Abstract: Over the past seven decades, particularly since the discovery of the first marine-derived nucleosides, spongthymidine and spongouridine, from the Caribbean sponge Cryptotethya crypta in the early 1950s, marine natural products have emerged as unique, renewable and yet under-investigated pools for discovery of new drug leads with distinct structural features, and myriad interesting biological activities. Marine sponges are the most primitive and simplest multicellular animals, with approximately 8900 known described species, although more than 15,000 species are thought to exist worldwide today. These marine organisms potentially represent the richest pipeline for novel drug leads. Mycale (Arenochalina) and Clathria are recognized marine sponge genera belonging to the order Poecilosclerida, whereas Biemna was more recently reclassified, based on molecular genetics, as a new order Biemnida. Together, these sponge genera contribute to the production of physiologically active molecular entities with diverse structural features and a wide range of medicinal and therapeutic potentialities. In this review, we provide a comprehensive insight and up-to-date literature survey over the period of 1976–2018, focusing on the chemistry of the isolated compounds from members of these three genera, as well as their biological and pharmacological activities, whenever available.

Keywords: marine sponges; Poecilosclerida; Biemnida; Mycale (Arenochalina), Biemna; Clathria; crambescidins; batzelladines; guanidine alkaloids; pteridine alkaloids; terpenoids; thiopepetides; macrolides; polyketides; indole alkaloids; pyrrole-containing alkaloids; nucleotides; terpenoids; steroids; fatty acids
1. Introduction

Current medical risks, including diabetes, chronic pains, hepatitis, hypertension, microbial infection, together with the emergence of multidrug-resistant microbes and different types of carcinoma, have motivated and encouraged scientists to search for new bioactive compounds with novel modes of action [1]. Naturally occurring compounds derived from plants, marine invertebrates and microorganisms have provided important platforms and ideal validated starting materials for drug development and manufacturing [2]. Marine natural products represent a potent, promising and valuable source of supply for new chemical entities possessing unprecedented and novel mechanisms of action [2–7]. At present, marine-derived compounds or derivatives thereof have contributed to seven approved drugs for the market: cytarabine (Cytosar-U®, Depocyst®, approved by FDA in 1969 for cancer treatment), vidarabine (Vira-A®, approved by FDA in 1976 as antiviral), ziconotide (Prialt®, approved by FDA in 2004 as analgesic for treatment of severe chronic pain), trabectedin (Yondelis®, ET-743, approved in the EU in 2007 as an anticancer), eribulin mesylate (Halaven®, approved by FDA in 2010 and by Heath Canada in 2011 for metastatic breast cancer treatment), brentuximab vedotin (Adcetris®, approved by FDA in 2011 for Hodgkin’s lymphoma cells, and in 2017 for cutaneous T-cell lymphoma) and omega-3 acid ethyl esters (Lovaza®, approved by FDA in 2004 for lowering blood triglyceride levels in adults with severe hypertriglyceridemia) [8,9]. Moreover, twelve marine natural products are being under exploration in different phases of clinical trials [8], and a number of them are in the preclinical pipeline. Despite being the most basal of metazoan animal phyla, marine sponges (Porifera) greatly contribute as prolific suppliers of potentially valuable novel compounds to the clinical pipeline, with almost 47% of all reported bioactive compounds from the marine environment. Several relevant reports have shown that almost 62.5% (i.e., 10 out of 16) of clinically approved medicines, or those in ongoing advanced clinical phases, are derived from marine invertebrates, including marine sponges [10,11]. Marine sponges of the genera Mycale (Arenochalina) (family Mycalidae), Clathria (family Microcionidae), and Biemna (family Desmacellidae) include diverse sponge species belonging to the orders Poecilosclerida and Biemnida. They are rich producers of diverse and physiologically active secondary metabolites [12,13] with a wide range of biological activities, including cytotoxic, antimalarial [14,15], anti-HIV [16], anti-inflammatory [17,18], enzyme inhibitors [19], antifungal and antibacterial properties [20,21]. Some of these compounds are chemotaxonomic markers, particularly for some Poecilosclerida marine sponges of the genera Batzella, Crambe and Monanchora [22]. The World Porifera Database [23] lists 14 valid species of Mycale (Arenochalina), 55 of Biemna, and 381 of Clathria. To the best of our knowledge, chemical investigations have previously been carried out only on nineteen species of the genus Mycale (Arenochalina), i.e., Mycale (Arenochalina) mirabilis and Mycale (Arenochalina) sp., M. rotalis, M. aff. graveleyi, M. laxissima, M. izuensis, M. fibrexilis, M. ancorina, M. (carmia) cf. spongiosa, M. adhaerens, M. magellanica, M. hentscheli, M. micracanthoxea, M. tenuispiculata, M. cecilia, M. laevis, M. lissochela and M. plumos. For the genus Biemna, only four species, including Biemna laboutei, Biemna sp., B. ehrenbergii, and B. fortes, were chemically studied, while eleven species of the genus Clathria, i.e., Clathria hirsuta, C. gombawuiensis, C. cervicornis, C. compressa, C. ariosa, Clathia. sp., C. calla, C. reitwardtii, C. lissosclera, C. basilana, C. strepsitoxa and C. pyramida were chemically investigated (Table 1). Due to our interest in the marine sponges of the order Poecilosclerida [22,24–26], we have reviewed the literature reporting the isolation of secondary metabolites from these three marine sponge genera, covering the period of 1976–2018. This up-to-date review focuses mainly on the chemistry of the isolated metabolites, although their biological and pharmacological properties are also discussed when they are available.
Table 1. Summary of the secondary metabolites isolated from the marine sponges belonging to the genera *Mycale (Arenochalina)*, *Biemna* and *Clathria*, their source organisms and biological activities.

