Abstract

Marine sponges continue to attract wide attention from marine natural product chemists and pharmacologists alike due to their remarkable diversity of bioactive compounds. Since the early days of marine natural products research in

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the 1960s, sponges have notoriously yielded the largest number of new metabolites reported per year compared to any other plant or animal phylum known from the marine environment. This not only reflects the remarkable productivity of sponges with regard to biosynthesis and accumulation of structurally diverse compounds but also highlights the continued interest of marine natural product researchers in this fascinating group of marine invertebrates.

Among the numerous classes of natural products reported from marine sponges over the years, alkaloids, peptides, and terpenoids have attracted particularly wide attention due to their unprecedented structural features as well as their pronounced pharmacological activities which make several of these metabolites interesting candidates for drug discovery. This chapter consequently highlights several important groups of sponge-derived alkaloids, peptides, and terpenoids and describes their biological and/or pharmacological properties.

4.1 Introduction

The true chemical and biological diversity of the marine environment is far from being understood today, and the oceans continue to be unique resources for bioprospecting providing a diverse array of natural products that are encountered in each group of marine organisms from prokaryotic bacteria and cyanobacteria to the top predators of the food chain such as sharks [1]. Nevertheless, the largest numbers of natural products reported since the early days of marine natural product research in the 1960s until today originate from marine invertebrates, with sponges being clearly at the top [2]. More than 5,300 different natural products are known from sponges, and more than 200 additional new metabolites from sponges are reported each year [3]. It is widely accepted today that the rich chemical diversity of sponges provides an effective chemical defense to these sedentary and soft-bodied organisms against environmental threats such as predation, overgrowth by fouling organisms, or microbial infections [4].

Numerous sponge-derived natural products such as the halichondrins, discodermolide, hemiasterlins, and arenastatin A exhibit also pronounced activities in pharmacologically driven screening programs and have been identified as lead compounds for the treatment of tumors, inflammation, and other diseases [5]. On the other hand, evidence is mounting that not all sponge-derived natural products are necessarily biosynthesized by sponges but may rather trace back to bacteria and other microorganisms that either reside within sponges or are inhaled by filter feeding [6, 7]. Examples of metabolites originally isolated from sponges that are in fact biosynthetic products of microorganisms include okadaic acid, a phosphatase inhibitor obtained from Halichondria sponges [8] that was shown later to be produced by dinoflagellates of the genus Prorocentrum [9]. Other examples include manzamine A and its 8-hydroxy derivative, antimalarial compounds first obtained from marine sponge of the genus Haliclona, that were isolated from a Micromonospora strain from the sponge Acanthostrongylophora sp. [7]. For many other compounds originally reported from sponges, a microbial origin is
likewise suspected even though clear evidence apart from obvious structural analogies with known microbial compounds is still lacking.

In this chapter, we will survey prominent groups of secondary metabolites derived from marine sponges and will focus on alkaloids, peptides, and terpenes which continue to attract wide attention of marine natural product researchers around the globe.

4.2 Alkaloids

Alkaloids are one of the most important classes of natural products providing drugs since ancient times. During the last decades, marine-derived alkaloids proved to be particularly important for drug discovery as exemplified by the new antitumor drug Yondelis® (ET-743). Marine alkaloids represent about one quarter of the more than 25,000 marine natural products reported to date, and a little more than half of them were obtained from sponges [2]. The present review will focus on three typical and major classes of sponge-derived alkaloids which include manzamine alkaloids, bromopyrrole alkaloids, and bromotyrosine-derived compounds.

4.2.1 Manzamine Alkaloids

The manzamines are polycyclic β-carboline-derived alkaloids. Manzamine A (1) (Fig. 4.1), the prototype of this group of compounds, was first isolated (as hydrochloride salt) in 1986 from an Okinawan sponge of the genus *Haliclona* and exhibited significant in vitro cytotoxicity against P388 murine leukemia cells with an IC₅₀ of 0.07 µg/mL (0.13 µM) [10].

Since the first report of 1, more than 50 further manzamine-type alkaloids have been identified from nine other different sponge genera belonging to four different taxonomic orders [11–14]. These compounds are characterized by featuring a fused and bridged tetra- or pentacyclic ring system, which is linked to a β-carboline moiety through an apparent Pictet-Splenger reaction involving an aldehyde known as ircinal A (2) as shown in Scheme 4.1 [15]. This proposed biogenetic pathway was supported

![Fig. 4.1 Structures of manzamine A (1), ircinals A (2), and B (3)]
Scheme 4.1  Plausible biogenetic pathway of manzamines A–C proposed by Baldwin and Whitehead [15]
by isolation of ircinals A (2) and B (3) (Fig. 4.1) from the Okinawan marine sponge *Ircinia* sp. [16]. Two further alkaloids isolated from a sponge of the genus *Amphimedon* which were designated as ircinols A and B were depicted to have opposite absolute configurations compared to 2 and 3, respectively [17] (Fig. 4.1).

In addition to ircinols A and B, Kobayashi et al. in 1994 isolated a further \(\beta\)-carboline alkaloid, keramaphidin B, that was considered as a plausible biogenetic precursor of ircinals A (2) and B (3) and manzamine alkaloids as well [18, 19] (Scheme 4.1).

The broad range of bioactivities exhibited by manzamine alkaloids includes cytotoxicity [10], insecticidal [20], and antibacterial [21] as well as the interesting in vivo curative activity against malaria in animal models [22, 23]. These findings increasingly stimulated research efforts to synthesize manzamine alkaloids and their derivatives as well to conduct structure-activity relationship (SAR) studies [24–26].

In 2008, Ibrahim et al. performed a SAR study on the 2-\(N\)-methyl modifications of manzamine A [27]. In this study, mono- and dimethylated quaternary carbolinium cations of manzamine A (1) were synthesized (6–8) (Fig. 4.2) and evaluated for their in vitro antiplasmodial and antimicrobial activities, cytotoxicity, and also for their potential as inhibitors of glycogen synthase kinase (GSK-3\(\beta\)) activity using molecular docking studies. Among the synthesized analogues,
2-N-methylmanzamine A (6) exhibited in vitro antiplasmodial activity (IC$_{50}$ 0.7–1.0 µM) but was less potent than manzamine A (1) (IC$_{50}$ 0.017–0.02 µM). However, 6 was less cytotoxic to mammalian kidney fibroblasts (Vero cells), and hence, the selectivity index was in the same range as for manzamine A (Fig. 4.2).

A new group of manzamine-related compounds includes nakadomarin A (9) [28], ma’eganedin A (10) [29], manadomanzamines A (11) and B (12) [30], and zamamidines A–C (13–15) [31, 32] which were isolated from different specimens of the sponge Amphimedon collected from Kerawa and Seragaki Islands, Okinawa, along with the unprecedented manzamine dimer, neo-kauluamine (16), from the common Indo-Pacific sponge genus Acanthostrongylophora [33, 34].

Zamamidines A–C (13–15) as well as manzamine A revealed inhibitory activities against Trypanosoma brucei brucei, the parasite causing sleeping sickness, (IC$_{50}$ values: 1.4, 1.4, 0.4, and 0.07 µM) and against Plasmodium falciparum (IC$_{50}$: 9.6, 16.3, 0.8, and 1.8 µM, respectively) [32]. In vitro analysis of several manzamine analogues against Toxoplasma gondii indicated significant activity. Manzamine A (1) displayed 70% inhibition of the parasite at 0.1 µM concentrations without displaying host cell toxicity. The activity significantly increased at concentrations of 1 and 10 µM even though it was accompanied by an increase in host-cell toxicity. As a result, manzamine A was selected for in vivo analysis. A daily intraperitoneal (i.p.) dose of 8 mg/kg of manzamine A, given for 8 consecutive days, beginning on day 1 following the infection, prolonged the survival of SW mice to 20 days, as compared to 16 days for untreated controls [35]. Additional information on the antiprotozoan activity of manzamines can be found in Chap. 21 (Fig. 4.3).

SAR studies and optimized dosing will probably further improve the in vivo efficacy of the manzamines against T. gondii. All new and known manzamines, with the exception of neo-kauluamine (16), induced 98–99% inhibition of Mycobacterium tuberculosis (H37Rv) with an MIC < 12.5 µg/mL. Manzamine A, E, and 8-hydroxymanzamine A exhibited MIC endpoints of 2.8, 5.5, and 5.5 µM, respectively [35].

In conclusion, manzamine alkaloids are valuable candidates for further investigation and possibly even development as promising leads against malaria and other serious infectious diseases. The need for developing antimalarials derived from novel structural classes and with unique mechanisms of action is important for the long-term and sustainable control of drug resistant Plasmodium strains.

The occurrence of manzamine alkaloids in seemingly unrelated sponge genera has raised speculations about a possible microbial origin of these compounds [36].

### 4.2.2 Bromopyrrole Alkaloids

Bromopyrrole alkaloids constitute a class of marine compounds found exclusively in marine sponges. Oroidin (17) (Fig. 4.4) was the prototype of this group and was first isolated from the marine sponge Agelas oroides in 1971 [37]. Oroidin (17) is considered as the key precursor for this group of compounds since many
Fig. 4.3 Structures of manzamine-related alkaloids (9–16)
bromopyrrole alkaloids constituting a pyrrole-imidazole unit can be considered as metabolic derivatives of the C_{11}N_5 skeleton of oroidin. Since the discovery of oroidin, more than 150 derivatives, with a wide variety of structures and interesting bioactivities, have been isolated from more than 20 different sponge taxa from different genera belonging mainly to the families Agelasidae, Axinellidae, and Halichondridae [38]. Their deterrent activity against predators is of ecological significance as shown for Caribbean reef sponges of the genus *Agelas* [39, 40]. Bromopyrrole alkaloids are also of interest due to their pronounced pharmacological activities including cytotoxicity, antimicrobial, and immunosuppressive activities which have driven the research interest of natural product chemists toward their total syntheses primarily during the last decade. These synthetic efforts lead to successful total syntheses of many bromopyrrole alkaloids such as dimeric pyrrole-imidazole alkaloids including sceptrin, oxysceptrin, and ageliferin [41]; nagelamides D [42] and E [41]; and hymenialdisine analogues [72].

Hymenidin (2-debromooroidin) (18), clathrodin (2,3-debromooroidin) (19), and sventrin (pyrrole N-methyloroidin) (20) were isolated from an unspecified Okinawan marine sponge of the genus *Hymeniacidon* [43] and from the Caribbean sponges *Agelas clathrodes* [44], and *A. sventres* [45], respectively. The biological activities of these compounds were found to be linked to the bromination pattern of the pyrrole moiety. For example, in a feeding assay, hymenidin exhibited lower deterrence against fishes as compared to oroidin [46]. N-methylation of pyrrole moiety in sventrin (20) likewise reduced fish feeding deterrence [45]. The reduction of voltage-dependent calcium elevation in PC12 cells was found to be directly proportional to the number of bromine atoms associated with the pyrrole ring in oroidin and hymenidin [47]. Oroidin, hymenidin, and clathrodin furthermore revealed pronounced anticholinergic and antiserotonergic activities [43, 45].
Dispacamides A–D (21–24) were isolated from four different species of the genus *Agelas* namely, *A. conifer*, *A. longissima*, *A. clathrodes*, and *A. dispar* [48, 49], in which the 2-aminoisimazole moiety was oxidized to an alkylidene glycyocyamidine. Dispacamide A (21) and B (22) differ from oroidin (17) and hymenidin (18), respectively, both with regard to the position of the double bond in the amine side chain and with regard to the presence of an aminoimidazolone moiety. Compounds (21) and (22) were found inactive with regard to anticholinergic and antiserotonergic activities. On the contrary, all dispacamides exhibited a remarkable antihistaminic activity on the guinea pig ileum through a reversible noncompetitive binding to histamine receptors, with dispacamide A (21) being the most active derivative [48]. Dispacamide C (23) and D (24) showed only mild activity in comparison which indicated the importance of the hydroxyl group in the side chain and also implicated that its orientation resulted in a notable reduction of antihistaminic activity [49]. Recently, debromodispacamides B and D were reported from *Agelas mauritiana* collected off the Solomon Islands [50].

Mukanadin A (= dispacamide D) (24) and B (25) have been isolated from the Okinawan sponge *Agelas nakamura* [51]. Mukanadin D (26) was obtained from the Jamaican sponge *Didiscus oleata* [52]. In mukanadin B (25), D (26), and compound (27), isolated from *Axinella verrucosa* [53], the 2-aminoimidazole unit of dispacamides is replaced by a hydantoin moiety.
Mauritamide A, isolated from the Fijian sponge *Agelas mauritiana*, was the first bromopyrrole alkaloid featuring a rare taurine moiety [54]. Taurine moieties are also present in tauroacidin A (28) and B (29), isolated from an Okinawan *Hymeniacidon* sp. [55]; in taurodispacamide (30), isolated from the Mediterranean sponge *Agelas oroides* [56]; and in its debromo derivative (31), isolated from *Axinella verrucosa* [53]. Interestingly, various pharmacological activities have been reported for these four compounds (28–31). Tauroacidsins A (28) and B (29) inhibited EGF receptor kinase and c-erbB-2 kinase activities (IC\(_{50}\) = 20 \(\mu\)g/mL) [55]. Taurodispacamide (30) showed significant antihistaminic activity [56], while its debromo derivative (31) showed potent neuroprotection through acting as glutamate and serotonin antagonist [53].

\[
\begin{align*}
\text{32} & \quad R = H \\
\text{33} & \quad R = \text{CH}_3 \\
\text{34}
\end{align*}
\]

Slagenins A–C (32–34) were isolated from the Okinawan marine sponge *Agelas nakamurai* [57]. They are characterized by an additional cyclization step in comparison to oroidin (17), the key precursor for this class. Both slagenins B (33) and C (34) were proven to be cytotoxic against murine leukemia L1210 cells in vitro with IC\(_{50}\) values of 21 and 19.5 \(\mu\)M, respectively, although slagenin A (32) proved to be inactive [57].

Polycyclic bromopyrrole alkaloids are thought to be derived from oroidin, the parent compound, through formation of one (or more) C–C or C–N bonds. Polycyclic bromopyrrole alkaloids can be divided into five major classes based on the oroidin atoms involved in the cylcization (Scheme 4.2) [56].

Debromohymenialdisine (35\(\alpha\)), hymenialdisine (36\(\alpha\)), and 3-bromohymenialdisine (37) (Scheme 4.2) represent the first cyclization mode of oroidin which occurs between C4 and C10. Debromohymenialdisine (35\(\alpha\)) was first isolated from the Great Barrier Reef sponge *Phakellia* sp. in 1980 [58], while hymenialdisine (36\(\alpha\)) was reported 2 years later from different sponge genera including *Acanthella*, *Axinella*, and *Hymeniacidon* [59–61]. 3-Bromohymenialdisine (37) was first isolated from the tropical marine sponge *Axinella carteri* [62]. All compounds (35\(\alpha\), 36\(\alpha\), and 37) were tested for cytotoxicity and insecticidal activity. In a cytotoxicity assay, debromohymenialdisine (35\(\alpha\)) was the most active compound against mouse lymphoma L5178Y cells with IC\(_{50}\) value of 1.8 \(\mu\)g/mL (4.1 \(\mu\)M) [62], while hymenialdisine (36\(\alpha\)) and 3-bromohymenialdisine (37) were essentially
equitoxic with $IC_{50} = 3.9 \mu g/mL$ for both. Both 35a and 36a exhibited insecticidal activity toward larvae of the pest insect *Spodoptera littoralis* (LD$_{50}$ values of 88 and 125 ppm, respectively), whereas 37 proved to be inactive in this assay [62].

