B, 8-hydroxymanzamine B, manzamine E, 12,34-oxamanzamine E and both 6-hydroxy derivatives, 12,28-oxamanzamine E, manzamine F, manzamine J, 8-hydroxymanzamine J, manzamine X, 6-deoxymanzamine X, and acantholactone (○ **Fig. 10**) [95–97]. It is important to notice here that the extraordinary complex dimer named *neo*-kauluamine was isolated from this sponge but had also been isolated previously from a species belonging to a new genus (and as yet undescribed) within the Petrosiidae family [98]. The huge pharmacological potential of these compounds showing antimicrobial and antialzheimer activities has been demonstrated [91]. Other researchers demonstrated the presence of manzamine A and its 8-hydroxy derivative as well as a highly original series of acanthomanzamines A–E and additional manzamine derivatives like acantholactam and pre-*neo*-kauluamine (○ **Fig. 11**) from *A. ingens* collected in the same area [99–101]. Two precursors of manzamine alkaloids were isolated from *Xestospongia* sp. collected in the Western Pacific (Papua New Guinea) and the structure of xestocyclamine A was later revised (○ **Fig. 11**) [102,103]. Finally, a large chemical diversity of complex bis-3-alkylpiperidines was isolated from *Xestospongia ingens* (Petrosiidae) collected in the Western Pacific (Papua New Guinea). It is worth noting here that the name of this sponge is no longer accepted and instead refers to *A. ingens* already mentioned previously. Ingenamine A was first isolated [104] and then ingamines A and B [105], madangamine A [106], and other analogues (○ **Fig. 11**) [107]. The unique alkaloid 8-hydroxymanzamine A was isolated from *Pachypellina* sp. (Phloedictyidae) but this species was later assigned to the same unnamed genus from the Petrosiidae family mentioned above [98, 108].

Distribution of Polyacetylenic Derivatives across the Haplosclerida

It has been impossible to find a chemical and logical classification of the polyacetylenic compounds produced by members of the Haplosclerida and the chemical structures do not give valuable information for identification of key enzymes leading to their synthesis. A pattern, however, does emerge linking *either* alkaloid *or* polyacetylene pathways in each species but never both (○ **Table 1**). Therefore, we report on a selection of compounds from this group in view of the taxonomic classification of the species in question as we did for the alkaloids.

A large diversity of polyacetylenes, mostly from the aikupikanyne group, was isolated from *Callyspongia* species, including *Callyspongia truncata, Callyspongia pseudoreticulata*, and *Callyspongia fistularis* (Callyspongiidae) [109–115]. Previously classified as *Siphonochalina* (also Callyspongiidae), *C. truncata* and *Callyspongia siphonella* uniquely produce polyacetylenic derivatives [116–118]. The change of genus indicates the difficulty with identifying haplosclerid sponges via morphological methods alone.
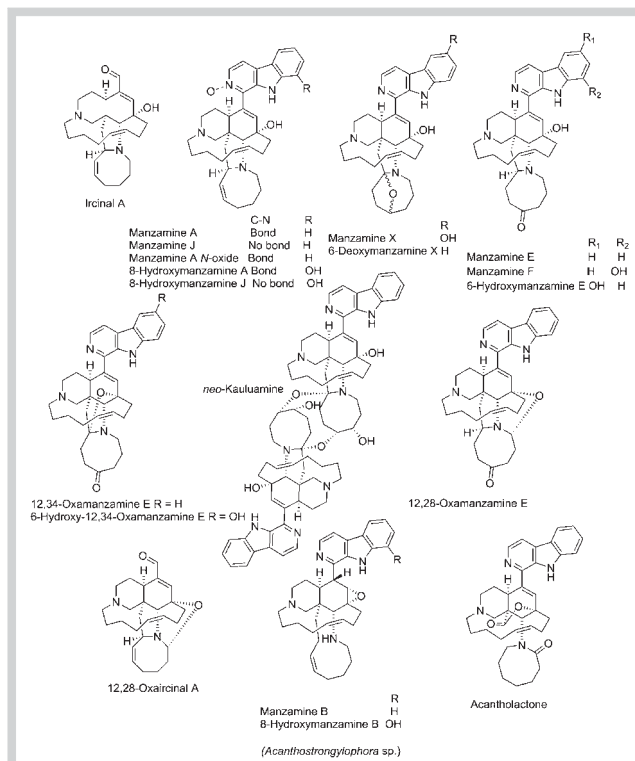