| Name | Compound Class | Marine Sponges | Collection | Bioactivities | Ref. |
|------|----------------|----------------|------------|--------------|------|
| Crambescidin 800 (1) | Pentacyclic guanidine | *Clathria (Thalysias) cervicornis* | - | Antimicrobial | 21 |
| Crambescidins 1–6 | Pentacyclic guanidine | *C. bulbotoxa* | Indonesia | Cytotoxic, antifungal | 28 |
| Norbatzelladine L (7) | Tricyclic guanidine | C. (Microciona) calla | Caribbean | Cytotoxic | 29 |
| Clathriadic acid (8) | Tricyclic guanidine | C. (Microciona) calla | Caribbean | Cytotoxic, antimalarial | 29 |
| Mirabilins A–F (9–14) | Tricyclic guanidine | *Mycale (Arenochalina) mirabilis* | Australia | Cytotoxicity, antimalarial | 30 |
| Netamines A–G (15–21) | Tricyclic guanidine | *Biemna laboutei* | Madagascar | Cytotoxic, antimalarial | 31 |
| Netamines H–N (22–28) | Tricyclic guanidine | *B. laboutei* | Madagascar | Cytotoxic, antimalarial | 32 |
| Netamines O–S (29–33) | Tricyclic guanidine | *B. laboutei* | Madagascar | Cytotoxic, antimalarial | 33 |
| Mirabilin G (34) | Tricyclic guanidine | *Clathria sp.* | Australia | Antibacterial, antifungal | 34 |
| Araiosamines A–D (38–41) | Indole cyclic guanidine | *C. (Thalysias) araiosa* | Vanuatu | Antibacterial, Anti-HIV-1 | 35 |
| 42–45 | Pyridoacridine | *Biemna sp.* | Okinawa | Cytotoxicity | 36 |
| 46 and 47 | Pyridoacridine | *Biemna sp.* | Indonesia | Enzyme inhibitor | 37 |
| 48 and 49 | Pyridoacridine | *Biemna sp.* | Japan | Cytotoxic | 38 |
| 50–53 | Pyridoacridine | *Biemna sp.* | Japan | Cytotoxic | 39 |
| Pseudoanchnazines A–C (54–56) | Pyridoacridine | *C. (Thalysias) basilana* | Indo-Pacific | Cytotoxic | 40 |
| Clathrymin A (57) | Quinolizine alkaloid | *Clathria sp.* | Argentina | Antibacterial | 41 |
| N-methylpyrrolidine (58) | Pyrrolidine Alkaloid | *C. frontifera* | India | Nr | 42 |
| 59–69 | Indole alkaloids | *M. fibrexis* | China | Cytotoxic | 43 |
| 70–83 | Pyrrole alkaloids | *M. micranthoxea* | Spain | Cytotoxic | 44 |
| 84–94 | Pyrrole alkaloids | *M. micranthoxea* | Venezuela | Cytotoxic | 45 |
| 95–97 | Pyrrole alkaloids | *M. tenusipudula* | India | Cytotoxic | 46 |
| 98–111 | Pyrrole alkaloids | *M. cecilia* | California | Cytotoxic | 47 |
| 112 and 113 | Pyrrole alkaloids | *M. issochelata* | China | Enzyme inhibitor | 48 |
| Clathrynamides A–C (114–116) | Bromine-containing amide | *Clathria sp.* | Sad-Misaki, Japan | Cytotoxic, inhibitors of starfish eggs | 49 |
| Microcionamides A&B (117&118) | Cyclic thiopeptide | *C. (Thalysias) abietina* | Philippines | Cytotoxic, antibacterial | 50 |
| Gombaramide A (119) | Cyclic thiopeptide | *C. (Thalysias) gombaruensis* | Korea | Cytotoxic, enzyme inhibitor | 51 |
| Azumamides (120–124) | Cyclic peptides | *Mycale izuensis* | Japan | Histone Deacetylase | 52 |
| Mycalisines (125–126) | Nucleotides | *Mycale sp.* | Japan | Inhibitors of starfish eggs | 53 |
| 127 and 128 | Nucleotides | *C. (Microciona) strepsitoxa* | Atlantic | Cytotoxic | 54 |
| 129 and 130 | Fatty acid | *M. laevis* | Caribbean | Cytotoxic | 55 |
| 131 | Fatty acid | *M. laxissima* | Caribbean | Cytotoxic | 56 |
| 132–134 | Fatty acid | *M. euplectellioides* | Red Sea | Cytotoxic | 57 |
| Micalamides A&B (135&136) | Polyketide | *Mycale sp.* | New Zealand | Cytotoxic, antiviral | 58 |
| Micalamide D (137) | Polyketide | *Mycale sp.* | New Zealand | Cytotoxic | 59–60 |
| Name                | Compound Class | Marine Sponges | Collection   | Bioactivities                        | Ref.  |
|---------------------|----------------|----------------|--------------|--------------------------------------|-------|
| 138–140             | Polyketide     | M. rotalis     | Mediterranean|                                      | 62–63 |
| 141–146             | Anthraquinone  | C. (Thalysias) hirsuta | Australia   |                                      | 64    |
| 147–149             | Macrolide      | Mycale sp.     | Japan        | Antifungal, cytotoxic                | 65    |
| 150                 | Macrolide      | M. adhaerens Lamb | Japan       | Cytotoxic                            | 66    |
| 152 and 153         | Macrolide      | Mycale sp.     | Japan        | Cytotoxic                            | 67    |
| 154–156             | Macrolide      | M. magellanica | Japan        | Cytotoxic                            | 68    |
| Peloruside A (157)  | Macrolide      | Mycale sp.     | New Zealand  |                                      | 69–70 |
| 158                 | Macrolide      | M. izuensis    | Japan        | Cytotoxic                            | 70    |
| 159                 | Macrolide      | M. hentscheli  | New Zealand  |                                      | 71    |
| 160                 | Macrolide      | Mycale sp.     | Japan        | Cytotoxic                            | 72    |
| 161 and 162         | Macrolide      | M. hentscheli  | New Zealand  |                                      | 73    |
| 165–169             | Sesquiterpene  | M. (Areonochalina) sp | Australia   | Antifungal, antitumor                 | 80–83 |
| Clathrin A–C (170–172) | Sesterterpene | Clathria sp | Australia |                                      | 84    |
| Clathric acid (173) | C21 terpenoid  | C. compressa   | Florida      | Antimicrobial                         | 20    |
| Clathrimide A&B (174&175) | C21 -terpenoid | C. compressa | Florida      | Antimicrobial                         | 20    |
| Gombaspiroketal A–C (176–178) | Sesterterpene | C. gombauvienisis | Korea      | Antibacterial, enzyme inhibitors      | 85    |
| 179 and 181          | Norterpene/triterpene | C. gombauvienisis | Korea      | Antibacterial                         | 86    |
| Rotalins (182–183)  | Diterpene      | M. rotalis     | Mediterranean|                                      | 87    |
| 185–189             | Cyclic norterpene peroxide | M. anchoring sp. | Australia |                                      | 89    |
| 190 and 191          | Cyclic norterpene peroxide | M. (carma) cf. spongiosa | Australia | Antimicrobial                         | 90    |
| 192 and 193          | Cyclic norterpene peroxide | Mycale sp. | Thailand    | Cytotoxic, antiviral                  | 91    |
| 194–201             | Cyclic peroxide/norditerpene | Mycale sp. | Australia   | Nr                                    | 92    |
| 202–204             | Cyclic norterpene peroxide | Mycale sp. | Australia   | Nr                                    | 93    |
| 205                 | Cyclic norterpene peroxide | Mycale sp. | Thailand    | Cytotoxic                             | 94    |
| 206 and 207          | Tetraterpene    | C. frondifera (=C. (Thalysias vulpina) sp) | Japan       |                                      | 95–96 |
| Contignasterol (208) | Steroid        | C. (Clathria) lissosclera | New Zealand | Histamine inhibitory                  | 17–18 |
| Clathriols A&B (209&210) | Steroid     | C. (Clathria) lissosclera | New Zealand | Anti-inflammatory, histamine inhibitory | 17–18 |
| Clathsterol (211)    | Sulphated sterol | Clathria sp. | Red Sea     | Anti-HIV-1                            | 16    |
| Biemansterol (212)   | Sterol         | Bienna sp.     | Okinawa, Japan | Cytotoxic                             | 97    |
| 213                 | Sterol         | Bienna sp.     | Okinawa, Japan | Cytotoxic                             | 98    |
| Foristerol (214)     | Sterol         | B. fortis      | China        | Nr                                    | 99    |
| 215                 | Sterol         | B. triraphis   | Madagascar   |                                      |       |
| Name   | Compound Class | Marine Sponges | Collection | Bioactivities                              | Ref.  |
|--------|----------------|----------------|------------|--------------------------------------------|-------|
| 216–224| Sterol         | B. fortis      | China      | Lymphocytes and hPTP1B inhibition          | 100   |
| 225 and 226 | Sterol      | B. ehrenbergi  | Red Sea    | Cytotoxic, antibacterial                   | 101   |
| 227–235| Sterol         | M. laxissima   | Caribbean  | Fertilized eggs inhibitors                 | 102–103|
| Mycapolyols A–F (184–189) | Mixed PKS/NPRS | M. izuensis   | Japan      | Cytotoxic                                  | 104   |
| 242    | Thio-sugar     | C. (Dendrocia) pyramida | Australia | Nr                                         | 105   |
| 243    | Glycol         | C. reinwardtti  | India      | Nr                                         | 106   |
| 244    | 1,5-Diamine    | Mycale sp.     | Kenya      | Cytotoxic                                  | 107   |
2. Chemistry and Biological Activities of the Secondary Metabolites Isolated from the Marine Sponges of the Genera Mycale (Arenochalina), Biemna and Clathria