Axinohydantoins (43–45) feature the same fused pyrroloazepine ring as present in hymenialdisine (36a). However, instead of a glycocyamidine ring, a pyrroloazepine ring is linked to a hydantoin ring via either (E) or (Z) double bond. (E)-axinohydantoin (43a) was isolated in 1990 from the sponge *Axinella* sp., and its structure was proven
by X-ray crystallography [63]. \((Z)\)-Axinohydantoin (43b) as well as the bromine derivatives (44b, 45b) were reported in 1997 [64] and 1998 [65], respectively. As for the axinohydatoins, the \((E)\) isomers of debromohymenialdisine (35b) and hymenialdisine (36b) have also been isolated [66].

Hymenin (46) is an \(\alpha\) adrenoceptor antagonist isolated from *Hymeniacidon* sp. and furthermore exhibits antibacterial activity against *Bacillus subtilis* and *Escherichia coli* [67]. Another hymenin analogue differing in the presence of a double bond between C9 and C10 was isolated from *Pseudaxynissa cantharella* [68], and it was named stevensine (= odiline) (48). 2-Debrominated derivatives of both hymenin (47) and stevensine (49) were isolated from the Indo-Pacific sponge *Stylissa carteri* [69]. Stevensine (48) has been demonstrated to play a major role in the chemical defense of the reef sponge *Axinella corrugata* against predators [70].

Hymenialdisine and its analogues are of interest due to their strong inhibitory activity against several protein kinases, such as CDKs, GSK-3\(\beta\), CK1, and Chk1, which are involved in regulating vital cellular functions such as gene expression, cellular proliferation, membrane transport, and apoptosis [71, 74]. Targeting these kinases has been appealing for the treatment of diseases like Alzheimer’s disease, type II diabetes, and cancer [72, 73] thereby providing a rationale for medication. In addition, hymenialdisines inhibited formation of several proinflammatory cytokines (IL-1, IL-2, IL-6, and NO) through inhibition of the NF-\(\kappa\)B signaling pathway [71] which is potentially valuable for treatment of serious inflammatory diseases such as rheumatoid arthritis and osteoarthritis or for treatment of cancer.

In 2009, an elegant review summarized all known hymenialdisines and provided a summary of their protein kinase inhibitory activities [75]. It came to the conclusion that (1) halogenation at R\(_1\) and R\(_2\) of the pyrrole ring does not significantly increase or decrease the activity of these compounds, (2) pyrrole derivatives appear to be more potent inhibitors than indole analogues which resulted in up to a fourfold reduction in activity, (3) a change in the geometry of the double bond (either \((E)\) or \((Z)\)) does not influence the activity, and (4) the existence of an aminoimidazolone ring, in particular the guanidine moiety, is crucial for the activity. Modifying the amino group dramatically decreased
activity possibly due to steric hindrance and loss of hydrogen bonding and hymenin (46), which features an aminooimidazole ring, proved to have much lower kinase inhibitory activity than hymenialdisine analogues [75].

The second cyclization mode, occurring between both N1 and N7 with C12, is exemplified, to the best of our knowledge, only in dibromoagelospongim (38) - (Scheme 4.2) which was isolated from the marine sponge Agelas sp. collected off the Tanzanian coasts [76]. Dibromoagelospongim (38) is closely related to dibromophakellin (39) (Scheme 4.2) in which N7 is bonded to C11 instead. The latter was first isolated in 1971 by Sharma et al. [77]. Later, several other phakellins have been reported from Pseudaxynissa cantharella [68] and Agelas sp. [78]. In 1997, a further derivative, phakellistatin, which differs from 39 in having a urea-type carbonyl instead of amino group present in the guanidine moiety, was isolated from the Indian Ocean sponge Phakellia mauritiana [79]. Phakellistatin exhibited potent antiproliferative activity against a variety of human cancer cell lines (IC50 values from 0.3 to 0.4 μM) [79].

The next cyclization mode of oroidin involving N7/C11 and C4/C12 affords a class of compounds called isophakellins, from which dibromoisophakellin (40) was the first derivative reported [80]. The compounds of this class are isomeric compared to the phakellins with the only difference in the linkage of imidazole C12 with C4 instead of N1.

The group of phakellins and isophakellins includes structurally complex metabolites known as palau’a-amines (50–52) or styloguanidines (53–55), respectively. In each of these compounds, the corresponding basic skeleton of phakellin or isophakellin is conjugated with an aminooimidazolyl propene unit.

Palau’a-amines (50–52) were reported from Stylotella agminata [81] and from Stylotella aurantium [82]. They revealed potent cytotoxicity against several cancer cell lines with IC50 values from 0.1 to 10 μg/mL along with antibacterial, antifungal, and immunosuppressive activities [81, 82]. Styloguanidines (53–55) were obtained together with palau’a-amines from the sponge Stylotella aurantium collected in the Yap Sea and exhibited potent inhibition of chitinase, a key enzyme involved, e.g., in the ecdysis of insects and crustaceans. The inhibition of this
enzyme affects the settlement of barnacles and hence could be a potential target for antifouling agents [83].

Agelastatin A (41) (Scheme 4.2) was the first reported member of the N1/C9 and C8/C12 cyclization series and was isolated from Agelas dendromorpha [84]. Other derivatives were later reported from the same sponge [85] as well as from Cymbastela sp. [86]. Agelastatins are potent antiproliferative agents against several cancer cell lines [85]. Moreover, agelastatin A (41) inhibited glycogen synthase kinase (GSK-3β), which could be useful for treatment of serious diseases including Alzheimer’s disease, cancer, and type II diabetes [71].

The last proposed cyclization mode of oroidin (17) occurring between N1 and C9, as shown in Scheme 4.2, affords cyclooroidin (42), first reported in the year 2000 from the Mediterranean sponge Agelas oroides [56]. Other members of this class of compounds include agesamides, isolated from an Okinawan sponge Agelas sp. [87], which differ from 42 in featuring a hydantoin ring instead of a glycocyamidine ring. Oxycyclostylidol, another compound of this class was the first pyrrole-imidazole alkaloid, reported containing an oxidized pyrrole moiety [88].

Cyclooroidin (42) can be considered as a biosynthetic precursor of the nonimidazole bromopyrrole alkaloids including longamides (56–60) and aldisines (61–64).

|   |   |   |
|---|---|---|
| R | R | R |
| Br | H | H |
| H | C_2H_5 | CH_3 |
| H | Br | Br |
| H | Br | Br |

Longamide A (56) was identified as a novel unusual pyrrolopiperazine alkaloid and was isolated as (9S) isomer from the Caribbean sponge Agelas longissima [89]. The 2-debromo derivative (= mukanadin A) (57) was obtained from the sponge Axinella carteri [90] together with 2-bromoaldisine (62), while aldisine (61) was reported from the sponge Hymeniacidon aldis [91]. 3-Bromoaldisine (63) and 2,3-dibromoaldisine (64) were isolated from Axinella damicornis and Stylissa flabelliformis [92]. Longamide B (58) has been isolated as a racemate from the Caribbean sponge Agelas dispar [93]. Hanishin, longamide B ethyl ester (59) was named after the Hanish Islands (Red Sea) where the sponge Acanthella carteri was collected [94].

Other smaller bromopyrrole alkaloids (65–73), which are considered as building blocks leading to oroidin (17), have been isolated from Agelas oroides (65) [36], Agelas flabelliformis (66) [96], Acanthella carteri (67, 68) [94], Axinella damicornis (69, 70) [92], Agelas nakamurai (71, 74) [97], Acanthostylotella sp.
Acanthamides A–D (77–80) were isolated from an Indonesian marine sponge *Acanthostylotella* sp. [98]. Antipredatory activity seems to be the main ecological function for these small bromopyrroles [36, 92, 94].

In 1981, dimeric bromopyrrole alkaloids have been reported for the first time from the Caribbean sponge *Agelas sceptrum* which gave the name sceptrin to one of the metabolites isolated (81) [99]. Historically, 81 is considered as the parent compound of this group and represents a symmetrical dimer of 2-debromooroidin. Sceptrin (81) displayed a broad spectrum of bioactivities such as antimicrobial activity against different bacterial and fungal pathogens [99]. In addition, it exhibited antiviral [100], antimuscarinic [45], and antihistaminic properties [49].

Later, dimeric bromopyrrole alkaloids were also reported from other genera of marine sponges including *Stylissa* [101, 102], *Axinella* [103], *Hymeniacidon* [104], and most frequently from *Agelas*. Among this group of
dimeric alkaloids, two series can be identified which include ageliferins and nagelamides.

Ageliferin (82), bromoageliferin (83), and dibromoageliferin (84) were first isolated from *Agelas conifera* and *A. cf. mauritiana* in 1989 by Rinehart [105]. Afterward, their detailed structural elucidation and stereochemistry were reported in 1990 by Kobayashi et al. [106]. Both 83 and 84 reduced voltage-dependent calcium entry in PC12 cells which leads to vasorelaxation [107].

Seven further ageliferin derivatives (85–91), methylated at one or at several of the pyrrole nitrogens, together with the formerly isolated bromo- (83) and dibromoageliferin (84) were obtained from the calcareous sponge *Astrosclera willeyana* collected off Ant Atoll, Pohnpei, Micronesia [108].

![Chemical structure of ageliferin and nagelamide derivatives](image)

Nagelamides comprise 15 dimeric bromopyrrole derivatives including nagelamides A–H [109], J–L [110, 111], and O–R [112, 113]. All of them were reported by Kobayashi et al. from different collections of an unspecified Okinawan sponge of the genus *Agelas* collected off Seragaki beach.
Nagelamides A–D (92–95) are connected via a C-C bond between C10 and C15'. Nagelamides E–G were proven to be diastereomers of ageliferin (82), bromoageliferin (83), and dibromoageliferin (84), respectively. Nagelamide J (96) is the first bromopyrrole alkaloid possessing a cyclopentane ring fused to an aminoimidazole ring [110]. In addition, nagelamide L (97) was identified as a unique dimeric bromopyrrole alkaloid containing an ester linkage [111].
Nagelamide Q (98) is a rare dimeric bromopyrrole alkaloid possessing a pyrrolidine ring, while nagelamide R (99) was the first bromopyrrole alkaloid featuring an oxazoline ring [113]. Nagelamides have been tested for antimicrobial activity against a vast array of bacterial and fungal pathogens including Bacillus subtilis, Escherichia coli, Micrococcus luteus, Staphylococcus aureus, Trichophyton mentagrophytes, Cryptococcus neoformans, Candida albicans, and Aspergillus niger. Most of the nagelamides showed antimicrobial activity with MIC values between 7.7 and 38.4 μM [109–113]. Nagelamides A, G, and H showed also inhibitory activity against protein phosphatase 2A, a major serine/threonine protein phosphatase involved in cellular growth and potentially in cancer development, with IC₅₀ values of 48, 13, and 46 μM, respectively [109].

4.2.3 Bromotyrosine Derivatives

(+)-Aeroplysinin-1 (100, Scheme 4.3) was the first reported member of this group of alkaloids. It was obtained from marine sponges belonging to the order Verongida. In 1970, Fattorusso et al. isolated 100 from Verongia aerophoba collected off the Bay of Naples (Italy) [114]. Later, it was also reported from other marine sponges from different geographic locations including Psammoposilla purpurea (Marshall Islands) [115], Aplysina laevis (Australia) [116], and Aplysia caissara (Brazil) [117]. Its (−)-isomer was first isolated from Ianthella ardis [118].

Aeroplysinin-1 (100) proved to be antiproliferative in small micromolar doses against various cancer cell lines such as Hela (human cervical carcinoma) and L5178Y (mouse lymphoma) in addition to human mammary and colon carcinoma cell lines [119–121]. In 2002, Rodríguez-Nieto et al. reported that 100 inhibited the growth of BAECs (bovine aortic endothelial cells) and induced apoptotic cell death [122]. Aeroplysinin-1 inhibits the endothelial cell migration and capillary tube formation in matrigel through inhibition of matrix-metalloproteinase 2 and urokinase in endothelial cell conditioned medium [119]. The same study reported in vivo inhibition of
Angiogenesis as demonstrated in the CAM (chick chorioallantoic membrane) assay and matrigel plug assay. Aeroplysinin-1 exhibited preferential cytotoxicity against L5178Y cells compared to murine spleen lymphocytes through reducing the incorporation rates of $^3$H-thymidine [119]. In vivo experiments by the same group revealed an antileukemic activity of 100 in L5178Y cell/NMRI mouse system. In conclusion, aeroplysinin-1 proved to be an inhibitor of both angiogenesis and tumor proliferation.

Various ecological and biochemical studies of *Aplysina* sponges suggested that aeroplysinin-1 arises through enzymatic biotransformation of more complex brominated isoxazoline alkaloids as a response to sponge tissue damage yielding

**Scheme 4.3** Enzymatic transformation of isoxazoline alkaloids in *Aplysina* sponges into aeroplysinin-1 (100) and a dienone analogue (101) [120, 123–127]
aeroplysinin-1 (100) and a dienone analogue (101) (Scheme 4.3) [120, 123–127] (Scheme 4.3).

Receptor tyrosine kinases (RTKs), such as the epidermal growth factor receptor (EGFR) and the platelet-derived growth factor receptor (PDGFR), are critically involved in the transduction of mitogenic signals across the plasma membrane and therefore in the regulation of cell growth and proliferation. Enhanced RTK activity is associated with proliferative diseases such as cancer, psoriasis, and atherosclerosis, while decreased function may be associated, for instance, with diabetes [128]. Aeroplysinin-1 inhibited tyrosine kinase activity of EGFR in vitro and blocked ligand-induced endocytosis of the EGF receptor and PDGF receptor in vitro [129]. Hence, a proposed EGFR-dependent mechanism of action was depicted; however, the compound showed no activity when tested in a whole-cell assay system [129].

Therefore, a series of aeroplysinin-1 analogues was synthesized and evaluated as RTK inhibitors to enhance membrane permeability in cell-based assays with retained tendency for nucleophilic covalent binding to the enzyme-binding site [128]. Four synthetic analogues (105–108) exhibited promising inhibitory activity against EGFR and PDGFR tyrosine kinases in cellular assays with IC50 values in the low micromolar range, but none of them have yet been assessed for antiangiogenesis.

Psammaplin A is a symmetrical brominated tyrosine metabolite containing a disulfide linkage and is usually obtained as a mixture of isomers, [(E,E)-isomer (109) and (E,Z)-isomer (110)] which differ in the configuration of their oxime groups.

In 1987, psammaplin A was reported simultaneously by Quiñoà and Crews [130] and Rodríguez et al. [131] from Psammoplysilla purpurea and Thorectopsamma xana sponges, both belonging to the order Verongida. Psammaplin A was also obtained from Aplysinella rhax [132] and Pseudoceratina purpurea [133] in addition to two Korean non-Verongid sponges of the genera Jaspis and Poecillastra.
Later, a vast diversity of psammaplins have been reported, including 13 monomeric psammaplins (A–M) isolated from the Indo-Pacific sponge *Pseudoceratina purpurea* [133], the Fijian sponge *Aplysinella rhax* (thought to be synonymous with *Pseudoceratina purpurea*) [136] and from two-sponge associations of *Jaspis* sp. And *Poecillastra* sp. collected from Korean waters [135].

In addition, dimeric psammaplin derivatives were obtained which occur either in an opened form such as bisaprasin A (111) and bispsammaplin A (112) or in a cyclized form represented by cyclobispsammaplin A (113). All of these compounds were reported from different Korean collections of sponges of the genera *Jaspis* and *Poecillastra* [134, 135]. Moreover, 11’-sulfate derivatives of 109 and 111 were isolated from the sponge *Aplysinella rhax* collected from Queensland (Australia) [132].