Fig. 10   Manzamine alkaloids from the sponge *Acanthostrongylophora* sp. (Petrosiidae).
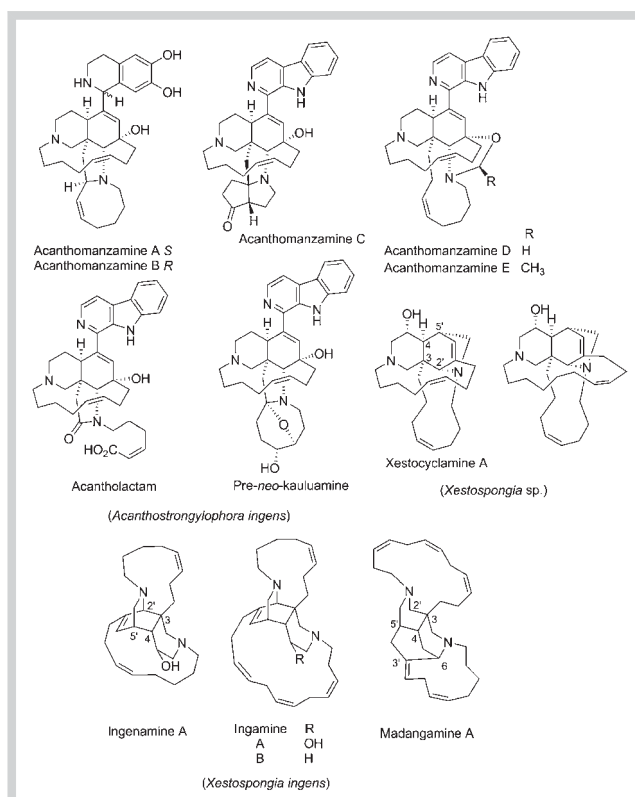

Fig. 11   Manzamine alkaloids from sponges *A. ingens* and *Xestospongia* (Petrosiidae).

From Chalinidae sponges, several renierins followed by fulvinol and the polyhydroxylated fulvynes were isolated from the Mediterranean sponge *Haliclona (Halichoclona) fulva* [119–121]. Some polyacetylenes were also isolated from *Haliclona* sp. collected in the Western Pacific (Palau) while polyhydroxylated osirisynes were isolated from *H. (Reniera) osiris* collected in the Northwestern Pacific (China) [122,123]. Other compounds from unidentified *Haliclona* species include Haliclonyne [124], lembehynes (Northwestern Pacific, Japan) [125,126], Halycinones A and B [127] (Western Pacific, Micronesia), and brominated derivative [128]. *Adocia* sp. provided adocyacetylenes A–D, and while this genus is now accepted as *Haliclona (Haliclona)* [129], it is likely that the genus *Adocia* will be re-errected in the near future (McCormack, unpublished data). How many different species are included in the above list and what their actual final classification will be is therefore as yet unknown and needs attention.

Among the family Niphatidae, the genus *Cribrochalina* has provided a large diversity of polyacetylenic compounds. Duryne was first isolated from *C. dura* collected in the Northwestern Atlantic (Bahamas) [130], while the Caribbean sponge *C. vasculum* afforded several simple acetylenic alcohols, including vasculyne [131–134]. Nepheliosyne B was isolated from *Niphates* sp. collected in the Western Pacific (New Caledonia) [135], and chlorinated acetylenic compounds were isolated from *Haliclona lunisimisis*, later renamed *Niphates lunisimisis* de Jesus & Faulkner [136].

The family Petrosiidae has yielded a large diversity of polyacetylenic products, mostly from sponges of the genus *Petrosia,* a genus that, unfortunately, also needs taxonomic revision. The Mediterranean sponge *Petrosia ficiformis* has afforded a large panel of polyacetylenic derivatives, including petroformynes 1–10 [137–144], while petrosolic acid was later isolated from *Petrosia* sp. from the red sea [145]. Aztequynols A and B were isolated from a Caribbean *Petrosia* sp. [146]. Northwestern Pacific species from this genus have generated many compounds, including Petrosynol and petrosynone isolated from *Petrosia* sp., [147], brominated derivatives from *P. (Petrosia) volcano* [148], corticatic acids A–E from *P. (Strongylophora) corticata* [149,150], petrocortynes A–H and petrosiacetylenes A–D and other analogues from *Petrosia* sp. collected in Korea [151–157], strongylodiols from *P. (Strongylophora)* sp. [158,159], polyacetylene carboxylic acids [160], neopetroformynes A–D and later miyakosynes A–F [161, 162], petroacetylene from *P. (Petrosia) solida* [163], and finally, petrosiols A–E from *P. (Strongylophora) strongylata* [164].