In this section, we provide insights into the chemical classes and biological activities of the marine sponge-derived secondary metabolites obtained from these three genera. For convenience, the isolated compounds are divided into fourteen major groups, according to their skeleton as well as their biosynthetic origins. Additionally, their biological potentialities are also discussed whenever applicable.

2.1. Guanidine-Containing Alkaldoids

Crambescidins, batzelladines, mirabilins and ptilocaulins are definite groups of marine cyclic guanidine-containing alkaloids that display potent biological activities, such as cytotoxic, antiviral, antifungal and anti-HIV-1 gp 120-human. These compounds were isolated from various marine sponge genera, like Batzella, Crambe, Monanchora and Ptilocaulis, and are chemotaxonomic markers for the marine sponges belonging to the orders Poecilosclerida and Axinellida [22,27]. Crambescidin 800 (1), a pentacyclic guanidine alkaloid, was isolated from the marine sponge Clathria (Thalysias) cervicornis, and was found to display potent antimicrobial activity against Acinetobacter baumannii, Klebsiella pneumoniae and Pseudomonas aeruginosa, with MIC values of 2, 1 and 1 μg/mL, respectively [21]. Recently, three new crambescidin-type alkaloids, including crambescidin 345 (2), crambescidin 361 (3) and crambescidin 373 (4), along with the known congeners 1, crambescidin 359 (5) and crambescidin 657 (6) (Figure 1), were isolated from the Indonesian marine sponge C. bulbotoxa. Interestingly, 3 was reported as a new crambescidin congener which possesses two identical saturated spiroamid six-membered ring on both sides, which is considered to be rare within the crambescidin family. Additionally, 3 bears a propyl group as an alkyl substituent of the left-sided tetrahydropyran moiety. Compounds 2–5, possessing only the pentacyclic guanidinium core (vessel), exhibited moderate cytotoxicity against the A431 cancer cell line with IC$_{50}$ values of 7.0, 2.5, 0.94 and 3.1 μg/mL, respectively. However, 1 and 6, featuring both the vessel and the long-chain ω-hydroxy fatty acid (anchor) motifs, displayed significant cytotoxicity with IC$_{50}$ values of 48 and 12 nM, respectively. Such variation in cytotoxicity highlighted the importance of the spermidine part, which could act as a spacer linking two sites of interaction [24]. Furthermore, 2–4 demonstrated a strong anti-oomycete activity against the plant pathogenic fungus Phytophthora capsici with a minimum inhibitory dose (MID) of 50 μg/disk, while 1 and 6 showed a weak activity with MID 100 mg/disk or even higher [28]. Two batzelladine derivatives, norbatzelladine L (7) and clathadiacid A (8) (Figure 1), were isolated from the Caribbean marine sponge C. (Microciona) calla. Compound 7 exhibited potent cytotoxicity against a variety of cancer cell lines, including breast cancer (MDA-MB-231), non-small cell lung cancer (A549) and colon cancer (HT29), with GI$_{50}$ = 0.7, 1.1 and 1.2 03BCg/mL, respectively, whereas 8 showed a weak antitumor activity with GI$_{50}$ = 13.5, >30 and >30 μM, respectively. Moreover, 7 displayed stronger (IC$_{50}$ = 0.4 μg/mL) antimalarial activity than 8 (IC$_{50}$ = 2.3 μg/mL) [29].