The cytotoxicity of psammaplin A (PsA, 109) toward a vast array of human cancer cells was studied by numerous groups [134, 135, 137–139]. PsA inhibits the
proliferation of BAECs [139]. It furthermore inhibits DNA synthesis and DNA gyrase [140], farnesyl protein transferase and leucine aminopeptidase [137], chitinase B from *Serratia mercescens* [136], in vitro replication of SV40 DNA through α–primase targeting [138], activation of peroxisome proliferator–activated receptor gamma [141], and histone deacetylases (HDACs) in cell-based assays, the latter having been highlighted as one of the key enzymes involved in both oncogenesis and angiogenesis, inducing cell cycle arrest and apoptosis [143–145]. PsA also inhibited DNA methyltransferase activity in vitro [142]. However, the lack of in vivo inhibition of DNA methylation suggests that this enzyme is not a major cellular target. Furthermore, it inhibited aminopeptidase N (APN), a Zn-dependent metalloproteinase that has been implicated in tumor invasion and angiogenesis [139]. Both homodimers and heterodimers were further assayed for antibacterial activity against methicillin-resistant *Staphylococcus aureus* and structure refinement of promising lead compounds through parallel synthesis afforded a series of antibacterial agents significantly more active than the natural product [140, 146].

Purealidin A (114) represents the prototype of a group of bromotyrosine-derived alkaloids that includes 17 additional purealidins (B–H and J–S) [147–153]. All compounds were isolated from different collections of the Okinawan sponge *Psammoplysilla purea* except for purealidins J and S that were obtained from the Fijian sponge *Druinella* sp. [153].
Purealidin A (114) exhibited cytotoxic activity against murine leukemia L1210 cells in vitro with IC₅₀ value of 2.1 μM [147], while purealidins C (115), N (116), P (117), and Q (118) showed cytotoxicity against human epidermoid carcinoma KB cells (IC₅₀: 4.3, 0.16, 10.2, and 1.6 μM, respectively) and murine lymphoma L1210 cells (IC₅₀: 3.2, 0.15, 3.8, and 1.3 μM, respectively) [148, 152]. In both cell lines, purealidin N (116) was found to be the most potent analogue followed by purealidin Q (118). Furthermore, purealidin C (115) proved antifungal and antibacterial [148] while purealidins P (117) and Q (118) revealed inhibitory activity against EGF receptor kinase with IC₅₀ values of 24.2 and 14.8 μM, respectively [152]. Eight purpurealidins (A–H) were isolated from the Indian sponge *Psammoplysilla purpurea* [154].

![Chemical structure](119)

All purpurealidins were screened for antibacterial and antifungal activities. Only purpurealidin B (119) showed moderate activity against *Staphylococcus aureus*, *Escherichia coli*, and *Vibrio cholerae* and weak activity against *Shigella flexineri* with MIC values of 10, >12, 25, and 100 µg/mL, respectively [154]. Suggested ecological roles for these bromotyrosine compounds are mainly feeding deterrents [121].

Psammaplysenes A–D (120–123) represent a group of bromotyrosine-derived alkaloids which have been obtained from *Psammoplysilla* sp. collected in the Indian Ocean [155] and from the Australian sponge *Psammoclemma* sp. [156]. Psammaplysen A (120) compensated for the loss of PTEN tumor suppressor by relocating the transcription factor FOXO1α to the nucleus (IC₅₀ = 5 μM) compared to psammaplysen B (121) (IC₅₀ = 20 μM) [155]. The growth-inhibiting PTEN phosphatase proved important for regulation of the growth-promoting PI3-kinase signal. Hence, loss of functional mutations in PTEN can result in an inappropriate increase in stimulatory signals, and such mutations have been linked with Cowden’s disease, a hereditary disease with a predisposition to breast, thyroid, and other cancers [155]. Both psammaplysen C (122) and D (123) showed cytotoxicity (IC₅₀ = 7 μM). Hence, their bioactivity in both P2X₇ and hemolysin specificity assays was attributed to cytotoxicity against the premonocytic cell line THP-1, which expresses the P2X₇ receptor [156]. In 2005, Georgiades and Clardy synthesized 120 and 121 by a flexible efficient route using 4-iodophenol as a common starting substrate [157].
The sponge *Aplysina gerardogreeni* collected at the Gulf of California yielded four cytotoxic dibromotyrosine-derived metabolites, aplysinones A–D (124–127) [158]. Cytotoxicity of aplysinones (A–D) was evaluated against three human tumor cell lines MDA-MB-231 (breast adenocarcinoma), A-549 (lung carcinoma), and HT-29 (colon adenocarcinoma) [158]. Against MDA-MB-231 cells, all aplysinones showed cytotoxicity with IC$_{50}$ values between 3.0 and 7.6 μM, whereas only aplysinone B (125) showed cytotoxicity against lung carcinoma A-549 cells with an IC$_{50}$ value of 4.1 μM. Furthermore, alplysinones A (124), B (125), and D (127) proved cytotoxic against colon adenocarcinoma HT-29 cells with IC$_{50}$ values of 9.1, 3.0, and 11.3 μM, respectively [158].
Antithrombotics (= anticoagulants) are crucial therapeutic agents for a number of thrombotic disorders such as myocardial infarction, angina, pulmonary embolism, and cerebrovascular incidences. The conventional antithrombotic therapy is performed by intravenous administration of heparin followed by oral treatment with warfarin. Besides being indirect and nonspecific inhibitors of coagulation serine proteases, both heparin and warfarin require very careful and costly monitoring to ensure safe therapeutic drug levels over treatment duration due to the high risk of bleeding. Therefore, enormous efforts focused on new plausible drug candidates with an improved efficacy-to-safety index compared to heparin and warfarin. Factor Xla (FXla) is a trypsin-like serine protease that plays a major role in the amplification phase of the coagulation cascade and in maintaining clot integrity. FXla is a unique target as its specific inhibitors might inhibit thrombosis without intimate interruption of normal hemostasis and thus might prevent or minimize the risks of hemostatic complications. In an attempt to achieve this target, Buchanan et al. isolated a series of bromotyrosine-derived alkaloids from two different collections of the Australian Verongid sponge Suberea clavata, trivially named as clavatadine A–E (128–132) [159, 160]. All clavatadines were tested for their inhibitory activities against factor Xla. Only clavatadines A (128) and B (129) inhibited selectively FXla with IC$_{50}$ values of 1.3 and 27 $\mu$M, respectively [159], while other clavatadines showed only weak inhibitory activity (17–37%) against FXla at concentrations up to 222 $\mu$M [160]. The crystal structure and molecular docking of 128 enabled understanding of SARs. Conclusively, they revealed that clavatadine A (128) can approach/bind in the S1–S1’ pocket of FXla by favorable interactions with Asp189 at its guanidine group on one end and the free carboxylate to either Arg37D or Lys192 of the other. This would result in a close contact between the side chain of Ser195 and the carbamate group of 128, which eventually leads to the covalent binding with FXla. Clavatadine B (129) is more than one order of magnitude less potent than 128, presumably due to weaker interactions between its amide group and either Arg37D or Lys192, compared to the carboxylate moiety in 128 [159].
Bastadins are heterodimers biogenetically derived from oxidative coupling of two brominated tyrosine-tyramine amides. To date, a total of 24 bastadin analogues have been isolated from the Indo-Pacific Verongid sponges *Ianthella basta* [161–171], *Ianthella quadrangulata* [172, 173], *Ianthella* sp. [174], and *Psammaplysilla purpurea* [175, 176] in addition to the Dendroceratid sponge *Dendrilla cactos* [177].

![Chemical structures of bastadin analogues](image_url)
Bastadins are structurally classified into three groups, according to the proposed biosynthetic pathway by Jaspars et al. [166] (Scheme 4.4), depending upon the degree and position of the phenolic couplings linking the monomeric units such as hemibastadin (133) (Scheme 4.4) [165, 178]. The linear (= acyclic) bastadins contain a single ether or biaryl linkage like in bastadin 1 (134) and bastadin 3 (135), while the macrocyclic members of the series possess either the bastaran skeleton (Scheme 4.4) including bastadin 4 (136), 6 (137), 9 (138), 16 (139), and 24 (140) in which the hemibastadin units are linked by phenolic ethers from C10 to C14 and from C29 to C33, or the isobastaran skeleton (Scheme 4.4) such as bastadin 13 (141), in which ethers link C9 to C14 and C29 to C33 (Scheme 4.4).

Bastadins were first isolated from the Australian sponge Ianthella basta and revealed potent in vitro antimicrobial activity against Gram-positive bacteria [161, 162]. Since then, bastadins have demonstrated a vast array of biological activities including cytotoxicity [163, 164, 173, 175, 177, 179], anti-inflammatory activity [163], inhibitory activity of topoisomerase II, dehydrofolate reductase, inosine 5’-phosphate dehydrogenase, 12- and 15-human lipoxygenases [166, 175, 180], and agonistic activity toward the sarcoplasmic reticulum Ca$^{2+}$ channel through modulation of the RyR FKBP12 receptor complex [168, 181, 182]. In addition, the antiangiogenic activity of the bastadins has been reported by Kobayashi et al. [169, 170]. Furthermore, Proksch et al. investigated the antifouling activity of selected sponge metabolites on settling of barnacle larvae, or cyprids, of Balanus improvisus [171].

The study included selected sponge-derived natural products displaying pronounced activity in other bioassays such as ageliferin (82), isofistularin-3 (102) (Scheme 4.3), and sceptrin (81) which are known to be fish deterrents [183, 184] and hymenidin (18) and 81 inhibit serotonin being involved in cypid settling behavior [106] in addition to psammaplin A (109), hemibastadin (133), bastadins 3 (135), 4 (136), 9 (138), and 16 (139). In this study, only bastadins and psammaplin A inhibited the settlement of the cyprids in a dose-dependent manner in a range of 0.1–10 μM [171].

However, hemibastadin (133) and psammaplin A (109) proved to be toxic to B. improvisus when tested at a dose of 10 μM. The antifouling activity of the active compounds is linked to the oxime moiety as a uniting structural feature. In order to justify this hypothesis, two synthetic products including debromohemibastadin-1 and L-tyrosinyltyramine, differing only in the presence of an oxime vs. amino function, were investigated. Although L-tyrosinyltyramine proved to be completely inactive even at a concentration of 100 μM, the oxime-bearing debromohemibastadin inhibited barnacle settlement at almost similar concentrations as the brominated derivatives thus corroborating the importance of the oxime function [171].

### 4.3 Peptides

Bioactive peptides from marine sponges are receiving considerable interest by natural product chemists and pharmacologists alike and represent
Scheme 4.4 Biosynthetic pathway of bastadins as proposed by Jaspars et al. [166]. Donor site = ● (phenolic oxygen) Acceptor site = ♦ (aryl bromine).
a well-established sector of marine natural products research. Most bioactive peptides from marine sponges comprise unique structures in comparison with those from other sources. For example, marine peptides are often cyclic or linear peptides containing unusual amino acids which are either rare or even absent in terrestrial and microbial peptides. In addition they frequently contain uncommon linkages between amino acids such as kapakahines isolated from a Pohnpei sponge *Cribrochalina olemda* [185–187].

Discodermin A (142) was the first bioactive peptide isolated from the marine sponge *Discodermia kiiensis* collected at Shikine Island (Japan) [188, 189]. Further chemical investigation of the extract of the same sponge resulted in the isolation of three additional discodermins B–D (143–145) [190], whereas bioassay-guided fractionation of the extract of *D. kiiensis* collected off Atami in the Gulf of Sagami (Japan) led to the isolation of discodermin E [191]. Structural study of discodermin E revealed the presence of a D-kynurenine residue replacing a D-Trp residue and a reversed sequence of the 12th and 13th residues from the N-terminus compared to discodermin A (142) [191]. In addition to discodermin E, three further congeners including discodermins F–H (146–148) were obtained from the latter sponge [192]. Discodermins A–H and the structurally related discobahamins A and B [193], polydiscamides A–D [194, 195], and halicylindramides A–E [196, 197] have been obtained from marine sponges of the genera *Discodermia, Ircina* and *Halichondria*, respectively. They represent a group of bioactive peptides containing 13 to 14 known as well as rare amino acid residues with a macrocyclic ring formed by lactonization of a threonine moiety with the carboxy terminal of the peptide chain. Halicylindramide E (149) is an exception as it is a linear peptide composed of 11 amino acids.
Discodermins A–D (142–145) revealed in vitro antibacterial activity [188–191]. They were later found to be potent inhibitors of phospholipase A₂ (PLA₂) and 142 inhibited the tumor promotion activity of okadaic acid [191]. In addition, discodermins F–H (146–148) were cytotoxic against P388 murine leukemia cells with IC₅₀ values of 0.6, 0.23, and 0.6 μM, respectively [192]. Discobahamins A and B exhibited weak antifungal activity against Candida albicans [193]. Polydiscamide A inhibited the proliferation of human lung cancer A549 cell line (IC₅₀ = 0.4 μM) in vitro and the growth of Bacillus subtilis (MIC of 1.8 μM) [194]. Interestingly, polydiscamides B–D acted as pain modulators by activating the sensory neuron-specific G protein coupled receptors (SNSRs), which are expressed solely in dorsal root ganglia [198]. Previous studies showed that SNSRs are key players in both acute and persistent pain [199]. Due to the highly restricted distribution of SNSRs in the body, ligands that interact with these receptors may potentially modulate pain with very few side effects [195]. Polydiscamides B–D showed potent agonist activity against human SNSR with EC₅₀ values of 1.26, 3.57, and 2.80 μM [195], and they were the first examples of nonendogenous compounds with human SNSR agonist activity. Therefore, they could potentially be modified for therapeutic use as pain modulators.

Halicylindramides A–D, featuring D-Phe and L-BrPhe instead of D-Leu and L-Phe (or L-Tyr) in discodermins, respectively, exhibited antifungal activity against Mortierella ramanniana at 7.5 μg/disk as well as cytotoxic activity against P388 murine leukemia cells with IC₅₀ values of 0.3, 0.1, 0.01, and 1.2 μM, respectively [196, 197].

Two families of closely related cyclic depsipeptides, the jaspamides and the geodiamolides, have been isolated from a variety of tropical marine sponges. Jaspamide (jasplakinolide) (150), obtained independently from Jaspis sp. collected off Palau [200] and Fiji [201] in 1986, was the first member of this group of depsipeptides to be reported. Thereafter, several reports on the presence of jaspamide in other sponge genera, including Auletta cf. constricta [202] and Hemiasterella minor [203] were published. Geodiamolides A (154) and B (155) were isolated from the Caribbean sponge Geodia sp. [204].
After the discovery of jaspamide (150) and its pronounced biological activities which include antifungal [205], anthelmintic, insecticidal [200, 201], and cytotoxic activity [206], sponges of the genus *Jaspis* have received considerable attention. Sixteen additional jaspamide derivatives (B–H and J–R) have been isolated from different collections of the marine sponge *Jaspis splendens* [207–211]. All jaspamide derivatives exhibited a consistent antiproliferative activity with IC₅₀ values ranging from 0.01 to 10 μM [210, 211] when tested against MCF-7 human breast adenocarcinoma, HT-29 colon carcinoma, or L5178Y mouse lymphoma cell lines.

The antimicrofilament activity was measured and paralleled the observed in vitro cytotoxicity. A thorough structural analysis indicated that the sole invariable residue in all jasmapamides is β-tyrosine whereas a wide variability of the alkylation and oxidation pattern of the polypropionate subunit as well as of the identity of the first two amino acids, namely, alanine and abrine (N-methyltryptophan), of the tripeptide portion was observed. Therefore, the β-tyrosine residue appeared to be the only strict common feature essential for biological activity in the tested tumor cell lines, mainly assuring a β-turn motif for the folding of the entire molecule [210]. Moreover, the modifications of the abrine residue, claimed as essential for the observed biological activity [212], appeared to have little influence on the observed antiproliferative effect with the exception of jaspamide N (153), where the β-hydroxylation of tryptophan unit causes a diminution of the biological activity. As suggested by Maier [213], the 1,3 methyl groups of the polypropionate subunit, imposing to the macrocycle conformational constraints through syn pentane...
interactions, play a significant role in assuring a correct folding of the entire molecule as suggested by the drop of activity for jaspamides F (151) and H (152).

