Abstract: Marine ecosystems (>70% of the planet's surface) comprise a continuous resource of immeasurable biological activities and immense chemical entities. This diversity has provided a unique source of chemical compounds with potential bioactivities that could lead to potential new drug candidates. Many marine-living organisms are soft bodied and/or sessile. Consequently, they have developed toxic secondary metabolites or obtained them from microorganisms to defend themselves against predators [1]. For the last 30–40 years, marine invertebrates have been an attractive research topic for scientists all over the world. A relatively small number of marine plants, animals and microbes have yielded more than 15,000 natural products including numerous compounds with potential pharmaceutical potential. Some of these have already been launched on the pharmaceutical market such as Prialt® (ziconotide; potent analgesic) and Yondelis® (trabectedin or ET-743; antitumor) while others have entered clinical trials, e.g., alpidin and kahalalide F. Amongst the vast array of marine natural products, the terpenoids are one of the more commonly reported and discovered to date. Sesterterpenoids (C_{25}) and triterpenoids (C_{30}) are of frequent occurrence, particularly in marine sponges, and they show prominent bioactivities. In this review, we survey sesterterpenoids and triterpenoids obtained from marine sponges and highlight their bioactivities.
Keywords: sesterterpenoids; triterpenoids; marine sponges

1. Introduction

Terpenes include primary and secondary metabolites, all biosynthesized from the five carbon isoprene building units [2]. Structural modification of these isoprene units leads a massively diverse range of derivatives with a wide array of chemical structures and biological properties. While higher plants’ terpenoids were already studied and ethnopharmacologically rationalized centuries ago, those from marine counterparts were not explored until the first half of the 20th century.

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 [3]. Secondary metabolites, including terpenes, play an important ecological role in marine organisms. Being sessile and soft bodied, marine organisms face a harsh competition for space, reproduction, maintenance of an unfouled surface and deterrence of predation [4]. Therefore, marine organisms have developed bioactive secondary metabolites as a potential defensive means against competitors and/or predators [1]. These compounds are rapidly diluted after being released into the water and hence have to be of outstanding potency to retain their efficacy. These bioactivity(ies) proved appealing for chemical ecologists as well as for pharmacologists in their search for new drugs to treat or cure serious ailments such as inflammatory, infectious and cancerous diseases.

Marine terpenoids dominate much of the literature expression with a huge number of derivatives having been obtained from marine resources. It seems pointless to compile a review that includes all major classes of marine terpenoids. Therefore, in this review we concentrate on two major classes of marine isoprenes from sponges, namely the sesterterpenoids ($C_{25}$) and triterpenoids ($C_{30}$) with particular attention placed on their biological activities.

Marine triterpenoids were the first terpenoids reported from marine resources and since then a vast array of derivatives have been documented. In this review, we cover steroidal saponins and isomalabaricane triterpenoids. In addition, marine sponges have been identified as one of the prime resources of sesterterpenes and hence we also survey this class of marine terpenoids.

2. Sesterterpenes ($C_{25}$)

Manoalide (1) 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 [5] with activity as an antibiotic against Streptomyces pyogenes and Staphylococcus aureus.

![Manoalide (1)](image1)

![Secomanoalide (2)](image2)
One year later, Scheuer reported three additional related metabolites from the same Palauan sponge, namely secemanoalide (2), (E)-neomanoalide (3) and (Z)-neomanoalide (4) [6]. All three compounds, as well as the parent compound (1), displayed antibacterial activity against Gram positive bacteria (Staphylococcus aureus and Bacillus subtilis) but were inactive against Escherichia coli, Pseudomonas aeruginosa and Candida albicans [6].

![Chemical structures of manoalide analogs](image)

Later, marine sponges belonging to the family Thorectidae, including species of the genera Luffariella [7–19], Hyrtios [20,21], Thorectandra [22], Cacospangia [23,24], Fasciospongia [25–28], Acanthodendrilla [29] and Aplysinopsis [30], 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 A$_2$ (PLA$_2$) [31–38]. Subsequently, many structurally related metabolites with PLA$_2$ inhibitory activity were also reported [8, 39–45]. PLA$_2$ is an enzyme that specifically catalyzes the hydrolysis of phospholipids at the $S_n$-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 [41]. Since manoalide revealed an irreversible inhibition of phospholipase A$_2$ (PLA$_2$) [33], the structure-activity relationships (SAR) of this compound attracted scientific interests to study and to understand both PLA$_2$ 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 1 and its analogs, such as the $\gamma$-hydroxybutenolide, $\alpha$-hydroxydihydropyran and trimethylcyclohexenyl ring systems, to the efficacy as PLA$_2$ inhibitors [36,41,45]. These studies indicated that (1) the existence of the hemiacetal in the $\alpha$-hydroxydihydropyran ring is crucial for irreversible binding, (2) the $\gamma$-hydroxybutenolide ring is involved in the initial interaction with PLA$_2$ and (3) the hydrophobic nature of the trimethylcyclohexenyl ring system allows non-bonded interactions with the enzyme that enhances the potency of these analogs. These studies suggested that the closed ring form of manoalide is the predominant molecular moiety that accounts for the selective and potent inhibition of PLA$_2$ [36].

Manoalide analogs also exhibited other bioactivities including molluscidical [10], cytotoxicity [13,14,16,20,23,26,29,30,47–49], inhibitory activity of Cdc25 phosphatase [46], nicotinic antagonistic activity [12] and fish deterrent properties [26,49]. 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 [35,38–40,43,44,50,51]. Manoalide (1) 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 [52].