Research focused on another petrosid genus led to the isolation of some polyacetylenic compounds from the Caribbean sponge *Xestospongia muta* [165], while several brominated derivatives were isolated from *Xestospongia testudinaria* from the Southwestern Pacific (Australia) [166–168]. Other compounds isolated from *Xestospongia* sp. include unsaturated fatty acids [169], melynes A–C [170], a polyhydroxylated derivative named nepheliosyne A analogous to fulvynes and osisirynes [171], and brominated unsaturated fatty acids [172].

With regard to the family Phloedictyidae, their unique isolated compounds were polyacetylenic derivatives, triangulynes A–H and pellynols A–D from the Western Pacific sponge (New Caledonia) *Oceanapia triangulate* [173,174], and another polyacetylene from *Oceanapia* sp. [175]

Integrating Chemistry and Biology
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A large diversity of novel compounds of interest have been isolated from haplosclerid sponges and this group is likely to be a focus of continued efforts in this area for the foreseeable future given the diversity of species and habitats available providing a huge diversity of chemicals in turn. This review provides tantalizing insights into possible patterns of shared structures and biosynthetic pathways between species. However, real insights are hampered by the fact that most species included have not been identified to species and have not been included in any modern phylogenetic study. It is important to convey to chemists about the ever-changing world of taxonomic classification given the new methods being employed, including phylogenetic analysis of DNA sequence data. This is never truer than for haplosclerid sponges. There is an urgent need to revisit the studied sponges to place them in the new phylogenetic classification (including patterns of ancestry and descent between species) being built for demosponges. Only an approach of fully identifying sponges at the species level for analysis of chemistry will provide real additional value to the usual tools of systematics, thus contributing significantly to integrative taxonomy. Marine natural chemists should work tightly with taxonomic specialists (including specifically a phylogenetic approach) of each group in order to publish relevant data. For example, some species groups, i.e., of unidentified *Haliclona* and *Xestospongia* species, produce alkaloids but also polyacetylenic compounds, which prevents us from reaching any clear conclusion regarding patterns of distribution of specific compounds across taxonomic groups. However, once understood, the presence of each family of compounds could help significantly in a proper classification and avoid misinterpretation of species identification/classification.

From ○ **Table 1**, several clues are provided for assisting sponge classification. First of all, the presence of both polyacetylenic and alkaloid compounds have never been reported in a single species. Both biosynthetic genes/pathways cannot, therefore, be present in a species. This observation leads us to suggest a clear separation between species producing alkaloids and species producing polyacetylenes. For example, *C. ridleyi* is the only known species of the genus *Callyspongia* that does not produce polyacetylenic compounds. In the same way, only one species of *Cribrochalina* sp. was found to produce alkaloids. This could lead to a clear revision of the taxonomy of these sponges. Finally, *Neopetrosia* species were found to produce alkaloids, while *Petrosia* species produce only polyacetylenic compounds. However, these two genera are currently placed in the same family, Petrosiidae, indicating that revision is required at different levels of the taxonomic hierarchy.

One undefined species of *Cribrochalina* (Niphatidae) produces only 3-alkylpyridine derivatives. Simple alkylation at the nitrogen atom of the pyridine leads to 3-alkylpyridiniums that can polymerize. Only the species of *Callyspongia* (Callyspongiidae), *Niphates*, and *Pachychalina* (Niphatidae) seem to stop the biosynthesis at this step for this group of alkaloids. Because these genera are distinct, revisiting the voucher samples could help to identify similarities between these species. The subsequent ability of some species to reduce the aromatic rings enabling a C-4/C-5′ connection between two cycles is shared by several species, including *Arenosclera brasiliensis* (Callyspongiidae) and *H. viscosa* (Chalinidae). Contrary to other families, members of Callyspongiidae seem unable to develop more complex alkaloids. In the same way, *Neopetrosia* (Petrosiidae) species only produce simple