![Chemical structures of 1–8.](image-url)
Six tricyclic guanidine alkaloids, mirabilins A–F (9–14), were isolated from a Southern Australian marine sponge *Mycale* (*Arenochalina*) *mirabilis* [30]. Later on, seven further cytotoxic tricyclic guanidine alkaloids, netamines A–G (15–21), were reported from a Madagascar marine sponge *Bienna laboutei*. These compounds showed an in vitro cytotoxic activity against three human cancer cell lines, i.e., NSCL (A549), colon (HT29), and breast (MDA-MB-231). While netamine C (17) showed GI$_{50}$ values of 4.3, 2.4 and 2.6 μg/mL, respectively, netamine D (18) exhibited slightly higher GI$_{50}$ values of 6.6, 5.3 and 6.3 μg/mL against these cancer cell lines [31]. An additional seven tricyclic alkaloids, netamines H–N (22–28), along with the known congeners netamine G (21) and mirabilins A (9), C (11) and F (14), were isolated from the same marine sponge. These compounds displayed cytotoxic and antimalarial activities. Netamine M (27) exhibited cytotoxicity against KB cancer cell line with the IC$_{50}$ in a micromolar range whereas netamine K (25) showed antiplasmodial activity against *Plasmodium falciparum* with the IC$_{50}$ value of 2.4 μg/mL [14]. Another five antimalarial tricyclic guanidine alkaloids, netamines O–S (29–33), were also isolated, together with the previously reported netamine E (19), from *B. laboutei*. Netamines O–Q (29–31) showed a promising in vitro antimalarial activity against *P. falciparum* with IC$_{50}$ values of 16.99 ± 4.12, 32.62 ± 3.44, and 8.37 ± 1.35 μg/mL, respectively. Moreover, these compounds also exhibited cytotoxic activity against the KB cancer cell line in the range of 10$^{-5}$ M [15]. A tricyclic guanidine alkaloid, mirabilin G (34), isolated from the Australian sponge *Clathria* sp., displayed a moderate antibacterial activity against Gram-negative bacterial strains, including *Escherichia coli* and *Serratia marcescens*, as well as antifungal activity against *Saccharomyces cerevisiae* [32]. Further chemical investigation of the marine sponge *Clathria* sp., collected from South Australia, resulted in the isolation of mirabilins C (11), F (14) and G (34), along with three new congeners, namely mirabilins H–J (35–37). Compounds 11, 14, 34–37 displayed no cytotoxicity against neuroblastoma (SH-SY5Y), gastric (AGS), colorectal (HT29) and intestinal (Intestine-407) cancer cell lines, with LD$_{50}$ > 30 μg/mL [33] (Figure 2).

Figure 2. Chemical structures of 9–37.
Another interesting group of marine cyclic guanidine alkaloids comprises those containing a bromoindole moiety. The tris-bromoindole cyclic guanidine alkaloids, ariasamine A–D (38–41) (Figure 3), were isolated from the marine sponge Clathria (Thalysias) ariasana, collected from Vanuatu. These compounds originated from an unusual mode of linear polymerization of tryptamine units involving a C–C bond formation. Compounds 38–41 were evaluated for their antimicrobial activity; however, none of them displayed significant antibacterial activity against S. aureus or anti-HIV activity [34].

![Chemical structures of 38–41.](image)

**Figure 3.** Chemical structures of 38–41.

### 2.2. Pyridoacridine, Pteridine, Tetrahydroquinolizine and N-methylpyrrolidone Alkaloids

Pyridoacridine alkaloids are a unique group of marine-derived metabolites and are one of the largest marine alkaloid families. Chemically, they feature a common tetracyclic hetero-aromatic parent-11H-pyrido[4,3,2-kl] acridine or 4H-pyrido[2,3,4-kl] acridone [35,36]. Among the three marine sponge genera, pyridoacridine alkaloids were exclusively isolated from *Bienna* species. Biennadin (42), 8, 9-dihydro-11-hydroxyascididemin (43), 8-hydroxyisocystodamine (44) and 9-hydroxyisocystodamine (45) (Figure 4), were reported from the Okinawan *Bienna* sp. Compounds 42 and 43 displayed a significant in vitro cytotoxicity against two tumor cell lines: human epidermoid carcinoma KB (with IC50 values of 1.73 and 0.209 μg/mL, respectively) and murine lymphoma L1210 (with IC50 values of 4.29 and 0.675 μg/mL, respectively) [37]. Moreover, labuanine A (46) was isolated, along with three previously described congeners, i.e., 42, 45 and isocystodamine (47) (Figure 4), from the Indonesian sponge *B. fortis*. All of these compounds induced multipolar neuritogenesis in more than 50% of Neuro 2A murine neuroblastoma cells at concentrations of 0.03–3 μM. Interestingly, 47 not only displayed the strongest neuritogenic activity but also activated an increase of the acetylcholinesterase level [38]. Matsunaga’s group [39] described the isolation of *N*-methylisocystodamine (48) and methoxymethylisocystodamine (49) (Figure 4), together with 47, from the marine sponge *Bienna* sp., collected at Oshima-Shinsone, Southern Japan. Both 48 and 49 were found to activate the erythroid differentiation of human leukemia K562 cells, with an ED50 value of 5 nM [39]. Later on, the same group [40] further isolated *N*-hydroxymethylisocystodamine (50) and neolabuanin A (51), together with the previously reported congeners eiconines A (52) and B (53), 42, 45 and 47 (Figure 4), from the same sponge. These compounds displayed cytotoxicity and activated differentiation of K562 leukemia cells into erythrocytes at a concentration of 5 μg/mL. Furthermore, 47 and 50 were the most active in inducing neuronal differentiation when compared to 42, 45 and 51. Interestingly, while 51 and 52 lowered this activity, 42, 47 and 53 showed no notable activity [40]. Another interesting group of marine-derived alkaloids are the pteridines, which represent a widely distributed family of naturally occurring alkaloids. Chemically, pteridine nucleus is composed of a pyrimidine ring fused with a pyrazine ring. Examples of this group are pseudoaanchnazines A–C (54–56) (Figure 4), which were isolated from the marine sponge *Clathria* sp., collected near the coast of Rio Negro, Argentina. Compound 54 showed a moderate inhibition against *E. coli* at 50 μg/disk [41]. Additionally, Sperry and Crews described isolation of a new tetrahydroquinolizinum ion, clathryimine A (57), which produced a decarboxylated derivative clathryimine B upon heating in CDCl3 (Figure 4),
from the Indo-Pacific marine sponge *C. basilana*, collected in Indonesia [42]. Radhika et al. [43] reported the isolation of *N*-methylpyrrolidone (58) (Figure 4) from *C. frondifera*, collected from the East coast of India.

![Figure 4. Chemical structures of 42–58.](image)

2.3. Monoindole Alkaloids

Wang et al. [44] reported the isolation of eleven brominated indole alkaloids, 59–69 (Figure 5), from the marine sponge *M. fibrexilis*. Since monoindole alkaloids were less common for this sponge family, the authors proposed that they could be specific for this species.