Geodiamolides A (154) and B (155) were first isolated from the Caribbean sponge *Geodia* sp. [204]. Geodiamolides C–F [214] and geodiamolide G (156) [215] have been reported from a *Cymbastela* sp. collected in Papua New Guinea. Geodiamolides H and I have been reported from the marine sponge *Geodia* sp. collected off Macqueripe Bay (Trinidad) [216]. Geodiamolide TA was isolated from the South African sponge *Hemiasterella minor* [203], while the structurally related neosiphoniamolide A has been obtained from the New Caledonian sponge *Neosiphonia superstes* [217]. In addition, geodiamolides J–P and R were isolated from the marine sponge *Cymbastela* sp. collected in Papua New Guinea [218].

There are now, to the best of our knowledge, 19 known members of the geodiamolide family of cyclodepsipeptides. Variations have been observed in all three amino acid positions and also in the polyketide portion of the molecule. However, comparison of their cytotoxicities showed that significant variation in the three amino acid residues causes only minor changes in the levels of cytotoxicity exhibited by this class of compounds. In contrast, geodiamolide G (156) (in vitro human glioblastoma/astrocytoma U373, IC\(_{50}\) 12 μM; in vitro inhibition of human ovarian carcinoma HEY, IC\(_{50}\) 13.4 μM) [215], with its modified polyketide fragment, is significantly less toxic than the analogous geodiamolide A (154) (in vitro inhibition of human glioblastoma/astrocytoma U373, IC\(_{50}\) 0.02 μM; in vitro inhibition of human ovarian carcinoma HEY, IC\(_{50}\) 0.07 μM) [218].

The jaspamide/geodiamolide family of metabolites occurs across taxonomically distant groups of sponge species [200–218]. It has been suggested that microorganisms associated with the respective sponges may be responsible for the production of these metabolites [203]. The isolation of chondramides, which are jaspamide analogues, from cultures of various strains of *Chondromyces crocatus* [219] strongly supported the hypothesis of a microbial origin for the jaspamides/geodiamolides.

Hemiasterlin (157) is a prototype of a group of antimitotic tripeptides which was first isolated together with geodiamolide TA in 1994 from the marine sponge *Hemiasterella minor* [203]. It revealed significant cytotoxicity against P388 leukemia cell line with IC\(_{50}\) value of \(~\)0.02 μM [203]. The related isomers hemiasterlins
A (158) and B (159) were obtained from sponges of the genus *Auletta* and *Cymbastella* in 1995 [215], whereas a fourth analogue, hemiasterlin C (160) was isolated from the marine sponge *Siphonochalina* sp. collected off the coast of Papua New Guinea in 1999 [220]. In 1996, an X-ray crystal structure analysis of the hemiasterlin methyl ester confirmed its linear structure and unusual amino acids existence [221]. All hemiasterlins (157–160) exhibited pronounced in vitro cytotoxicity against a variety of human and murine cell lines with IC50 values in the nanomolar range [215]. The potent antiproliferative activity of hemiasterlins was found to be due to the induction of mitotic arrest in metaphase with cellular dynamics similar to those of known tubulin binders, such as the chemotherapeutics paclitaxel or vinblastine, at ED50 values ranged from 0.5 nM (hemiasterlin) to 28 nM (hemiasterlin B) [222].

Extensive SAR studies demonstrated that HTI-286, a simpler synthetic analogue of hemiasterlin (157) with a phenyl substituent replacing the N-methyltryptophan, is more potent than 157 [221], whereas an analogue of HTI-286 with a para-methoxyl substituent on the benzene ring was even more potent [220]. Other structural elements, including the geminal β,β-dimethyl group and the N-methyl on the first amino acid residue (N terminus), the isopropyl and an olefin in the homologated γ-amino acid (C terminus) including a terminal carboxylic acid or methyl ester, were essential for activity. The aryl side chain on the N terminus could be replaced synthetically by alkyl groups (e.g., tert-butyl) while still retaining potent activity [223–226]. Preclinical studies showed that HTI-286 causes tumor regression and growth inhibition of human xenografts in mice [227]. An open-label phase I clinical trial of HTI-286 was completed in patients with advanced solid tumors; however, there were no objective responses and common toxicities observed including neutropenia, nausea, alopecia and pain [228]. Therefore, phase II trials have been halted. Nevertheless, there is still interest in HTI-286 according to recent results including high antitumor activity in androgen-dependent and androgen-independent mouse models of refractory prostate cancer and in a newly established in vitro taxane-resistant prostate PC-3 cell line [229].

Arenastatin A (161) is another example of cytotoxic cyclic depsipeptides that was isolated from the Okinawan marine sponge *Dysidea arenaria* [230]. Arenastatin A exhibited potent cytotoxicity against KB human epidermoid
carcinoma cells with IC$_{50}$ value of 8.3 pM [230]. Its absolute configuration [231] and its total synthesis [232] were reported.

From the family Dysideidae, dysinosins A–D (163–166) have been reported [233, 234]. Dysinosin A (163) was isolated from a new genus of sponges found near Lizard Island (Australia) [233]. Afterward, it was reisolated together with the other three dysinosins B–D from the Australian marine sponge *Lamellodysidea chlorea* [234]. Dysinosins are structurally related to the cyanobacterial metabolites aeruginosins [235–237]. Aeruginosin 98-A (162) was reported in 1994 as a thrombin and trypsin inhibitor from the cyanobacterium *Microcystis aeruginosa* [235]. Not surprisingly, dysinosins A–D also exhibited inhibitory activity against thrombin (IC$_{50}$ values of 0.17–5.1 μM) and factor VIIa (IC$_{50}$ values of 0.09–1.32 μM) [233, 234]. Dysinosins A–D (163–166) were further investigated to assess their SARs. The X-ray structural analysis of dysinosin A (163) revealed a hydrogen bonding network forming the dysinosin-A-thrombin complex [233]. The introduction of a sugar unit at C-13 in dysinosin B (164) gave a slight increase in inhibition of factor VIIa compared to both dysinosins A (163) and C (165) (0.09 μM compared to 0.108 and 0.124 μM, respectively), while selectivity relative to thrombin decreased to 1.9 compared to 4.2 and 4.4, respectively [234]. Desulfated dysinosin D (166) was found to be ten times less potent against both factor VIIa and thrombin compared to other sulfated dysinosins, indicating the importance of the sulfate group [234].
Phakellistatins and hymenamides are two groups of proline-rich cyclopeptides. They were isolated mainly from different species of the marine sponge genera *Phakellia* and *Hymeniacidon*, respectively. However, phakellistatins 1–14 and isophakellin 3 were isolated from different species of the genus *Phakellia* [238–247], and two conformers of phakellistatin 2 have been reported from the Fijian marine sponge *Stylotella aurantium* [248]. Phakellistatin 1 (167) was the first reported congener from the Indo-Pacific (Truk Archipelago) marine sponge *Phakellia costata* [238]. Phakellistatin 1 revealed moderate cytotoxicity against P388 cells (IC$_{50}$ = 9.0 μM) [238]. Amongst the reported phakellistatins to date, phakellistatins 2 (168) [239], 6 (169) [242], and 11 (170) [244] exhibited the most potent antiproliferative activity against P388 murine leukemia cell line with IC$_{50}$ values of 0.4, 0.2, and 0.2 μM, respectively. Moreover, phakellistatin 6 (169) was more active than phakellistatin 2 (168) against a panel of six human cancer cell lines, namely, ovarian (OVCAR-3), brain (SF-295), renal (A498), lung (NCI-H460), colon (KM2OL2), and melanoma (SK-MEL-5) cell lines, with GI$_{50}$ ranges of 0.02–0.09 μM [242] and 1.2–3.6 μM [239], respectively.

Hymenamides (A–K) have been isolated from the Okinawan marine sponge *Hymeniacidon* sp. [249–252]. Hymenamides A (171) and B (172) were reported in 1994, and only the latter exhibited cytotoxicity against L1210 and KB tumor cell lines.
with IC₅₀ values of 3.8 and 7.2 μM, respectively [249]. In addition to hymenamide B, only hymenamide J (174) showed cytotoxicity against L1210 and KB tumor cell lines (IC₅₀ values of 2.4 and 0.7 μM, respectively), while hymenamide H (173) exhibited cytotoxicity only against L1210 cells (IC₅₀ = 7.0 μM) [252].

Beside hymenamides, hymenistatin 1, a proline-rich cyclo-octapeptide, was also purified from the marine sponge *Hymeniacidon* sp. collected in Palau [253]. Hymenistatin 1 was active against the P388 murine leukemia cell line (IC₅₀ 3.9 μM) [253]. In addition, it was found to exert an immunosuppressive effect (both in the humoral and cellular immune responses) comparable to that of the well-known immunosuppressive agent cyclosporin [254].

From other sponges of the same order Halichondrida, axinastatins [255, 256], axinellins A–C [257, 258], and stylissamides A–D [259] have been reported.
from different species of the marine sponge genus *Axinella*, the Fijian marine sponge *Stylotella aurantium* and *Stylissa caribica*, respectively. They all exhibited mild to moderate antiproliferative activity. However, from a Jamaican collection of *Stylissa caribica*, two proline-rich cyclic heptapeptides, stylisins 1 and 2, have been isolated. In contrast to other peptides, stylisins 1 and 2 proved inactive in antimicrobial, antimalarial, anticancer, anti-HIV-1, anti-Mtb, and anti-inflammatory assays [260]. Kapakahines A–G are also proline-containing cyclic peptides isolated from a Pohnpei sponge *Cribrochalina olemda* (order Haplosclerida) [185–187]. They share a unique structural feature: two tryptophan residues (Trp-1 and Trp-2) are not linked by an amide bond but by a N–C bond from the indole nitrogen of Trp-1 to the β-indole carbon of Trp-2. Kapakahine B (175) was the first reported congener, and it exhibited moderate cytotoxicity against P388 cells (IC$_{50}$ = 5.9 μM) [185]. All other kapakahine derivatives exhibited moderate to weak cytotoxic activity [186, 187]. Their structures, however, were found to be unique and of biogenetic interest.

Haligramides A and B were also identified as proline-rich cyclopeptides from the marine sponge *Haliclona nigra* collected from the northern coast of Papua New Guinea [261]. The cyclic depsipeptides, halipeptins (A–D), were isolated from another species of the genus *Haliclona* collected in Vanuatu [262, 263]. Although, haligramides A and B exhibited moderate activity in the cytotoxicity assay against four human tumor cell lines [261], halipeptin A (176) revealed no significant results in either cytotoxicity, antifungal, antiviral, or antimicrobial assays [262].

![Chemical structure of halipeptin A](image)

Interestingly, halipeptin A (176) was found to possess potent in vivo anti-inflammatory activity, causing about 60% inhibition of edema in mice at the dose of 0.3 mg/kg (i.p.) compared to indomethacin and naproxen (ED$_{50}$ of 12 and 40 mg/kg, respectively) [262].

Recently, euryjanicins (A–D) have been reported from the Caribbean marine sponge *Prosuberites laughlini* [264, 265]. They are cycloheptapeptides containing two or three prolines, an array of apolar residues, and one or two aromatic residues. Euryjanicins A, C, and D each contain a serine residue, whereas euryjanicin B possesses one threonine unit. When tested against the National Cancer Institute 60 tumor cell line panel, all euryjanicins displayed weak cytotoxicity [265].
Theonellamides (A–F) are a group of cytotoxic peptides with novel amino acid residues and complex bicyclic macrocyclic rings isolated from the marine sponge *Theonella* sp. collected off Hachijo-jima Island (Japan) [266, 267].

![Chemical Structure](image)

Theonellamide F (177) was the first reported congener exhibiting antifungal activity against pathogenic fungi *Candida* sp., *Trichphyton* sp., and *Aspergillus* sp. at MIC values between 1.8 and 7.3 μM. It is also cytotoxic against L1210 and P388 leukemia cells with IC$_{50}$ values of 1.9 and 1.6 μM, respectively [266]. In addition, all other theonellamides (A–E) were cytotoxic against P388 cells (IC$_{50}$’s between 0.5 and 2.8 μM) [267].

Polytheonamides (A–C) are polypeptides consisting of 20 amino acid residues with unprecedented structural features. They were reported from the marine sponge *Theonella swinhoei* (Hachijo-jima Island, Japan) [268, 269]. Polytheonamides exhibited potent cytotoxic activity against P388 cells (IC$_{50}$ = 13.5–15.5 pM) [269].

Cyclotheonamides A (178) and B (179) are cyclic peptides containing unusual amino acid residues, i.e., vinylogous tyrosine (V-Tyr), α-ketohomoarginine (K-Arg), and β-linked-diaminopropionic acid (Dpr). They were isolated from the marine sponge *Theonella swinhoei* (Japan) [270] together with two additional congeners C and D [271], whereas cyclotheonamide E was isolated from a morphologically different specimen of *Theonella swinhoei* [271]. Chemical investigation of the marine sponge *Theonella* sp. collected off Tanegashima Island led to the isolation of cyclotheonamides E2 and E3 [272], while cyclotheonamides E4 and E5 were obtained from the Okinawan marine sponge *Ircinia* sp. [273]. Cyclotheonamides (A–E) and (E2–E5) were found to possess potent inhibitory activity against serine proteases including thrombin, trypsin, and plasmin [270–273]. Their mode of action was elucidated by X-ray crystallography of the complex between cyclotheonamide A (178) and human α-thrombin which disclosed that (1) the binding of 178 to the catalytic triad of the enzyme is achieved through forming a network of hydrogen bonds between the α-keto group of the K-Arg residue and the hydroxyl group of Ser195 of the enzyme, (2) V-Tyr residue proved to be involved in the bonding mechanism, and (3) cyclotheonamide D which
possesses D-Leu instead of D-Phe in 178 showed comparable activity against thrombin; thus, a further hydrophobic amino acid can replace D-Phe [271].

However, a comparative X-ray study against either human \( \alpha \)-thrombin or bovine \( \beta \)-trypsin revealed that cyclotheonamide A (178) inhibited trypsin stronger than thrombin (IC\(_{50} = 16\) and 23 nM, respectively) [272]. These results were substantiated to the more favorable (1) aromatic interaction of the D-Phe in 178 with Tyr39 and Phe41 in trypsin than with Glu39 and Leu41 in thrombin and (2) interaction of \( N \)-formyl Dpr residue with Gly174 and Gln175 in trypsin than Ile174 and Arg175 in thrombin [272]. Since the cyclotheonamides exhibited potent inhibitory activity against serine proteases, the marine sponge *T. swinhoei* has been thoroughly investigated. From a specimen collected off Hachijo-jima Island in 1993, pseudotheonamides A\(_1\), A\(_2\), B\(_2\), C, D, and dihydrocyclotheonamide A were isolated [273]. Pseudotheonamides A\(_1\) (180), A\(_2\) (181), and B\(_2\) (182) are linear pentapeptides embracing the rare piperazinone and piperidinoiminomimidazolone ring systems, while pseudotheonamide C (183) contains V-Tyr instead of a piperazinone ring. Pseudotheonamide D, a tetrapeptide lacking a \( C \)-terminal K-Arg unit and dihydrocyclotheonamide A, is a reduction product of cyclotheonamide A (178). Peptides 180–183 and dihydrocyclotheonamide A inhibited thrombin with IC\(_{50} \) values of 1.0, 3.0, 1.3, 0.19, 1.4, and 0.33 \( \mu \)M, respectively, whereas they inhibited trypsin with IC\(_{50} \) values of 4.5, >10, 6.2, 3.8, >10, and 6.7 \( \mu \)M, respectively [274]. As revealed by a SAR study of cyclotheonamides, potent inhibition of serine proteases is associated with the presence of the \( \alpha \)-keto group of K-Arg residue [270–273]. Therefore, it was not surprising that pseudotheonamides, in which the \( \alpha \)-keto group was either modified or missing, showed only moderate activity [274]. Thus, cyclotheonamides and pseudotheonamides inhibited serine proteases including trypsin and thrombin. These results suggested that cyclotheonamides and pseudotheonamides may be useful for treatment of asthma and other disorders associated with inflammation of the respiratory tract in addition to coagulatory disorders [273].
Theonellapeptolides are a group of tridecapeptide lactones characterized by the presence of high proportions of D-amino acids, N-methyl amino acids and β-amino acids. Theonellapeptolide Id (184) was the first reported congener from the Okinawan marine sponge *Theonella swinhoei* [275]. From the same specimen, theonellapeptolides (Ia–Ic, Ie, and Iid) have also been purified [276–280], whereas theonellapeptolide Iie was isolated from an Indonesian specimen of *T. swinhoei* collected using SCUBA in Baranglompo Island [281]. From the same Indonesian specimen, four cyclic depsipeptides named barangamides (A–D) have been reported [281, 282].