bis-3-alkylpiperidine derivatives. *Neopetrosia* could be hypothesized then to be closer to some *Callyspongia* sponges, and recent phylogenetic classification suggests that some *Neopetrosia* are placed within the same major clade as *Callyspongia* (Clade A) [8, 21]. Much more complex alkaloids are produced by few species distributed in several families, which also raises questions regarding the reliability of the classification. *H. densaspicula, H. sarai,* a *Reniera* sp. (Chalinidae), and *Pachychalina alcaloidifera* (Niphatidae) are able to produce complex alkaloids, but no manzamines have been isolated from these species. It appears that clearly this ability should gather some *Haliclona* species. As for the extremely complex alkaloid manzamines, members of the genera *Acanthostrongylophora* (Petrosiidae)*, Haliclona* (Chalinidae), and *Amphimedon* (Niphatidae) were found to produce them. These compounds are not characteristic of the Petrosiidae, as most species of this family produce only polyacetylenes.

A diversity of polyacetylenic compounds is found distributed across all of the five families of Haplosclerida included so far and their patterns of occurrence should trigger careful examination of the studied species. For example, four *Callyspongia* species (Callyspongiidae) produce compounds very similar to two *Haliclona* species (Chalinidae), two *Cribrochalina* species, and one *Niphates* species (Niphatidae), but most of the polyacetylenic compounds are really representative of *Petrosia* and *Xestospongia* genera (Petrosiidae). Recent molecular phylogenies suggest that *Callyspongia* and some *Haliclona* fall into one major clade (Clade A) at the base of which appears *Cribochalina* [8, 22]. *Niphates* species fall into a distantly related clade, also with some *Haliclona* (Clade C), while species from *Petrosia* and *Xestospongia* are distributed across multiple clades (but distinct from the aforementioned genera) and are poorly represented on phylogenetic trees drawn from molecular data as yet [8, 22].

The value of a chemosystematics approach for haplosclerid sponges has been questioned in the past due to disagreement between patterns of chemical diversity and morphological classification [176]. With molecular data throwing light on possible evolutionary pathways in sponges, it is evident that the morphological classification is flawed and is likely to change, and this is especially true for the Haplosclerida. An additional concern could be the varying influence of microbes residing in sponge tissue, which may be responsible for some of the compounds isolated. A diversity of microbial sequences has been reported from some *Haliclona* species and *Xestospongia*, amongst others [177–180], even though these studies do not show the presence of microbes in the sponge tissue nor do they confirm the source of compounds of interest as being from sponge or microbial cells. Sponges filter feed and concentrate microbes and microbial constituents from their environment, and these elements will be present in approaches that only isolate DNA sequences from sponge cells (even though they may only represent food for the sponge). Therefore, the presence of many bacterial DNA sequences in sponges does not equate directly to a sponge-bacterial association or to the production of detectable levels of compounds of interest by said bacteria. Ultrastructural studies on Irish and Mediteranean *Haliclona* species (Marra, unpublished data) show extremely low numbers of bacterial cells in four species, while an association between one or very few bacteria is evident in three species and many bacterial species are evident in one. Consideration of such patterns in these and other species will also be required to truly understand how patterns of microbial diversity impact patterns of chemical diversity.

Conclusion
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Our main conclusion is that chemical diversity does not fit with the current classification of this major group of marine sponges, but supports a clear revision of all the species of the Order Haplosclerida included in chemical publications taking into account the presence or absence of key enzymes leading to 3-alkylpyridine derivatives or polyacetylenes. Despite apparent discrepancies there are tantalizing insights that patterns of chemical diversity may well agree in good part with an updated classification that incorporates molecular and other data including morphology. Assessment of the possible bacterial origin of sponge-derived compounds should also be considered. Three other limitations to this approach are the existence of mistakes made in the identification of the species under investigation, a discrepancy between a classical taxonomic approach utilizing shared sponge morphological characters and the approach that uses molecular phylogenetic methods, and, thirdly, poor sampling of the huge diversity of sponges and the chemistry they contain. However, we believe that this review should help in the further development of an integrative approach between biology and chemistry for this group of sponges. The issues highlighted here are not restricted to the group of marine sponges included, but are relevant to all organisms that are of interest in the search for novel chemistry for whatever reason and where taxonomy is still unresolved. New advances in 'omics' sciences, and especially metabolomic approaches using mass spectrometry and nuclear magnetic resonance with some characteristic signals, could quickly give important clues for integrative systematics.

Conflict of Interest
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The authors declare no conflict of interest.

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