![Figure 5. Chemical structures of 59–69.](image)
2.4. Pyrrole-Containing Alkaloids

Fourteen pyrrole-containing metabolites, named mycalazols (70–81) and mycalazals (82–83) (Figures 6 and 7), were isolated from *M. micracanthoxea*, collected at the Southern coast of Spain. Compounds 70–83 displayed a potent in vitro cytotoxicity with ED\(_{50}\) values in the micromolar range, against five cancer cell lines: P388, SCHABEL mice lymphoma, A549 human lung carcinoma, HT29 human colon carcinoma and MEL28 human melanoma, and 75–76 and 81 were the most active analogues [45].

Figure 6. Chemical structures 70–76.

Figure 7. Chemical structures 77–83.
A further eleven pyrrole-containing metabolites, 84–94 (Figure 8), were isolated from the same sponge, collected in the Caribbean Sea in Venezuela. The structures of these compounds were elucidated by analysis of their NMR, HRMS and GC-MS data. Compound 84 was the most active against *Leishmania mexicana* promastigotes, with LD$_{50}$ value of 12 µg/mL [46]. Three 5-alkylpyrrole-2-carbaldehydes (95–97) (Figure 8) were reported from *M. tenuispiculata*, collected in Southern India [47], while an additional fourteen 5-alkylpyrrole-2-carbaldehyde analogues, with varying alkyl side chains, named mycalazals (98–108) and mycalenitriles (109–111) (Figure 8) were isolated from *M. Cecilia*, collected in California. These compounds displayed growth inhibition activity against nine cancer cell lines, with GI$_{50}$ values below 5 µg/mL, being 103 the most cytotoxic against the LNcaP cell line, with a GI$_{50}$ value of 0.2 µg/mL. Compounds 98, 99 and 102 displayed remarkable cytostatic activity on this tumor cell line, with TGI (Total Growth Inhibition) values of 3.3, 2.6 and 2.8 µg/mL, respectively. Compounds 109–111 exhibited potent cytotoxicity with high selectivity against PANCI human pancreas, LOVO human colon, and HELA human lymphoma cell lines [48]. It is interesting to point out that the cytotoxicity exhibited by mycalazals and mycalenitriles is affected by the structural features of the alkyl side chains, including their length, the number and position of the unsaturations [48]. Recently, Xue et al. [49] described isolation of mycalenitrile-15 (112) and mycalenitrile-16 (113) from the Chinese *M. lissochela*. Compound 112 displayed a remarkable PTP1B (Protein-tyrosine phosphatase 1B) inhibitory activity with an IC$_{50}$ value of 8.6 µM.

Figure 8. Chemical structures 84–113.
2.5. Bromine-Containing Amides

Three brominated acetylenic amides, clathrynamides A–C (114–116) (Figure 9), were isolated from the Japanese marine sponge Clathria sp., collected from the Sad-misaki coast. Compound 114 displayed potent inhibitory activity against the mitotic cell division of starfish eggs at a very low concentration, with an IC\(_{50}\) value of 6 ng/mL, and cytotoxicity against the human myeloid K-562 cell line with an IC\(_{50}\) value of 0.2 µg/mL. Compounds 115 and 116 were less active than 114 against the mitotic cell division of starfish eggs, with IC\(_{50}\) values of 0.2 and 1 µg/mL, respectively. Based on the IC\(_{50}\) values of 114–116, it is clear that the presence of a primary amide in the molecule plays an important role in the inhibitory activity of the mitotic cell division of starfish eggs [50].

![Figure 9. Chemical structures of 114–116.](image)

2.6. Cyclic Peptides/Thiopeptides

Two cyclic thiopeptides, microcionamides A (117) and B (118), were isolated from C. (Thalysias) abietina, collected from the Philippines. Compounds 117 and 118 displayed a significant cytotoxicity against the human breast tumor cell lines, MCF-7 and SKBR-3, with the IC\(_{50}\) values of 125/98 nM and 177/172 nM, respectively. Furthermore, 117 and 118 also displayed inhibitory activity against Mycobacterium tuberculosis (H\(_{37}\)Ra), with MIC value of 5.7 µg/mL [51]. Another cyclic thiopeptide, gombamide A (119) (Figure 10) was isolated from the Korean marine sponge C. gombawuiensis. 119 exhibited a weak cytotoxicity against K562 and A549 cell lines with the IC\(_{50}\) values of 6.9 and 7.1 µg/mL, respectively. Moreover, 119 also exhibited a moderate inhibitory activity against Na\(^+\)/K\(^+\)-ATPase with IC\(_{50}\) of 17.8 µg/mL [52]. Five cyclic tetrapeptides, azumamides A–E (120–124), were isolated from the marine sponge M. izuensis. These compounds displayed a potent HDAC (Histone Deacetylase) inhibitory activity with the IC\(_{50}\) values of 0.045 to 1.3 µM, using enzymes obtained from K562 human leukemia cells. Compounds 120–124 represented the first examples of cyclic peptides with HDAC inhibition activity recorded from marine invertebrates [33].

![Figure 10. Chemical structures of 117–124.](image)
2.7. Nucleotides

Two guanine-nucleotides, mycalisines A (125) and B (126) (Figure 11), from the Japanese sponge Mycale sp., were found to inhibit a cell division of the fertilized starfish (Asterina pectinifera) eggs with MIC<sub>50</sub> of 0.5 and 200 µg/mL, respectively [54]. Two 8-oxoisoguanine-nucleotides, 127 and 128 (Figure 11), were isolated from Clathria (Microciona) strepitosax, collected from the Northeastern Atlantic. These compounds did not exhibit any significant antimicrobial or cytotoxic activity [55].

![Figure 11. Chemical structures of 125–128.](image)

2.8. Fatty Acids

(Z)-16-pentacosenoic acid (129) and (Z)-18-pentacosenoic acid (130) were isolated from the hydrolyzed phospholipids of the Caribbean sponge M. laevis [56], while (5Z)-2-methoxy-5-hexadeconic acid (131) (Figure 12) was reported from M. laxissima [57]. Chemical investigation of the Red Sea M. euplectellioides led to the identification of hexacosa-(6Z,10Z)-dienoic acid methyl ester (132), hexacosa-(6Z,10Z)-dienoic acid (133) and icosa-(8Z,11Z)-dienoic acid methyl ester (134) (Figure 12). Compounds 132–134 displayed weak cytotoxicity against A549 human lung carcinoma, U373 glioblastoma and PC-3 prostate cancer cell lines [58].