Biological activity of theonellapeptolides include cytotoxicity, ion-transport activity for Na⁺, K⁺, and Ca²⁺ ions [278], Na⁺, K⁺-ATPase inhibitory activity [283], and mild immunosuppressive activity [281]. However, other theonellapeptolide
(III series) exhibiting in vitro cytotoxicity against the P388 cell line (IC\textsubscript{50} = 5.2 \mu M) have also been reported from a New Zealand deep-water sponge, \textit{Lamellomorpha strongylata}, belonging to a different order compared to \textit{T. swinhoei} [284].

The cyclic depsipeptides, papuamides (A–D), were isolated from two-sponge associations of \textit{Theonella mirabilis} and \textit{T. swinhoei} collected in Papua New Guinea [285]. They contain a number of unusual amino acids including 3,4-dimethyl-glutamine, \(\beta\)-methoxytyrosine, 3-methoxyalanine, and 2,3-diaminobutanoic acid or 2-amino-2-butenoic acid residues. Papuamides also contain a previously undescribed 2,3-dihydroxy-2,6,8-trimethyldeca-(4\(Z\),6\(E\))-dienoic acid moiety linked to a terminal glycine residue. In addition, they were the first marine-derived peptides reported to contain 3-hydroxyleucine and homoproline residues [285]. Papuamides A (185) and B (186) inhibited the infection of human T-lymphoblastoid cells by HIV-1\textsubscript{RF} in vitro with an EC\textsubscript{50} of approximately 2.6 nM [285]. Papuamide A (185) was also cytotoxic against a panel of human cancer cell lines with a mean IC\textsubscript{50} of 0.05 \mu M [285].

Mirabamides (A–D) are cyclic depsipeptides structurally related to papuamides. However, mirabamides were isolated from an aqueous extract of the marine sponge \textit{Siliquariaspongia mirabilis} (Chuuk Lagoon, Micronesia), and they differ from papuamides in either being chlorinated (4-chlorohomoproline) and/or glycosylated (\(\beta\)-methoxytyrosine 4\(^{\prime}\)-O-\(\alpha\)-L-rhamnopyranside) derivatives [286]. A comparative study to determine the effects of mirabamides on HIV-1 infection was performed using two different viral strains, namely, HXB2 (T-cell-tropic virus) and SF162 (macrophage-tropic virus) in HIV-1 neutralization assay. In addition, HIV-1 envelope-mediated cell fusion assay was also carried out to determine whether the compounds act at early stages of infection, i.e., viral entry.

Results of testing mirabamides (A–D) and papuamide A revealed that mirabamides A (187), C (188), and D (189), as well as papuamide A (185) inhibit
HIV-1 envelope-mediated fusion with activities comparable to those observed in the neutralization assays [286]. Mirabamide A (187) and papuamide A (185) were found to be the most potent inhibitors in the fusion assay, with respective IC$_{50}$ values of 41 and 73 nM, while mirabamides C (188) and D (189) inhibited fusion at lower micromolar concentrations (IC$_{50}$’s between 0.14 and 3.9 μM) [286]. Mirabamide B is the only mirabamide containing a 2,3-dehydro-2-aminobutanoic acid residue instead of the 2,3-diaminobutanoic acid residue (Dab) that is present in other mirabamides as well as in papuamides A (185) and B (186). Interestingly, mirabamide B was consistently found to be less potent than other mirabamides (187–189) in both neutralization and fusion assays. Thus, the Dab residue in this class of peptides appeared to be important for anti-HIV activity [286].

As for the role of β-methoxytyrosine residue (β-OMe Tyr), mirabamide A (187), with rhamnosylated β-Tyr residue, was found to be the most potent analogue among the four mirabamides. This indicates that Tyr residues bearing substitutions at the 4’ position can be tolerated with no deleterious effect on antiviral activity and that the presence of a free 4’ hydroxyl on the Tyr unit is not essential [286]. In summary, the reported results disclosed that mirabamide A (187) is equipotent to papuamide A (185) (which also contains a β-OMe Tyr residue), whereas theopapuamide A (190), which was isolated from a Papua New Guinea lithistid sponge Theonella swinhoei and lacks a β-OMe Tyr residue, was inactive [287]. One hypothesis that would be consistent with these results is that the β-OMe Tyr residue imparts a specific conformation required for binding to target protein(s) involved in HIV-1 entry [286]. However, neither 4-chlorohomoproline nor β-methoxytyrosine 4’-O-α-L-rhamnopyranoside that are present in mirabamides affected their anti-HIV activities [286].

Celebesides A–C (193–195) and theopapuamides (B–D) together with 190 were isolated from the marine sponge Siliquariaspongia mirabilis (Sulawesi Island, Indonesia) [288].
Celebesides are unusual cyclic depsipeptides that comprise a polyketide moiety established as 7,9-dihydroxy-8,10-dimethyltrideca-2,4-dienoic acid (Ddtd) and five amino acid residues including an uncommon 3-carbamoyl threonine and a phosphoserine residue in celebesides A (193) and B (194). Celebeside A (193) neutralized HIV-1 in a single-round infectivity assay with an IC$_{50}$ value of 2.1 μM, while its nonphosphorylated analogue, celebeside C (195), was inactive at concentrations as high as 60 μM [288]. This correlates the observed anti-HIV activity of celebesides to the presence of phosphoserine in the molecule.

Theopapuamides A–C (190–192) showed cytotoxicity against HCT-116 human colon carcinoma cells in vitro with IC$_{50}$ values between 1.3 and 2.5 μM, and they also exhibited strong antifungal activity against wild-type and amphotericin B–resistant strains of Candida albicans at loads of 1–5 μg/disk [288]. However, celebesides (A–C) displayed neither antibacterial nor antifungal activities against the tested microorganisms at concentrations up to 50 μg/disk [288].

Perthamides (B–D) are further examples of cyclic depsipeptides isolated from two different collections of the lithistid sponge Theonella swinhoei [289, 290]. Perthamide B was identified as a cytotoxic peptide [289], while perthamides C (196) and D (197) lacked antiproliferative activity on KB cell line up to a dose of 10 μg/mL [290].
Interestingly, perthamides C (196) and D (197) reduced carrageenan-induced mouse paw edema significantly in vivo causing 60% and 46% reduction of edema at a dose of 300 μg/kg (i.p.) similar to halipeptin A (176) [290]. These data compare well with the most common NSAID sold in the pharmaceutical market, naproxen (ED₅₀ = 40 mg/kg), and clearly indicate that perthamides C and D in addition to halipeptin A are about 100 times more potent. Furthermore, the observed in vivo activity implies that these compounds are able to access the site of inflammation [262, 290].

The microsclerodermins (A–I) are a family of antifungal cyclic hexapeptides which have been isolated from different collections of the lithistid sponges Theonella sp. and Microscleroderma sp. [291–293]. Microsclerodermins A (198) and B (199) were the first reported members of this family from the New Caledonian lithistid sponge Microscleroderma sp. [291]. Both of them, together with microsclerodermin F, showed potent antifungal properties by inhibiting the growth of C. albicans at 2.5 and 1.5 μg/disk, respectively [291–293]. In addition, microsclerodermins F–I showed nearly similar in vitro cytotoxic activity against HCT-116 cell line (IC₅₀'s of 1.0–2.5 μM) [293].

Koshikamide A₁ (200) and A₂ are linear peptides that were isolated from the sponge Theonella sp. collected off the Koshiki-jima Island (Japan) [294, 295]. Koshikamide B (201) was isolated from two separate collections of the marine sponge Theonella sp. [296]. Koshikamide B (201) is a 17-residue peptide lactone composed of six proteinogenic amino acids, two D-isomers of proteinogenic amino acids, seven N-methylated amino acids, and two unusual amino acid residues, namely, N⁵-carbamoylasparagine and 2-(3-amino-2-hydroxy-5-oxopyrrolidin-2-yl) propionic acid. Koshikamides A₁ (200), A₂ and B (201) exhibited cytotoxicity against P388 murine leukemia cells in vitro with IC₅₀ values of 1.7, 4.6, and 0.2 μM, respectively [294–296].
Keramamides (A–J and K–N) are a group of cyclic peptides isolated from different collections of the Okinawan marine sponge Theonella sp. [297–302]. They were named after the location of the first collection of the sponge which was Kerama Island, Okinawa. Keramamides A (202) and L (208) are characterized by having an ureido bond and a 6-chloro-N-methyltryptophan residue. Keramamides B (203) and (C–E) contain an oxazole ring as a structural feature, while keramamides (F–H) and (J–K) share the presence of a thiazole ring. Keramamides M (209) and N (210) are sulfate esters of keramamides D (204) and E (205), respectively.

Most of the known keramamides feature in vitro cytotoxic activity when tested against L1210 murine lymphoma (IC_{50}'s between 0.5 and 2.3 µM) and KB human epidermoid carcinoma (IC_{50}'s between 0.45 and 6.2 µM) cell lines [299–302]. Among the tested congeners, keramamides K (207) and L (208) were the most potent derivatives with IC_{50} values of 0.77 and 0.5 µM against L1210 cells and 0.45 and 0.97 µM against KB cells, respectively [301].

202 \( R_1 = \text{OH} \)

208 \( R_1 = \text{H} \)
203

206 $R = H$
207 $R = CH_3$

204 $R_1 = H$ $R_2 = CH_3$
205 $R_1 = H$ $R_2 = C_2H_5$
209 $R_1 = SO_3H$ $R_2 = CH_3$
210 $R_1 = SO_3H$ $R_2 = C_2H_5$
Callipeltins are a group of marine peptides with unusual structural features and remarkable biological activities isolated from the marine sponges *Callipelta* sp. [303, 304] and *Latrunculia* sp. [305–307]. Callipeltin A (211) is the parent compound of this family which comprises 12 further congeners (B–M). Apart from the cyclic congeners, callipeltins A and B, all the other callipeltins are linear derivatives structurally related to callipeltin C (212) which, in turn, represents the acyclic counterpart of callipeltin A (211). Structurally, the most distinctive feature of callipeltins is the presence of several nonproteinogenic units while from a biological point of view, callipeltin A displays a broad range of bioactivities, including antiviral, antifungal, and cytotoxicity against several human tumor cell lines and regulatory activity of the myocardial force of contractions [303–309]. The unusual structural features of callipeltins and the interesting biological activities have aroused considerable interest among the synthetic chemistry community.

As a result, all nonproteinogenic units in this group of metabolites, namely, (3S,4R)-3,4-dimethyl-L-pyroglutamic acid (the N-terminus unit in callipeltin B) [310], (2R,3R,4S)-4-amino-7-guanidino-2,3-dihydroxyheptanoic acid [311], (2R,3R,4R)-3-hydroxy-2,4,6-trimethylheptanoic acid [312] linked to the N-terminus of callipeltins A, C, D, and F–I; and (R)-β-methoxy-D-tyrosine were obtained in a stereoselective manner [313].
Homophymine A (213) was isolated as the principal active constituent of the New Caledonian lithistid sponge *Homophymia* sp. [314]. Homophymine A is a cyclic depsipeptide structurally related to other aforementioned marine peptides isolated from the order Lithistida such as callipeltin A, papuamides, theopapuamides, and mirabamides which are well known for their potent HIV-inhibitory activity. In addition to the common structural features, homophymine A (213) contains two hitherto unprecedented residues, i.e., the 4-amino-2,3-dihydroxy-1,7-heptandioic acid and 2-amino-3-hydroxy-4,5-dimethylhexanoic acid. Homophymine A exhibited cytoprotective activity against HIV-1 infection with an IC₅₀ of 75 nM [314]. Recently, nine additional homophymines, namely, B–E (214–217) and A1–E1 (213a–217a) have been isolated from the same sponge [315]. From the structural point of view, homophymines (A1–E1) feature the 4-amino-6-carbamoyl-2,3-dihydroxyhexanoic acid residue compared to the corresponding (A–E) possessing the same residue in its carboxy form.
All homophymines were subjected to an antiproliferative activity assay against a wide panel of cell lines including human and simian cancer and noncancer cells and displayed potent cytotoxicity (IC$_{50}$ values between 2 and 100 nM) [315]. A comparison of activities against different tumor cell lines showed a moderate selectivity toward PC3 human prostate and OV3 ovarian carcinoma cell lines. However, when the sensitive and their resistant counterpart cell lines were compared (MCF7/MCF7R, HCT116/HCT15, HLC60/HL60R), no significant difference was observed [315]. Homophymine A1–E1 (213a–217a) exert stronger biological activity compared to the corresponding congeners A–E (213–217) [315]. Further extensive biological investigations were carried out to distinguish whether the homophymines possess antiproliferative and/or acute toxic activity. The results strongly suggested that the toxic effect of homophymines was due to an acute and a nonspecific toxicity toward various tested human cell lines [315].

Azumamides A–E (218–222), isolated from the Japanese marine sponge *Mycale izuensis*, are five cyclic tetrapeptides that exhibit potent histone deacetylase (HDAC) inhibitory activity (IC$_{50}$’s of 0.045–1.3 μM) [316]. Furthermore, azumamide A (218) at a concentration of 19 μM significantly inhibited angiogenesis [316]. Only few examples of marine HDAC inhibitors are known up to date such as psammaplin A (PsA, 109) (see Section 4.2.3) obtained from marine sponge *Pseudoceratina purpurea* [133], whereas azumamides A–E (218–222) were the first examples of cyclic peptides with HDAC inhibitory activity isolated from marine organisms.
After the crystal structure of the complex between a HDAC-like protein and the HDAC inhibitor, trichostatin A (TSA) [317], had been solved, interesting insights into the binding modes of HDAC inhibitors were disclosed [318]. According to the TSA structure, a plausible binding mode to the enzyme is by inserting the long aliphatic chain of TSA into the hydrophobic pocket of the enzyme. Then, the terminal hydroxymic group coordinates with a zinc ion at the polar bottom of the pocket while the aromatic dimethylaminophenyl portion of TSA makes contact with the pocket entrance and an adjacent surface group thereby capping the pocket. Trapoxin A [319] and apicidin [320] are the parent congeners of two classes of HDAC inhibitory cyclic tetrapeptides containing groups that may be analogous to the aliphatic side chain of TSA. Trapoxins possess a 2-amino-8-oxo-9,10-epoxy-decanoic acid, in which the epoxide moiety is thought to bind irreversibly to the enzyme [317], while the apicidins comprise a 2-amino-8-oxo-decanoic acid, with the keto group being responsible for zinc chelation [321].

The corresponding terminal function for azumamides is probably the amide or the carboxylate group. Despite that the affinity of an amide group to zinc is much weaker than that of a carboxylic acid, azumamides A (218) and B (219) with an amide end showed equivalent levels of HDAC inhibitory activity as C (220) and E (222) congeners, which have carboxylate functionality [316].

In conclusion, many peptides from marine sponges showed potent activities such as antitumoral, antiviral, immunosuppressive, antifungal as well as cardiac stimulant properties. However, these bioactivities cannot clearly explain their in situ role inside the marine sponges. Interestingly, the most striking feature of this class of metabolites is the preponderance of nonproteinogenic amino acids suggesting that these metabolites are the result of the NRPS/PKS pathways of microorganisms, proposing that symbiotic microorganisms, including cyanobacteria, are the real producers of these metabolites. Therefore, the symbiotic associations within sponges and other marine invertebrates need further intensive research which will ultimately unravel the innate sources of these bioactive metabolites.