![Figure 12. Chemical structures 129–134.](image)

2.9. Polyketides Derivatives

Mycalamides A (135) and B (136) (Figure 13) were isolated from Mycale sp., collected from Otago Harbour, New Zealand. Both compounds exhibited a potent in vitro anti-HSV-1 activity. Compound 136 was a more potent antiviral agent than 135, with the Minimum Active Doses (MAD) of 1–2 and 3.5–5.0 ng/disk, respectively. Furthermore, 136 exhibited stronger (IC<sub>50</sub> = 0.7 ± 0.3 ng/mL) cytotoxicity than 135 (IC<sub>50</sub> = 3.0 ± 1.3 ng/mL) against P-388 cancer line [59,60]. Additionally, mycalamide D (137) (Figure 13), along with 135 and 136, were also reported from Mycale sp., collected from New Zealand [61]. Compounds 135 and 137 displayed significant cytotoxicity against three cell lines: non-tumorigenic pig kidney (LLC-PK<sub>1</sub>), human lung carcinoma (H441) and human neuroblastoma (SH-SY5Y) cell lines. Furthermore, 135–137 exhibited remarkable cytotoxicity in a nanomolar range against lymphoma P-388 cells with IC<sub>50</sub> values of 5.2, 1.3 and 65.5 ± 5.5 nM, respectively. From a structure-activity point of view, the cytotoxic potency is inversely proportional to the number of the methoxy groups as well as the polarity of the compounds (Figure 13) [61]. Within the polyketide group, acetogenins were also isolated from the marine sponge of the genus Mycale.
Giordano et al. [62] reported the isolation of two polybrominated C\textsubscript{15} acetogenins (138–139) from \textit{M. rotalis}, and subsequently, Notaro et al. isolated the C\textsubscript{15} nonterpenoid brominated ether (140) from the same sponge [63].

![Chemical structures of 135–140.](image)

**Figure 13.** Chemical structures of 135–140.

### 2.10. Anthraquinones

Six rhodocomatulin-type anthraquinones, including the previously reported rhodocomatulin 5, 7-dimethyl ether (141) and rhodocomatulin 7-methyl ether (142), together with the new 6-methoxyrhodocomatulin 7-methyl ether (143), 3-bromo-6-methoxy-12-deethylrhodocomatulin 7-methyl ether (144), 3-bromo-6-methoxyrhodocomatulin 7-methyl ether (155) and 3-bromorhodocomatulin 7-methyl ether (146) (Figure 14), were isolated from the marine sponge \textit{C. hirsuta}, collected from the Great Barrier Reef, Australia. Compounds 141 and 142 were also isolated from the marine sponge \textit{Comatula rotalaria} [64].

![Chemical structures of 141–146.](image)

**Figure 14.** Chemical structures of 141–146.

### 2.11. Macrolides

Three trioxazole containing macrolides, mycalolides A–C (147–149) (Figure 15), isolated from the Japanese \textit{Mycale} sp., displayed antifungal activity against some pathogenic fungi. These compounds also showed a promising cytotoxicity against the B-16 cancer cell line, with IC\textsubscript{50} values ranging from 0.5 to 1.0 ng/mL [65]. 13-Deoxytedanolide (150) (Figure 15), along with 147–148, were also isolated from the Japanese sponge \textit{M. adhaerens}. Compound 150 exhibited significant cytotoxicity against P388 leukemia cells, with an IC\textsubscript{50} value of 94 pg/mL [66]. The chemical investigation of \textit{Mycale} sp., collected from New Zealand, afforded a potent cytotoxic thiazole-containing macrolide, pateamine (151) (Figure 15). Compound 151 displayed significant and selective cytotoxicity against P388 cells with an IC\textsubscript{50} value of 0.15 ng/mL [67]. Thiomycalolides A (152) and B (153) (Figure 15), another two trioxazole-containing macrolides, were reported from \textit{Mycale} sp., collected at Gokasho Bay, Japan. Both compounds were cytotoxic against human leukaemia P388 cells with an IC\textsubscript{50} of 18 ng/mL [68]. Further analogues, including 30-hydroxymycalolide A (154), 32-hydroxymycalolide A (155) and 38-hydroxymycalolide B (156) (Figure 15), were isolated, together with 147–149, from the
Japanese *M. magellanica*. Compounds 154–156 showed cytotoxicity against L1210 cells, with IC<sub>50</sub> values of 0.019, 0.013 and 0.015 µg/mL, respectively [69,70]. Peloruside A (157), another cytotoxic macrolide, was isolated from *Mycate* sp., collected from New Zealand. This compound exhibited a remarkable cytotoxicity against P388 with IC<sub>50</sub> value of 18 nM [71]. Additionally, 30, 32-dihydroxymycaloloide A (158) (Figure 15) was isolated from the Japanese sponge *M. izuensis* as a cytotoxic compound against HeLa cells with IC<sub>50</sub> value of 2.6 ng/mL [72].

![Chemical structures of 147–158.](image)

A bisoxazole-containing macrolide, secomycalolide A (159) (Figure 16), was isolated from a Japanese *Mycate* sp., together with 147 and 154. By using a chymotrypsin-like substrate, 159, 147 and 154 displayed a promising proteasome inhibition activity, with IC<sub>50</sub> values of 11, 30 and 45 µg/mL, respectively [73]. Later on, peloruside B (160) (Figure 16), another potent cytotoxic macrolide, was isolated from the New Zealand sponge *M. hentscheli*. Compound 160 showed strong cytotoxicity against human myeloid leukemia cells (HL-60) and human ovarian carcinoma 1A9 cells with IC<sub>50</sub> values of 33 ± 10 and 71 ± 6 nM, respectively [74]. Additionally, miuramides A (161) and B (162) (Figure 16) were identified from *Mycate* sp., collected from Japan. Both compounds showed significant cytotoxicity against 3Y1 cells with IC<sub>50</sub> value of 7 nM [75]. Very recently, Suo et al., described
the isolation of pelorusides C (163) and D (164) (Figure 16), also from the New Zealand sponge *M. hentschelii*. Both compounds showed cytotoxicity against HL-60 cell line, with IC_{50} values of more than 2 and 15 μM, respectively [76]. A structure-activity analysis revealed that pelorusides A–D (157, 160, 163 and 164) (Figures 15 and 16) stabilize microtubules by binding to β-tubulin, similar to the antitumor drug paclitaxel, highlighting the potential of these compounds as promising anticancer drug candidates [74,75,77–79].