4.4 Terpenes

Terpenes include primary and secondary metabolites, all biosynthesized from the five carbon isoprene building units [322]. Structural modification of these isoprene units leads a massively diverse range of derivatives with a wide array of chemical structures and biological properties. Steroidal terpenoids were the first marine isoprenes to be discovered by Bergmann during the 1930s–1940s, particularly sterols that were obtained from various marine macroorganisms [323]. Since then, a huge number of terpenoidal secondary metabolites have been obtained from marine resources. In addition to our recent review on this topic [324], we will survey two major classes of marine isoprenes from sponges, namely, the sesterterpenoids (C25) and triterpenoids (C30) with particular attention of their biological activities.
4.4.1 Sesterterpenes (C25)

Manoalide (223) is the parent compound of a series of marine sponge metabolites belonging to the sesterterpene class. Manoalide was first reported in 1980 by Scheuer from the marine sponge *Luffariella variabilis* (class Demospongiae; order Dictyoceratida; family Thorectidae) collected in Palau [325] with activity as an antibiotic against *Streptomyces pyogenes* and *Staphylococcus aureus*. One year later, Scheuer reported three additional related metabolites from the same Palauan sponge, namely, secocomanoalide (224), *(E)*-neomanoalide (225), and *(Z)*-neomanoalide (226) [326].

All three compounds, as well as the parent compound (223), displayed antibacterial activity against Gram positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) but were inactive against *Escherichia coli*, *Pseudomonas aeruginosa* and *Candida albicans* [326].

Later, marine sponges belonging to the family Thorectidae, including species of the genera *Luffariella* [327–339], *Hyrtios* [340, 341], *Thorectandra* [342], *Cacospongia* [343, 344], *Fasciospongia* [345–348], *Acanthodendrilla* [349], and *Aplysinopsis* [350], were also found to be rich sources of novel bioactive sesterterpenoids related to manoalide.

Manoalide was further investigated and found to be a potent inhibitor of phospholipase A2 (PLA2) [351–358]. Subsequently, many structurally related metabolites with PLA2 inhibitory activity were also reported [328, 359–365]. PLA2 is an enzyme that specifically catalyzes the hydrolysis of phospholipids at the *S*-2 position to produce a lysophospholipid and arachidonic acid, which in turn provides the substrate for proinflammatory mediators such as leukotrienes, prostaglandins, and thromboxanes, collectively known as the eicosanoids [361]. Since manoalide revealed an irreversible inhibition of phospholipase A2 (PLA2) [353], the structure-activity relationships (SAR) of this compound attracted scientific interests to study...
and to understand both PLA₂ function and mechanism of action in the whole cell. Therefore, several studies were successfully performed to determine the contributions of the various functional groups incorporated in 223 and its analogues, such as the γ-hydroxybutenolide, α-hydroxydihydropyran, and trimethylcyclohexenyl ring systems, to the efficacy as PLA₂ inhibitors [356, 361, 365]. These studies indicated that (1) the existence of the hemiacetal in the α-hydroxydihydropyran ring is crucial for irreversible binding, (2) the γ-hydroxybutenolide ring is involved in the initial interaction with PLA₂, and (3) the hydrophobic nature of the trimethylcyclohexenyl ring system allows nonbonded interactions with the enzyme that enhances the potency of these analogues. These studies suggested that the closed ring form of manoalide is the predominant molecular moiety that accounts for the selective and potent inhibition of PLA₂ [356].

Manoalide analogues also exhibited other bioactivities including molluscidical [330], cytotoxicity [333, 334, 336, 340, 343, 346, 349, 350, 367–369], inhibitory activity of Cdc25 phosphatase [366], nicotinic antagonistic activity [332], and fish deterrent properties [346, 369]. Therefore, chemical synthesis and derivatization of manoalide attracted much interest leading to a better understanding of the structure-activity relationships (SAR) and/or for the plausible mechanism of action [355, 358–360, 363, 364, 370, 371]. Manoalide (223) was licensed to Allergan Pharmaceuticals and reached phase II clinical trials as a topical antipsoriatic. Its development was, however, discontinued due to formulation problems. The compound is now commercially available as a biochemical standard tool to block the action of PLA₂ [372].

Luffariellolide (227) is a sesterterpenoid analogue of secomanoalide (224), which was first reported from a Palauan sponge Luffariella sp. [328]. Structurally, luffariellolide differed in having C-24 as methyl group instead of an aldehyde functionality as in secomanoalide, and it was obtained as the (Z) isomer as well.
In contrast to the irreversible inhibitory action of manoalide (223) toward PLA$_2$, luffariellolide (227) is a slightly less potent but a partially reversible inhibitor. This meant that 227 became a more preferable anti-inflammatory agent for potential pharmacological investigation [328]. In addition to luffariellolide (227), its 25-$O$-methyl (228) and 25-$O$-ethyl derivatives (229), five related sesterterpenes, acantholides (A–E), were obtained from the Indonesian sponge *Acanthodendrilla* sp. [349]. Acantholide D (230) and E (231) represent rare variants for the C$_{14}$–C$_{20}$ segment in this type of linear sesterterpenes in which they have the 1-acetylcyclopentan-5-ol moiety replacing the trimethylcyclohexenyl ring. Luffariellolide (227) and its 25-$O$-methyl congener (228), as well as acantholide E (231), were cytotoxic against the mouse lymphoma L5178Y cell line with IC$_{50}$ values of 8.5, 1.8, and 16.8 $\mu$M, respectively. Interestingly, these results suggest that the 25-$O$-methyl group in 228 and the stereochemistry of 1-acetylcyclopentan-5-ol in 231 play an important role [349]. Luffariolides (A–J) represent a related group of sesterterpenoidal analogues, which have been obtained from different collections of the Okinawan marine sponge *Luffariella* sp. [333, 334, 336].

All luffariolides exhibited significant cytotoxicity against murine lymphoma L1210 cells with IC$_{50}$ values ranging between 2.9–19.3 $\mu$M. Among them, luffariolides A (232, IC$_{50}$ 2.9 $\mu$M), B (233, IC$_{50}$ 3.23 $\mu$M), E (234, IC$_{50}$ 3.0 $\mu$M), and F (235, IC$_{50}$ 3.8 $\mu$M) were the most active ones [333, 334, 336].
Luffariellins A (236) and B (237) [327] together with their respective 25-acetoxy derivatives (240 and 241) [338] were isolated from the marine sponge *Luffariella variabilis* collected off different locations in Palau and in Australia, whereas luffariellins C (238) and D (239) were obtained from the shell-less marine mollusc *Chromodoris funerea* collected from the Kaibakkulake shores in Palau [373].

![Chemical structures of luffariellins and luffarins](image)

Luffariellins (236–241) are all characterized by the 1-isoproprenyl-2-methylcyclopentane ring system replacing the trimethylcyclohexenyl moiety in other manoalide analogues. Despite this discrepancy in chemical structure, luffariellins A (236) and B (237) retain identical functional groups as present in manoalide (223) and secomanoalide (224), respectively. Therefore, not surprisingly, each respective pair was shown to have similar anti-inflammatory properties to 223 and 224 [327]. Luffarin metabolites comprise another group of compounds represented by 28 derivatives. Twenty-six of them, luffarins (A–Z), have been reported from the Australian marine sponge *Luffariella geometrica* [332], while the other two were obtained from the Adriatic Sea sponge *Fasciospongia cavernosa* [348]. Based on the chemical structures, luffarins have been classified into 14 bicyclic sesterterpenes, luffarins (A–N); one bicyclic bisnorsesterterpene, luffarin O; one monocyclic sesterterpene, luffarin P; and six acyclic sesterterpenes, luffarin (Q–V), in addition to four diterpenoidal derivatives, luffarin (W–Z) [332]. All luffarins were tested for antimicrobial activity against *Staphylococcus aureus*, *Micrococcus* sp., and *Saccharomyces cerevisiae*. Only luffarins C–F (244–247), K (248), and L (249) showed activity against both *S. aureus* and *Micrococcus* sp. [332], whereas luffarins
A (242) and M (250) revealed only mild activity against the latter. Moreover, some luffarins were also found to be effective inhibitors of nicotinic receptors [332].

Biosynthetically, a relationship could be recognized between the various luffarins as illustrated in Scheme 4.5. Luffarins appear to belong to the same enantiomeric series as reported for manoalide-type marine natural products. It is also curious to note that no acyclic luffarins incorporated the hydroxylated butenolide functionality. Perhaps the most interesting luffarins from a biosynthetic point of view are luffarins B (243) and O (243a), which were the first examples of a hitherto unknown cyclization pattern in compounds of this class [332].

Another example of bicyclic sesterterpenes are thorectandrols A–E (253–257) that were isolated from a Palauan collection of the marine sponge *Thorectandra* sp. [367, 368] together with the parent compounds of this group palauolide (251) and
palauolol (252). Palauolide (251) was obtained first as an antimicrobial sesterterpene from a three-sponge association collected in Palau [374], while palauolol (252) was identified as an anti-inflammatory sesterterpene from the Palauan sponge *Fascaplysinopsis* sp., and chemically, it was recognized as being a secondary alcohol that upon dehydration yields 251 [375].

All thorectandrols (253–257) in addition to palauolide (251) and palauolol (252) were tested for antiproliferative activity against 6 to 12 human tumor cell lines depending on sample availability [368]. Palauolol (252) was active against all tested cell lines except A549 (non-small cell lung cancer), with IC₅₀ values in the range 1.2–1.7 μM, while palauolide (251) showed a diminished activity. On the other hand, thorectandrols (A–E) revealed only weak to no cytotoxicity against the tested cell lines (IC₅₀'s 70–100 μM). While firm deductions on the structural requirements for activity were not possible, it appeared that the presence of both the hemiacetal lactone functionality and the 16-hydroxyl group in palauolol (252) enhanced cytotoxicity compared to palauolide (251) and other thorectandrols [368].

Cacospongionolides (258–262) were isolated from different collections of the marine sponge *Fasciospongia cavernosa* (= *Cacospongia mollior*) collected from the Mediterranean Sea [343, 346, 369, 376]. Cacospongionolides A (258), B (259), and its 25-deoxy derivative (260) revealed a bicyclic sesterterpenoidal skeleton, resembling luffarins and thorectandrols, with the addition of a γ-hydroxybutenolide moiety. The other cacospungionolides C (261) and D (262) are acyclic diterpenoidal derivatives. Despite the structural relation with luffarins and thorectandrols, cacospungionolides (258–260) together with cacospungionolide D (262) exhibited significant cytotoxicity [343, 346, 369, 376]. This notion
suggested a possible relation between the presence of the γ-hydroxybutenolide moiety and the cytotoxicity.

Petrosaspongiolides A (263) and B (264) were the first cheilantane sesterterpene lactones to be isolated from a New Caledonian sponge incorrectly assigned to the genus Dactylospongia [377] and then reassigned as a new genus and a new species: Petrosaspongia nigra (Bergquist 1995 sp. nov., class Demospongiae; order Dictyoceratida; family Spongidae) [378]. From another New Caledonian collection of the same sponge, 15 additional petrosaspongiolide congeners (C–R) were isolated [379, 380].
From the chloroform extract of another Dictyoceratida sponge of the genus *Spongia*, 21-hydroxy derivatives of petrosaspongolides K (266a) and P (270a) were isolated in addition to four other pyridinium alkaloids named spongidines A–D (273–276) [381]. Spongidines were found to be structurally related to petrosaspongolide L (267) particularly in the presence of pyridine ring. Petrosaspongolides (A–L) were subjected to in vitro cytotoxicity assay against the human bronchopulmonary NSCLC-N6 carcinoma cell line. They revealed IC\textsubscript{50} values ranging between 1.0–32.2 \textmu M [379]. Petrosaspongolides C (265) and K (266) exhibited the highest potency with IC\textsubscript{50} values of 1.0 and 3.5 \textmu M, respectively. However, petrosaspongolides A (263) and B (264) were the least cytotoxic congeners in vitro with IC\textsubscript{50} values of 28.0 and 32.2 \textmu M, respectively; 263 inhibited tumoral proliferation in vivo at 20 mg/kg without significant toxicity when tested on immunosuppressed rats carrying a bronchopulmonary tumor (NSCLC-N6) [379].
Petrosasponiolides M–R (268–272) revealed the presence of a γ-hydroxybutenolide moiety and a hemiacetal function. Due to these structural similarities to manoalide (223), petrosasponiolides (M–R) have received special attention from the scientific community to study their inhibitory activity against PLA2 from different resources to point out their specificity. Two main groups of PLA2 enzymes have been reported [382], the secretory PLA2 (sPLA2 groups I, II, III, V, IX, and X with relatively small molecular weights) and the cytosolic PLA2 (cPLA2 groups IV, VI, VII, and VIII with higher molecular weights). Inhibition of specific PLA2 constitutes a potentially useful approach for treating a wide variety of inflammatory disorders such as septic shock, adult respiratory distress syndrome, arthritis, and acute pancreatitis [381]. Petrosasponiolides M–R (268–272) together with 21-hydroxy derivatives of petrosasponiolides K (266a) and P (270a), and spongidines A–D (273–276) were tested on five different sPLA2s belonging to the groups I (Naja naja venom and porcine pancreatic enzymes), II (human synovial recombinant and rat air-pouch secretory enzymes), and III (bee venom enzyme) [380, 381].

Among petrosasponiolide derivatives, 268 and 270a inhibited mainly human synovial PLA2 with IC50 values of 1.6 and 5.8 μM, respectively, compared to manoalide (223) (IC50 = 3.9 μM) [380, 381]. Petrosasponiolide M (268) also inhibited bee venom PLA2 enzyme with IC50 of 0.6 μM, compared to 223 (IC50 of 7.5 μM) [380]. The mechanism of action of petrosasponiolides M–R (268–272) as anti-inflammatory marine metabolites has been the topic for many research articles [383–388]. The covalent binding of 268 to bee venom PLA2 has been investigated by mass spectrometry and molecular modeling. The mass increment observed was consistent with the formation of a Schiff base by reaction of a PLA2 amino group with the hemiacetal function at the C-25 atom of the petrosasponiolide M γ-hydroxybutenolide ring [383]. The molecular mechanism of inactivating the bee venom and the human type IIA secretory PLA28 by petrosasponiolides R (272) [387] and M (268) [388], respectively, has been investigated. In both cases, either covalent (imine formation) and/or noncovalent (van der Waals) interactions contributed to the inhibitory activity against PLA2 enzymes [387, 388]. Due to potent anti-inflammatory properties of petrosasponiolides, their chemical synthesis has been investigated. Recently, the first enantioselective synthesis of petrosasponiolide R (272) has been successfully performed [389].
4.4.2 Triterpenes (C$_{30}$)

Steroidal triterpenes were the first marine isoprenes to be discovered in the 1930s. Scientific interest has been driven toward these metabolites due to the isolation of biosynthetically unprecedented derivatives possessing a broad spectrum of bioactivity (ies). Marine triterpenoids have been reported from various marine macroorganisms. In this section, we survey two examples of triterpenoidal metabolites, namely, isomalabaricane triterpenes and steroidal saponins obtained from marine sponges, with particular attention being drawn to their pharmacological significance.

4.4.2.1 Isomalabaricane Triterpenes

Malabaricol (277) is the chief triterpene constituent of a yellow pigment obtained from the wood of the terrestrial plant _Ailanthus malabarica_ (family Simaroubaceae), after which the whole group of related compounds was named [390–392]. Malabaricane, the trivial name of this group of compounds, was given to the hydrocarbon system (3$S^*,3aR^*,5aS^*,9aS^*,9bS^*$)-3a,6,6,9a-tetramethyl-3-(1,5,9-trimethyldecyl) perhydr-obenz[e]indene, where the tricyclic nucleus has a _trans-anti-trans_ ring junction [391, 392].

![Chemical Structure](image)

The malabaricanes are structurally characterized by a tricyclic triterpenoid core and a conjugated polyene side chain [390–392], whereas the isomalabaricane skeleton is embedded in a 4,4,8,10-tetramethyl-perhydrobenz[e]indene with a _trans-syn-trans_ ring junction, that leads to an unfavorable twist-boat conformation for the central ring [393, 394]. Isomalabaricane triterpenes were first reported from a Fijian collection of the sponge _Jaspis stellifera_ [393] and the Somalian marine sponge _Stelletta_ sp. [394]. Since then, they have been isolated from several genera of marine sponges belonging to the order Astrophorida including members of the genera _Rhabdastrella_ [395, 400, 402, 406, 413, 414, 416, 420], _Stelletta_ [397–399, 405, 408, 412], _Jaspis_ [401, 407, 409, 418, 419, 421, 422], and _Geodia_ [403, 410, 415]. Isomalabaricane triterpenoids having polyene conjugated functionality can be classified into three groups: (1) stelletins principally possessing the $\gamma$-pyrone functionality, which could be ring-opened in some of its congeners yielding the side chain with terminal free carboxylic acid and methyl moieties, (2) stelliferins oxygenated at C-22, and (3) globostellatic acids whose main feature is a carboxyl group at C-4. In addition to triterpenoids, the isomalabaricane core has also been recognized in some sesqui- and/or sesterterpenes. The isomalabaricane terpenoids were sometimes trivially named according to their sponge origin. Upon light exposure, the isomalabaricane-type terpenes readily isomerize at the C-13 position.
Therefore, during isolation and characterization processes, they rapidly equilibrate into a 1:1 mixture of the $13E$ and $13Z$ isomers [398–400, 408, 409, 418, 419]. Nevertheless, these compounds continue to gain a great deal of attention because of their significant cytotoxic activity [399, 409], whereas the nature of the natural isomer, either $13E$ or $13Z$ or both, is still unresolved. Recently it was reported that the $^1H$ NMR spectrum of a crude extract obtained from the fresh sponge *Rhabdastrella* aff. *distinca* (Hainan, the South China Sea) revealed that it mostly contained isomalabaricanes with the $13E$-configuration (H-15 of most derivatives appeared around 7.0 ppm). Thus, the $13Z$ isomers were suggested in this case to be formed through isomerization during the isolation and analytical procedures [406].

Stelletins comprise the first group of isomalabaricane-type triterpenoids. Stelletin A (278) was recognized in 1981 as a yellow triterpenoidal pigment from the Fijian marine sponge *Jaspis stellifera* [393]. Later, it was obtained together with its $E$ isomer, stelletin B (279), from the marine sponge *Stelletta tenuis* collected off Hainan Island, China [397]. Stelletin A (278) revealed significant cytotoxicity against murine leukemia P388 cell line with IC$_{50}$ of 2.1 nM [397].

Stelletin G (284), with an opened $\gamma$-pyrone and featuring terminal -COOH and -CH$_3$ functionalities, was isolated together with 278 from *J. stellifera* [393]. Later, stelletins G (284) was reported from the Australian marine sponge *Stelletta* sp. together with stelletins E (282) and F (283) [398]. The $E$ isomer of stelletin G (284) was isolated from the marine sponge *Rhabdastrella globostellata* collected from the South China Sea, and it was given the trivial name rhabdastrellic acid–A (285)
Research interests have been intensively driven toward this group of triterpenoidal derivatives, which led to the isolation of eight further stelletins C, D, and H–M [398–400, 402, 405] in addition to 22,23-dihydrostelletin D [401].

Rhabdastrellins A–F (286–291), along with stelletins L (292) and M (293), were obtained from the marine sponge Rhabdastrella aff. distinca collected from a coral reef off Hainan in the South China Sea [406]. Four of the rhabdastrellins (286–289) exhibited a primary alcohol moiety at C-29 instead of a methyl group as for the stelletins and the other two rhabdastrellins E (290) and F (291). All rhabdastrellins and stelletins L and M share a hydroxyl group at C-3 instead of a carbonyl group as in other stelletins [406]. The antiproliferative profile of stelletins A–F (278–283) has been examined at the National Cancer Institute (NCI, Australia) against 60 cell lines. Due to the rapid isomerization upon light exposure, stelletins were tested as isomeric pairs. Stelletin C(280)/D(281) pair was the most potent derivative with a mean panel GI50 of 0.09 μM. The stelletin E(282)/F(283) pair was approximately ten times less potent (mean GI50 of 0.98 μM) [399]. Apoptotic cell death is a stress response of cells to cytotoxic agents that might be executed either through a receptor-mediated pathway that activates caspase-8 or through a receptor-independent pathway that involves the cyclin-kinase inhibitors p53/p21. Both pathways lead to a translocation of proapoptotic Bax protein to the mitochondria, thereby resulting in a dissipation of mitochondrial membrane potential, activation of caspase-3, and execution of the apoptotic machinery [404].
Stelletin A (278) demonstrated a differential cytotoxicity against human leukemia HL-60 cells (IC\textsubscript{50} 0.9 \textmu M) compared to human prostate cancer LNCaP cells (IC\textsubscript{50} 260 \textmu M) by activation of NADPH oxidase, which induces oxidative cell death through a FasL–caspase-3-apoptotic pathway [403]. Stelletins B (279) and E (282) revealed selective cytotoxicity toward p21-deficient human colon tumor HCT-116 cells with IC\textsubscript{50} values of 0.043 and 0.039 \textmu M, respectively [400]. Stelletins L (292) and M (293) exhibited selective cytotoxicity against stomach cancer AGS cells with IC\textsubscript{50} values of 3.9 and 2.1 \textmu M, respectively [405]. Rhabdastrellic acid–A (285) also inhibited proliferation of human leukemia HL-60 cells with an IC\textsubscript{50} value of 1.5 \textmu M through inhibition of the PI3K/Akt pathway and induction of caspase-3–dependent apoptosis [396]. Only rhabdastrellin A (286) possessed moderate inhibitory activity toward human leukemia HL-60 cells (IC\textsubscript{50} = 8.7 \textmu M) while other rhabdastrellins were inactive (IC\textsubscript{50} > 20 \textmu M) [406].

Stelliferins are the second group of isomalabaricane triterpenes. To the best of our knowledge, 13 compounds belonging to this group have been reported. In addition to stelliferins A–F (294–299), which have been isolated from the Okinawan marine sponge Jaspis stellifera [407], stelliferin G (300) and 29-hydroxy derivatives of stelliferins A (301) and E (302) have been isolated from an unidentified species of the genus Jaspis collected near Tonga [409].

The 29-hydroxy derivative of stelliferin D (303) together with 3-epimeric isomers of 301 and 302 were reported from the marine sponge Stelletta globostellata collected by SCUBA off Mage-jima Island, Japan [408], whereas stelliferin riboside (294a), the first example of a glycosylated stelliferin, was isolated from the Fijian sponge Geodia globostellata [410].
Stelliferins A–F (294–299) exhibited potent in vitro antineoplastic activities against murine lymphoma L1210 cells (IC$_{50}$ of 1.1–5.0 μM) and human epidermoid carcinoma KB cells (IC$_{50}$ of 2.8–13.0 μM) [407], while the isomeric mixture of stelliferin G (300) and 29-hydroxystelliferin A (301) showed the highest inhibitory activity against the melanoma MALME-3 M cell line with IC$_{50}$ values of 0.2 and 0.4 μM, respectively [409]. Stelliferin riboside (294a) displayed moderate cytotoxicity against ovarian A2780 cancer cells (IC$_{50}$ = 60 μM) [410].

Due to the significant antiproliferative activity exhibited by stelletins and stelliferins, research efforts have been directed toward their chemical synthesis. In 1999, Raeppel et al. successfully synthesized the common trans-syn-trans perhydrobenz[e]indene moiety in the isomalabaricane-type terpenoids, which enabled the chemical synthesis of stelletins and stelliferins [411].

Globostellatic acid (304) is the prototype of the third group of isomalabaricane-type triterpenoids sharing carboxylation at C–4. It was first isolated together with three other derivatives, globostellatic acids (B–D), from the marine sponge Stelletta globostellata collected off Mage Island near Kagoshima, Japan [412]. Other globostellatic acid congeners, (F–M), and X methyl esters, have been reported from different collections of the Indonesian marine sponge Rhabdastrella globostellata [413, 414]. Globostellatic acids revealed potent cytotoxicity similar to the stelletins and stelliferins. Globostellatic acids (A–D) demonstrated significant cytotoxicity against murine leukemia P388 cells with IC$_{50}$ values of 0.2–0.8 μM [412]. For cytotoxicity toward mouse lymphoma L5178Y cells, the 3-O-deacetyl congeners, globostellatic acids H/I (305/306) were the most active with an IC$_{50}$ of 0.31 nM. However, acetylation of the C-3 hydroxyl group decreases its bioactivity abruptly, as in globostellatic acids J/K (307/308), with an IC$_{50}$ of 8.28 nM. The reverse was found for the 13Z isomer of stelliferin riboside (294a) that revealed higher activity than its 3-O-deacetyl congener with IC$_{50}$ values of 0.22 and 2.40 nM, respectively [413].

On the other hand, globostellatic acids showed only moderate or no cytotoxicity against either human cervix carcinoma HeLa or rat pheochromocytoma PC-12 cell lines [413]. Two globostellatic acid X methyl esters (309 and 310), possessing the 13E-geometry, inhibited proliferation of human umbilical vein endothelial cells
(HUVECs), 80- to 250-fold greater in comparison to several other cell lines and hence inhibited angiogenesis which, if pathologically uncontrolled, accompanies several diseases such as atherosclerosis, arthritis, diabetic retinopathy, and cancer. $13E,17E$-Globostellatic acid X methyl ester (309) also inhibited basic fibroblast growth factor (bFGF)-induced tubular formation and vascular endothelial growth factor (VEGF)-induced migration of HUVECs. In addition, 309 induced apoptosis of HUVECs without affecting their VEGF-induced phosphorylation of ERK1/2 kinases [414].

Geoditins, which are stelliferin-related isomalabaricane triterpenoids, are mainly oxygenated at both C-22 and C-25. Five geoditins (311–315) were obtained from the marine sponges Geodia japonica [415] and Rhabdastrella aff. distinca [416] collected at different locations in the South China Sea.

\[
\begin{align*}
304 &= \\
305 &= R = H \Delta^{13(14)}E \\
306 &= R = H \Delta^{13(14)}Z \\
307 &= R = \text{OCOCH}_3 \Delta^{13(14)}E \\
308 &= R = \text{OCOCH}_3 \Delta^{13(14)}Z \\
309 &= \Delta^{17(20)}E \\
310 &= \Delta^{17(20)}Z \\
311 &= R_1, R_2 = O, \Delta^{13(14)}E = Z, \Delta^{23(24)}E = E \\
312 &= R_1 = H, R_2 = \text{OAc}, \Delta^{13(14)}E = Z, \Delta^{23(24)}E = E \\
313 &= R_1, R_2 = O, \Delta^{13(14)}E = Z, \Delta^{23(24)}E = Z \\
314 &= R_1, R_2 = O, \Delta^{13(14)}E = E, \Delta^{23(24)}E = Z \\
315 &= R_1 = H, R_2 = \text{OAc}, \Delta^{13(14)}E = Z, \Delta^{23(24)}E = Z
\end{align*}
\]
Geoditins (311–315) were submitted for bioassays against several human tumor cell lines including HL-60 (promyelocytic leukemia), PC-3MIE8 (prostate carcinoma), BGC-823 (gastric carcinoma), MDA-MB-423 (breast carcinoma), Bel-7402 (hepatocellular carcinoma), and HeLa (cervical carcinoma) cells. Isogeoditin A (313) showed significant cytotoxicity toward the former three cell lines with IC_{50} values of 0.3, 0.2, and 1.0 μM, respectively. 13E-isogeoditin A (314) revealed no cytotoxic activity, implying that the Z-geometry at C-13 enhances antiproliferative activity compared to the E-form [416]. Geoditin A (311) proved to be cytotoxic against HL-60 cells (IC_{50} = 6.7 μM), while geoditin B (312) exhibited relatively weak cytotoxicity. Mechanistically, geoditin A (311) markedly induced reactive oxygen species (ROS), decreased mitochondrial membrane potential, and mediated a caspase-3 apoptosis pathway [417].

Jaspiferals (316–325) and aurorals (326–329) are isomalabaricane-type terpenoids differentiated into nortriterpenoids, norsesterterpenoids, and norditerpenes possessing a 3α-hydroxy group. Jaspiferals A–G (316–322) were purified from the Okinawan marine sponge Jaspis stellifera [418], while the 3-O-acetyl and methyl ester derivatives of jaspiferals B (323), D (324), and E (325) were obtained from a new species of Jaspis collected at the Vanuatu Islands [419]. Aurorals (326–329) have been isolated from the New Caledonian marine sponge Rhabdastrella globostellata [420]. Jaspiferals A–G (316–322) exhibited in vitro cytotoxicity against murine lymphoma L1210 cells with IC_{50} values of 1.6–10.4 μM, whereas only jaspiferals E–G (320–322) revealed antineoplastic activity against human epidermoid carcinoma KB cells (IC_{50} of 5.2–14.7 μM) [418]. Jaspiferol G (322) exhibited antifungal activity against Cryptococcus neoformans (MIC, 144 μM) and Trichophyton mentagrophytes (MIC, 36 μM) and antibacterial activity against Sarcina lutea (MIC, 144 μM), while the mixture of jaspiferals E (320) and F (321) showed antifungal activity against T. mentagrophytes (MIC, 134 μM) [418]. On the other hand, the 3-O-acetyl, methyl ester derivatives of jaspiferals B (323), D (324), and E (325) revealed weak cytotoxicity against L1220 cells (IC_{50} > 8.8 μM) [419].
Aurorals (326–329), which differ from jaspiferals C–F (318–321) by the presence of a primary alcohol group at the C-4 position, exhibited stronger cytotoxicity against KB cells. The isomeric mixtures of aurorals (326/327), (328/329), and jaspiferals C/D (318/319) showed IC\textsubscript{50} values of 0.5, 22.2, and 13.3 μM, respectively, while jaspiferals E/F (320/321) were inactive up to 27 μM [420].

Jaspolides represent another example of isomalabaricane-type terpenoids of either monomeric or dimeric congeners. Monomeric congeners of jaspolides could be classified into triterpenes, jaspolides A (330) and B (331); sesterterpene, jaspolide F (335); diterpenes, jaspolides C (332) and D (333); and nortriterpene, jaspolide E (334) which were all isolated from the marine sponge Jaspis sp. collected from the South China Sea [421]. A presumable biogenetic transformation scheme of jaspolides A–F (330–335) (Scheme 4.6) revealed that light-induced isomerization is responsible for the jaspolides A/B (330/331) and C/D (332/333) isomeric pairs. In addition, it substantiated jaspolide D (333) as a precursor to jaspolide F (335), formed through condensation with an isoprenyl pyrophosphate (IPP) followed by oxidation at a terminal methyl group [421]. Jaspolides G (336) and H (337) are dimeric isomalabaricane congeners which were isolated from the same Chinese sponge Jaspis sp., and their proposed biogenetic pathway (Scheme 4.7) suggested that they were derived from stelletin A (278) yielding the left moiety and the nortriterpene, geoditin A (311) yielding the right moiety [422].

Jaspolide B (331) arrested HL-60 cells in the G\textsubscript{2}/M phase of the cell cycle and induced apoptosis in a dose- and time-dependent manner. Jaspolide B with an IC\textsubscript{50} value of 0.61 μM exhibited a comparable efficacy to that of paclitaxel (IC\textsubscript{50} = 0.78 μM). These results suggested 331 to be a promising anticancer agent for chemotherapy of leukemia by prohibiting cell cycle progression at the G\textsubscript{2}/M phase and triggering apoptosis [423].