**Figure 16.** Chemical structures of 159–164.

### 2.12. Terpenoids

Five sesquiterpenes, including two sesquiterpene phenols (+)-curcuphenol (165) and (+)-curcudiol (166), along with three minor compounds, 167–169 (Figure 17), were reported from an Australian marine sponge *Mycale (Arenochalina)* sp. [80]. Compound 165 displayed in vitro cytotoxicity against P388 murine leukemia and human tumor cell lines (IC_{50} = 7 μg/mL), HCT-8 (colon; MIC = 0.1 μg/mL), mammary (MDAMB; MIC = 0.1 μg/mL) [80] and NSLC (A549; MIC = 10 μM) [81], as well as antifungal activity against *Candida albicans* and *Cryptococcus neoformans* (MIC = 15 μM) [81,82]. Moreover, 165 also showed antibacterial activity against both *Staphylococcus aureus* and methicillin-resistant *S. aureus*, with MIC value below 20 μM [82]. On the contrary, 166 only exhibited weak antifungal activity against filamentous fungi and *Candida albicans* with MIC = 250 μg/mL [81,83]. Three terpenoid metabolites, clathrins A–C (170–172) (Figure 17), were isolated from the marine sponge *Clathria* sp., collected from the Great Australian Bight. Compound 170 represents the first example of a marine sesquiterpene/benzenoid in which the “benzenoid” residue retained a nonaromatic shikimate character, while 171 and 172 are rearranged norditerpenes. However, 172 was thought to be an artefact, which represents the oxidized form of 171 [84]. The unusual bicyclic C_{21}-diterpenoids, including clathric acid (173) and two acyl taurine derivatives, clathrimides A (174) and B (175) (Figure 17), were isolated from the marine sponge *C. compressa*, which was collected in Florida [20]. These compounds were tested for antibacterial activity against several Gram-positive and Gram-negative bacteria. However, only 173 was found to exhibit weak antibacterial activity, with MIC = 52 μg/mL against *S. aureus* (ATCC 6538P), and with MIC = 64 μg/mL against both methicillin-resistant *S. aureus* (ATCC 33591) and vancomycin-resistant *S. aureus* (VRSA), while 174 and 175 exhibited no activity at the highest concentration tested (128 μg/mL). Moreover, none of the compounds showed activity against Gram-negative bacteria [20]. Three tetracyclic sesterterpenes, gombaspiroketals A–C (176–178) (Figure 18), were isolated from the Korean sponge *C. gombawuiensis*, and showed in vitro cytotoxicity against K562 and A549 cell lines, with IC_{50} values of 1.45, 2.02,
0.85 and 0.77, 1.87, 4.65 μg/mL, respectively. Furthermore, 176 and 178 also exhibited antibacterial activity against several strains of Gram-positive bacteria, including *S. aureus, Bacillus subtilis* and *Kocuria rhizophila*, with MIC values of 25.0, 6.25, 12.5 and 25.0, 6.25, 25.0 μg/mL, respectively, and against Gram-negative bacteria *Salmonella enterica* and *Proteus hauseri*, with MIC values of 12.5, 6.25 and 25.0, 12.5 μg/mL, respectively. Moreover, 176–178 also inhibited the enzymes Na⁺/K⁺-ATPase and isocitrate lyase (ICL) with IC₅₀ = 10.9, 77.9, 18.7 and 57.4, >100, 66.3 μg/mL, respectively, and their inhibitory activity was hypothesized to be due to the three-dimensional structure of the spiroketal motif [85]. Phorone B (179) and ansellone C (180) (Figure 18), along with a nortriterpene sodium O-sulfonato-glucuronide saponin gombaside A (181) (Figure 18), were also isolated from *C. gombawuiensis*. Compound 181 features a rare 4,4,14-trimethyl pregnane skeleton. Compounds 179–181 exhibited moderate cytotoxicity against A549 and k562 cancer cell lines with IC₅₀ values of 4.7/3.9, 5.4/4.5 and 2.1/1.8 μg/mL, respectively. Interestingly, while 181 showed antibacterial activity against *B. subtilis* and *P. hauseri* with MIC values of 1.6 and 3.1 μg/mL, respectively, 179 and 180 were inactive (MIC > 100 μg/mL) [86]. Rotalins A (182) and B (183) are two diterpenes reported from the Mediterranean *M. rotalis* [87] while mycgranol (184) (Figure 18) is a diterpene, isolated from the Kenyan *M. aff. graveleyi* [88].

Norsesterterpene cyclic peroxides are a distinct class of marine sponges-derived metabolites. Five norsesterterpene cyclic peroxides, 185–189 (Figure 19), were isolated from the Australian marine
sponge *M. ancorina* [89]. Capon et al. [90] reported the isolation of further two norsesesterterpene cyclic peroxides, 190–191 (Figure 19), from *M. (Carmia)* cf. *spongiosa*, collected from New South Wales, Australia. Compounds 190–191 were isolated from the CH$_2$Cl$_2$ soluble fraction, which exhibited antimicrobial activity against *B. subtilis* and *Saccharomyces cerevisiae*. Mycaperoxides A (192) and B (193) (Figure 19), isolated from the Thai *Mycale* sp., were found to display in vitro potent cytotoxicity against three cancer cell lines, P-388, A-549 and HT.29 with IC$_{50}$ of 0.5-1.0 µg/mL, and antiviral activity against several viruses, including HSV-1. Moreover, these compounds also showed antibacterial activity against *B. subtilis* and *S. aureus* [91]. A further five cyclic peroxides, 185, 186, 189, mycaperoxides C (194) and D (195), along with six norterpenes, 196–201 (Figure 20), were isolated from *M. sp.* From Australia [92]. A re-investigation of *Mycale* sp., collected from New South Wales, Australia, allowed the identification of two further mycaperoxides F (202) and G (203) and a norterpenone ketone (204) (Figure 20) [93]. Similarly, re-examination of the Thai *Mycale* sp., by Phuwapraisirisan et al., led to the isolation of mycaperoxide H (205) (Figure 20), which was cytotoxic against the HeLa cancer cell line with IC$_{50}$ = 0.8 µg/mL [94].

![Figure 19. Chemical structures 185–193.](image1)

Two aromatic keto-carotenoids, clathriacine (206) and trikentriohodine (207) (Figure 20), were isolated from the marine sponge identified as *C. frondifera*, which, if correct, is now a junior synonym of *C. (Thalysias) vulpine* [95,96].

![Figure 20. Chemical structures of 194–207.](image2)
2.13. Steroidal Compounds

Three highly oxygenated steroids, named contignasterol (208) and clathriols A (209) and B (210) (Figure 21), were isolated from the New Zealand marine sponge C. (Clathria) lissosclera. While 208 exhibited a histamine release inhibitory activity with an IC$_{50}$ = 0.8 ± 0.32 µg/mL, 209 and 210 showed anti-inflammatory activity against the production of superoxide stimulated with N-formyl-methionine-leucine-phenylalanine (fmlp) or phorbol myristate acetate (PMA), with IC$_{50}$ values of -33/27 and 140/130 µg/mL, respectively. Moreover, 209 also displayed a 72% inhibition of the histamine release in peritoneal mast cells and a 76% inhibition of human peripheral blood neutrophil at a concentration of 30 µM [17,18]. Bioassay-guided fractionation of the CHCl$_3$-MeOH crude extract of the marine sponge Clathria sp., collected from the Red sea, resulted in the isolation of a sulfated sterol, clathsterol (211) (Figure 21), which displayed moderate antiviral activity against HIV-1 at a concentration of 10 µg/mL [16]. Biemansterol (212), along with the previously reported 24β-methylcholesta-5,7,22-dien-3β-ol (213) (Figure 21), were isolated from the Okinawan marine sponge Biemna sp. [97]. Compound 212, which possesses a rare 22, 25-diene side chain displayed in vitro cytotoxicity against murine lymphoma L1210 and human epidermoid KB cell lines, with IC$_{50}$ values of 3 and 1.3 µM, respectively [97]. Foristerol (214) (Figure 21), a steroid featuring an unusual seven-membered lactone ring, was reported from the Chinese marine sponge, B. fortis [98], while 5α, 8α-epidioxy-24(S)-ethylcholesta-6-en-3β-ol (215) (Figure 21) was isolated from the Madagascar marine sponge B. triraphis [99]. Huang and Guo [100] described the isolation of nine steroids, including melithasterol B (216), (24R)-ergosta-7,22-dien-3-ol, 5, 6-triol (217), (24R)-ergosta-4, 6, 8(14), 22-tetra-en-3-one (218), (24R)-ergosta-4, 7, 22-trien-3-one (219), (24R)-ergosta-6, 22-dien-5, 8-epidioxy-3-ol (220), 6-hydroxycholestan-4-en-3-one (221), cholest-4-en-3-ol, 6-dione (222), cholest-4-en-3-one (223) and cholest-5, 22-dien-3-one (224) (Figure 21), from the Chinese marine sponge B. fortis. Compound 222 displayed mild inhibition of T- and B-lymphocytes proliferation and potent hPTP1B inhibitory activity, with IC$_{50}$ = 1.6 µM [100]. Youssef et al. [101] reported the isolation of ehrenasterol (225) and (22E)-ergosta-5, 8, 22-trien-7-one-3β-ol (226), along with the previously reported (24R)-ergosta-6, 22-dien-5, 8-epidioxy-3-ol (220) and 216 (Figure 21), from the Red Sea marine sponge B. ehrenbergi. Compound 225 exhibited antibacterial activity with an inhibition zone of 20 mm at 100 µg/disc against E. coli. Moreover, both 225 and 226 showed weak cytotoxicity against a human colon adenocarcinoma (HCT-116) cancer cell line, with IC$_{50}$ of 45 and 40 µg/mL, respectively [101]. The steroidol oligoglycosides, mycalosides A–I (227–235) (Figure 22), were isolated from the Caribbean sponge M. laxisima. These compounds represent the first examples of steroidol oligoglycosides reported from marine sponges. The fraction containing 227–235, along with the pure mycaloside A (227) and mycaloside G (233), showed growth inhibition of fertilized eggs of the marine urchin Strongylocentrotus nudus, with EC$_{50}$ of 7.4 and 3.2 µg/mL, respectively [102,103].

2.14. Miscellaneous Compounds

The unprecedented cytotoxic PKS/NPRS metabolites, mycapolyols A–F (236–241) (Figure 23), were isolated from a Japanese M. izuensis. These compounds displayed cytotoxic activity against the HeLa cells, with IC$_{50}$ values of 0.06, 0.05, 0.16, 0.40, 0.38 and 0.90 µg/mL, respectively [104]. On the other hand, the first naturally occurring 5-thiosugar, 5-thio-D-mannose [105] while diethylene glycol dibenzoate (243) was reported from C. reinwardtii, collected at the Mandapam coast in the Gulf of Mannar, Tamilnadu, India [106]. 1,5-Diazacyclohexanicosane (244) (Figure 23), an aliphatic cyclic diamine was isolated from the Kenyan Mycale sp. [107]. Compound 244 exhibited significant cytotoxicity against A549 human lung carcinoma, HT29 human tissue carcinoma, and MDA-MB-231 human breast adenocarcinoma, with GI$_{50}$ values of 5.41, 5.07 and 5.74 µM, respectively.
Figure 21. Chemical structures of 208–226.

Figure 22. Chemical structures 227–235.
3. Conclusions and Prospects

This review presents extensive documented data, focusing on chemical diversity and biological activities of the secondary metabolites, isolated from the three marine sponge genera: *Mycale (Arenochalina)*, *Bienna* and *Clathria*, demonstrating these marine species as prolific sources of structurally diverse bioactive compounds. Despite their production of tricyclic guanidine-containing alkaloids, these sponges are classified under two different orders: *Mycale (Arenochalina)/Clathria* (under the order Poecilosclerida) and *Bienna* (under the order Biemmida), as recent molecular data revealed that *Bienna* is not related to the Poecilosclerida, and hence a new order Biemmida was given for the genus *Bienna*. This finding could highlight the important question of using secondary metabolites as taxonomic markers. Another important chemical feature is the uniqueness of the production of pyridoacridine alkaloids by *Bienna* sponges, which implies the relatedness of *Bienna* genus to the order Poecilosclerida. The two hundred and forty-four metabolites reported in this review are put together into fourteen major chemical classes, according to their structural characteristics and biosynthetic origin. The vast array of bioactivities exhibited by some of these metabolites make these marine sponge genera some of the most attractive biological targets, worthy of further exploration.

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**Abbreviations**

The following abbreviations are used in this manuscript:

- **EC**<sub>50</sub>  Half maximal Effective Concentration
- **GI**<sub>50</sub>  Half maximal Growth Inhibition
- **HIV-1**  Human Immunodeficiency Virus 1
- **IC**<sub>50</sub>  Half maximal Inhibitory Concentration
- **MIC**  Minimum Inhibitory Concentration
- **MAD**  Minimum active Dose
- **MID**  Minimal Infective Dose
- **LD**<sub>50</sub>  Lethal Dose 50 (median concentration of a toxicant that will kill 50% of the test animals within a designated period)
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