In a further study with human hepatoma cells, jaspolide B (331) inhibited the growth of Bel-7402 and HepG2 cells with IC\textsubscript{50} values of 29.1 and 29.5 μM, respectively. Incubation with 0.5 μM of 331 caused time-dependent induction of
Scheme 4.6 (continued)
Scheme 4.6 Proposed biogenetic transformation of jaspolides (A–F) [421]
Scheme 4.7 Postulated biogenetic pathway of jaspolides G and H [422]
apoptosis in Bel-7402 as confirmed by the enhancement of mitochondrial masses, cell membrane permeability, and nuclear condensation. In conclusion, the anticancer effect of jaspolide B involves multiple mechanisms including apoptosis induction, cell cycle arrest, and microtubule disassembly, but these were weaker than observed for colchicine, a well-known microtubule-disassembly agent [424]. These multiple mechanisms of jaspolide B, especially the apoptosis induction, pose interesting perspectives for further exploration of the isomalabaricane-type terpenes as potential anticancer agents.

Since the class of isomalabaricane terpenoidal metabolites has been reported in the literature from different sponge species of the genera Rhabdastrella, Stelletta, Jaspis, and Geodia as shown above, the identity of these sponges has been questioned and reevaluated. Interestingly, the taxonomic reevaluation of these sponges revealed that they all might be reassigned to Rhabdastrella globostellata (class Demospongiae; order Astrophorida; family Ancorinidae) [400]. However, this could not be ascertained for the isomalabaricane producing Stelletta sp. from Somalia [394] and Stelletta tenuis from China [397]. The latter, collected from an identical location (Hainan Island), was taxonomically recognized as R. globostellata [395].

4.4.2.2 Steroidal Saponins
In the Kingdom Animalia, steroidal and triterpene glycosides are predominant metabolites of starfishes and sea cucumbers, respectively [427]. In addition, these types of glycosides have also been isolated from marine sponges. To the best of our knowledge, around 80 triterpenoidal sponge glycosides have been reported to date, including erylosides [427–434], formosides [435, 436], nobiloside [437], and sokodosides [438] from different sponge species of the genus Erylus; sarasinoides from the marine sponges Asteropus sarasinosum [440–443], Melophlus isis [444], and M. sarassinorum [445]; mycalosides from Mycale laxissima [446–448]; ectyoplasides and feroxosides from the Caribbean marine sponge Ectyoplasia ferox [449, 450]; ulosidosides from Ulosa sp. [451, 452]; wondosterols from a two-sponge association [453]; and pachastrelloside A from a marine sponge of the genus Pachastrella [454]. The majority of these glycosides belong to norlanostane-triterpenoidal saponins, derived from lanosterol or related triterpenes as a result of oxidative elimination of one or two methyl groups.

Penasterol (338), an acidic steroidal metabolite closely related to lanosterol (339) and possessing potent antileukemic activity, was originally isolated from the Okinawan marine sponge Penares sp. in 1988 [425]. Penasterol together with its analogues penasterone and acetylpenasterol, isolated from the Okinawan marine sponge Penares incrustans, inhibit IgE-dependent histamine release from rat mast cells [426].

Eryloside A (340) was the first eryloside congener isolated from the Red Sea sponge Erylus lendenfeldi (class Demospongiae; order Choristida; family Geodiidae) [427]. Twenty-eight additional erylosides (A–F, F₁–F₇, G–V) have been reported from different species of the genus Erylus including E. goffrilleri [429, 434], E. formosus [430, 433], E. nobilis [431] in addition to another collection
of E. lendenfeldi [432]. For eryloside A (340), antitumor activity against murine leukemia P388 cells with an IC₅₀ = 5.7 µM and antifungal activity against Candida albicans (MIC = 21.1 µM) have been reported [427]. Eryloside E (341), glycosylated at C-30 through an ester linkage with the rare t-butyl substitution of the side chain, was isolated from an Atlantic sponge Erylus goffrilleri [429]. It revealed immunosuppressive activity with an EC₅₀ of 1.8 µM and a therapeutic index (TI) of 9.5, which indicated that the immunosuppressive effect is specific and is not due to a general cytotoxic effect [429].
Eryloside F (342) was reported from two collections of the marine sponge *E. formosus* [430] and exhibited potent thrombin receptor antagonistic activity. Furthermore, it inhibited platelet aggregation in vitro. Against hepatocyte HepG2 cells, 342 possessed little activity [430]. Erylosides F₁ (343) and F₃ (344) were isolated along with nine other congeners from the Caribbean sponge *E. formosus* [433]. In contrast to its 24-epimer, eryloside F₃ (344) induced early apoptosis in Ehrlich carcinoma cells at 130 μM, while erylosides F (342) and F₁ (343) activated the Ca²⁺ influx into mouse spleenocytes at the same doses [433].

Erylosides K (345) and L (346) have been obtained together with 340 from another collection of the Red Sea marine sponge *Erylus lendenfeldi* [432]. While 345 was identified as the 24,25-didehydro congener of eryloside A, eryloside L (346) incorporated a naturally unprecedented 8α,9α-epoxy-4α-methyl-8,9-secocholesta-7,9(11),14-triene skeleton [432]. Erylosides A (340) and K (345) led to a 50% mortality rate in the brine shrimp assay at a concentration of 0.14 mM. Eryloside L (346) was inactive at the same concentration [432]. In addition to erylosides, the marine sponges *E. formosus* and *E. nobilis* produced other steroidal saponins identified as formosides A (347) [435] and B (348) [436] and nobiloside (349) [437], respectively, whilst sokodosides A (350) and B (351) have been obtained from the marine sponge *Erylus placenta* [438]. A convergent synthesis of the trisaccharides of 351 has been successfully performed [439]. Formoside A (347) was first reported by Jaspars and Crews in 1994 from the Caribbean marine sponge *Erylus formosus* [435]. Later, it was isolated together with formoside B (348) from another collection of the same sponge from the Bahamas [436]. Formoside A (347) and its N-acetyl galactosamine derivative, formoside B (348) possess deterrent properties against predatory fish. Therefore, they were suggested to have important ecological functions, resembling those ascribed to similar compounds present in sea stars, sea cucumbers, and terrestrial plants [436].

Nobiloside (349), a penasterol saponin, was reported from the marine sponge *E. nobilis* collected off Shikine-jima Island, Japan [437], and revealed the presence of a carboxylic group at C-30 in addition to uronic acid moieties. Nobiloside (349) inhibited neuraminidase from the bacterium *Clostridium perfringens* with an IC₅₀ of 0.5 μM [437].

![Diagram of saponin structures](attachment:image.png)
Sokodosides A (350) and B (351) were obtained from the marine sponge *E. placenta* collected off Hachijo Island, Japan [438]. They possessed a novel carbon skeleton as characterized by the presence of a combination of an isopropyl side chain and the 4,4-dimethyl steroid nucleus. Moreover, sokodoside B (351) exhibited double bonds at unusual positions $\Delta^{8(9),14(15),16(17)}$.

Both sokodosides displayed moderate antifungal activity against the fungus *Mortierella ramanniana* and the yeast *Saccharomyces cerevisiae* but no antibacterial activity was found. Additionally, sokodosides A (350) and B (351) exhibited cytotoxic activity against P388 cells with IC$_{50}$ values of 103 and 62 $\mu$M, respectively [438].
Sarasinosides follow erylosides in the number of isolated metabolites. To date, 21 sarasinoside congeners have been reported, which all feature a carbonyl group at C-23 position. Sarasinoside A₁ (352) was the first steroidal saponin reported in the literature, even before eryloside A (340), from the Palauan marine sponge Asteropus sarasinsum, together with other eight new congeners that had been described [440–442]. Then, from the same sponge collected in the Solomon Islands, four additional sarasinosides (D–G) were reported [443]. From each of the marine sponges Melophlus isis (Guam) [444] and M. sarassinorum (Indonesia) [445], four sarasinoside congeners were isolated. Among the sarasinoside congeners known to date, sarasinoside A₁ (352) and B₁ (353) exhibited piscicidal activity against Poecilia reticulata with LD₅₀ values (48 h) of 0.3 and 0.6 µM, respectively [440, 442]. Sarasinoside A₁ is known to possess moderate cytotoxicity in vitro against leukemia P388 [441] and K562 [444] cell lines with IC₅₀ values of 2.2 and 5.0 µM, respectively. Sarasinoside A₃, which differs from A₁ (352) in having Δ⁸(9),14(15) instead of Δ⁸(9) unsaturation, exhibited mild cytotoxic activity with an IC₅₀ of 13.3 µM [444]. In the agar diffusion antimicrobial assay (10 µg/disk), sarasinoside A₁ showed strong and selective activity against the yeast S. cerevisiae but was inactive against B. subtilis and E. coli. On the other hand, sarasinoside J (354) was active against S. cerevisiae and showed moderate antibacterial activity against B. subtilis and E. coli [445].

Mycalosides include 11 steroidal saponin congeners that were isolated from the Caribbean marine sponge Mycale laxissima (class Demospongiae; order Poecilosclerida; family Mycalidae) collected near San Felipe Island,
Cuba [446–448]. They were all characterized by having oxygenated C-4, C-15, and C-21 positions.

Mycaloside A (355) and G (356) as well as the total glycoside fraction did not influence nonfertilized eggs and the developing embryo up to the 8-blastomere stage at concentrations of up to 94.6 μM. However, these compounds were effective as spermatostatics when preincubated for 15 min with sea urchin sperm with an EC50 of 3.04 μM. The total glycoside fraction generated a less toxic effect (EC50 = 7.03 μg/mL) [447].

Ectyoplasides A (357) and B (358) were first isolated from the Caribbean sponge *E. ferox* (class Demospongiae; order Axinellida; family Raspaliidae) collected along the coasts of San Salvador Island, Bahamas [449]. The compounds are C-4 norpenasterol triterpenoidal derivatives. Later, ectyoplasides were reisolated together with feroxosides A (359) and B (360) from the same sponge collected along the coasts of Grand Bahama Island [450]. Feroxosides have been shown to be unusual C-4 norlanostane triterpenes glycosylated with a rhamnose-containing tetrasaccharide chain.
Against murine fibrosarcoma WEHI164, murine leukemia P388, and murine monocyte-macrophage J774 cell lines, both ectyoplasides (357 and 358) exhibited moderate in vitro cytotoxic activity with IC$_{50}$ values ranging from 9.0 to 11.4 µM [449], while against the latter cell line, feroxosides (359 and 360) were mildly cytotoxic (IC$_{50}$ = 17.6 µM) [450].

Pachastrelloside A (361) was obtained from the marine sponge *Pachastrella* sp. (Kagami Bay, Japan) and revealed the presence of a cholest-5,24-diene-2α,3β,4β,7α-tetraol aglycone that was glycosylated at the C-4 and C-7 positions with β-D-xylopyranose and β-D-galactopyranose moieties, respectively [454]. A Korean sponge association composed of *Poecillastra wondoensis* and *Jaspis wondoensis* resulted in the isolation of wondosterols A–C (362–364), which are structurally related to 361 [443]. Wondosterols were shown to have a β-OH group at C-7, and they were all diglycosylated at C-3 with β-D-xylopyranose connected to β-D-galactopyranose.
Wondostersols A–C (362–364) were weakly cytotoxic against P388 cells (IC$_{50}$ = 63 μM), and at a concentration of 10 μg/disk, only 362 and 364 showed antibacterial activities against P. aeruginosa and E. coli [453]. Pachastrelloside A (361) inhibited cell division of fertilized starfish (Asterina pectinifera) eggs at 35 μM [454].

### 4.5 Concluding Remarks

The enormous diversity of marine natural products combined with improved global concerns to find new therapeutic agents for the treatment of different ailments provide the stimulus to evaluate marine natural products in clinical trials. Marine drug discovery faces many obstacles including a sufficient supply and the low concentrations of some compounds that may account for less than 10$^{-6}$% of the wet weight [6]. However, there have been substantial advances, suggesting that sustainable sourcing could be achievable. Since the continuous and exhaustive harvesting of terrestrial drug lead resources proved to be unreliable and resulted in the frequent re-isolation of known compounds, researchers from academia and from pharmaceutical companies alike are now turning their focus to the sea in search for new lead structures from nature. Nevertheless, the large-scale production of marine natural products for clinical use is a real challenge, and, therefore, environmentally sound and economically feasible alternatives are required.

Chemical synthesis is among the first strategies to be explored, but unfortunately, the structural complexity of marine metabolites with novel mechanisms of action and high selectivity has resulted in only a few successful examples of this strategy such as the conus toxin ziconotide [455]. A second strategy, but also as labor-intensive, is to study the pharmacological significance of marine natural product pharmacophores and then attempt to define the critical pharmacophore that can result in practical drugs based on a marine prototype via chemical synthesis, degradation, modification, or a combination of these.

Aquaculture of the source organisms, including sponges, tunicates, and bryozoans, with an aim at securing a sustainable supply of the active constituent(s), has progressed notably in cancer applications. However, in most cases, the biomass currently generated is still far from that required should a marine-based drug finally enter the pharmaceutical market [456]. Furthermore, the cultivation of invertebrates in their natural environment is subject to several hazards and threats, such as destruction by storms or diseases. An intriguing strategy has been to identify the true producers of bioactive compounds and to explore whether or not they are of microbial origin including bacteria, cyanobacteria, or fungi that are known to thrive within the tissues of marine invertebrates.

If bacterial or other associated microorganisms prove to produce the compounds of interest, a careful design of special culture media would be crucial for large-scale fermentation, e.g., ET-743 production. Currently, only 5% or less of the symbiotic bacteria present in marine specimens can be cultivated under standard
conditions [457]. Consequently, molecular approaches offer particularly promising alternatives through the transfer of biosynthetic gene clusters to a vector suitable for large-scale fermentation, thereby avoiding the obstacles in culturing symbiotic bacteria. Oceans will play a potential role in the future to control and relieve the global disease burden. In spite of the substantial development that has been achieved in disclosing novel drug leads from marine resources, more efforts are still required for more chemical entities to reach to clinical applications.

4.6 Study Questions

1. Considering that oroidin is believed to be the precursor of most of the spongal bromopyrrole alkaloids, delineate a plausible biogenetic pathway connecting oroidin with other bromopyrrole alkaloids.

2. What are the main molecular targets of hymenialdisine and analogues, and what are the structural requirements that are responsible for the biological activities of these compounds?

3. Depict the biogenetic relationships between the sponge-derived alkaloids aeroplysinin-1, aerophobin-2, and isofistularin-3. What is the amino acid precursor for these alkaloids? Depict the wound-induced biotransformation of brominated isoxazoline alkaloids in *Aplysina* sponges.

4. The bastadins are important bromotyrosine-derived sponge metabolites. Depict a plausible biogenetic scheme that explains the formation of bastadins in sponges. What are the most important biological activities of bastadin derivatives?

5. The jaspamides are important sponge-derived depsipeptides. What are the most promising biological activities of these compounds? Do they bear structural resemblances to other natural products that might support the notion that some sponge metabolites are derived from microorganisms?

6. Azumamides are the first cyclic peptides with histone deacetylase (HDAC) inhibitory activity isolated from marine organisms. Briefly discuss the structural resemblance between azumamides and trichostatin A (TSA) and their relevance for HDAC inhibitory activity.

7. To which group of terpenes does manoalide belong? What are the most prominent biological activity and mode of action of manoalide?

8. Isomalabaricane triterpenes comprise a group of marine sponge natural products with polyene conjugated functionality. Briefly enumerate with examples the different classes of isomalabaricane triterpenes.

9. Jaspolides represent an example of isomalabaricane-type terpenoids including both monomeric and dimeric congeners. Classify different jaspolides based on their chemical structures and depict a plausible biogenetic pathway of the dimeric jaspolide congeners.

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