Luffariellolide (5) is a sesterterpenoid analog of secomoalide (2), which was first reported from a Palauan sponge Luffariella sp. [8]. Structurally, luffariellolide differed in having C-24 as methyl group instead of an aldehyde functionality as in 2 and it was obtained as the (Z) isomer as well.

In contrast to the irreversible inhibitory action of manoalide (1) towards PLA2, luffariellolide (5) is a slightly less potent, but a partially reversible inhibitor. This meant that 5 became a more preferable anti-inflammatory agent for potential pharmacological investigation [8].

In addition to luffariellolide (5), its 25-O-methyl (6) and 25-O-ethyl derivatives (7), five related sesterterpenes, acantholides A–E, were obtained from the Indonesian sponge Acanthodendrilla sp. [29]. Acantholide D (8) and E (9) 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 (5) and its 25-O-methyl congener (6), as well as acantholide E (9), 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 6 and the stereochemistry of 1-acetylcyclopentan-5-ol in 9 play an important role [29].

Luffariolides A–J represent a related group of sesterterpenoidal analogs, which have been obtained from different collections of the Okinawan marine sponge Luffariella sp. [13,14,16].

All luffariolides exhibited significant cytotoxicity against murine lymphoma L1210 cells with IC_{50} values ranging between 2.9–19.3 \mu M. Amongst them, luffariolides A (10, IC_{50} 2.9 \mu M), B (11, IC_{50} 3.23 \mu M), E (12, IC_{50} 3.0 \mu M) and F (13, IC_{50} 3.8 \mu M) were the most active ones [13,14,16].
Luffariellins A (14) and B (15) [7] together with their respective 25-acetoxy derivatives (18 and 19) [18] were isolated from the marine sponge Luffariella variabilis collected off different locations in Palau and in Australia, whereas luffariellins C (16) and D (17) were obtained from the shell-less marine mollusc Chromodoris funerea collected from the Kaibakku lake shores in Palau [53].

Luffariellins (14–19) are all characterized by the 1-isoproprenyl-2-methylcyclopentane ring system replacing the trimethylcyclohexenyl moiety in other manoaide analogs. Despite this discrepancy in chemical structure, luffariellins A (14) and B (15) retain identical functional groups as present in manoalide (1) and secomanoalide (2), respectively. Therefore, not surprisingly each respective pair was shown to have similar anti-inflammatory properties to 1 and 2 [7].

Luffarin metabolites comprise another group of compounds represented by 28 derivatives. 26 of them, luffarins A–Z, have been reported from the Australian marine sponge Luffariella geometrica [12], while the other two were obtained from the Adriatic Sea sponge Fasciospongia cavernosa [28]. 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 [12].

All luffarins were tested for antimicrobial activity against Staphylococcus aureus, Micrococcus sp., and Saccharomyces cerevisiae. Only luffarins C–F (22–25), K (26) and L (27) showed activity against both S. aureus and Micrococcus sp. [12], whereas luffarins A (20) and M (28) revealed only mild activity against the latter. Moreover, some luffarins were also found to be effective inhibitors of nicotinic receptors [12].

Biosynthetically, a relationship could be recognized between the various luffarins as illustrated in Figure 1. 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 (21) and O (21a), which were the first examples of a hitherto unknown cyclization pattern in compounds of this class [12].

![Diagram of luffarin structures and biosynthetic pathway]

**Figure 1.** Postulated biosynthetic relationship between all known *Luffariella* metabolites [12].
Another example of bicyclic sesterterpenes are thorectandrols A–E (31–35) that were isolated from a Palauan collection of the marine sponge *Thorectandra* sp. [47,48] together with the parent compounds of this group palauolide (29) and palauolol (30). Palauolide (29) was obtained first as an antimicrobial sesterterpene from a three sponge association collected in Palau [54]. While palauolol (30) 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 29 [55].

All thorectandrols (31–35) in addition to palauolide (29) and palauolol (30) were tested for antiproliferative activity against six to twelve human tumor cell lines depending on sample availability [48]. Palauolol (30) was active against all tested cell lines except A549 (non small lung cancer), with IC$_{50}$ values in the range 1.2–1.7 µM, while palauolide (29) showed a diminished activity. On the other hand, thorectandrols A–E revealed only weak to no cytotoxicity against the tested cell lines (IC$_{50}$’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 (30) enhanced cytotoxicity compared to palauolide (29) and other thorectandrols [48].

Cacospongionolides (36–40) were isolated from different collections of the marine sponge *Fasciospongia cavernosa* (=*Cacospongia mollior*) collected from the Mediterranean Sea [23,26,49,56]. Cacospongionolides A (36), B (37) and its 25-deoxy derivative (38) revealed a bicyclic sesterterpenoidal skeleton, resembling luffarins and thorectandrols, with the addition of a γ-hydroxybutenolide moiety. The other cacospongionolides C (39) and D (40) are acyclic diterpenoidal derivatives. Despite the structural relation with luffarins and thorectandrols, cacospongionolides...
(36–38) together with cacospongionolide D (40) exhibited significant cytotoxicity [23,26,49,56]. This notion suggested a possible relation between the presence of the γ-hydroxybutenolide moiety and the cytotoxicity.

Petrosaspongiolides A (41) and B (42) were the first cheilantane sesterpene lactones to be isolated from a New Caledonian sponge incorrectly assigned to the genus Dactylospongia [57] and then reassigned as a new genus and a new species: Petrosaspongia nigra (Bergquist 1995 sp. nov., class Demospongiae; order Dictyoceratida; family Spongidae) [58].

From another New Caledonian collection of the same sponge, 15 additional petrosaspongiolide congeners (C–R) were isolated [59,60].
From the chloroform extract of another Dictyoceratida sponge of the genus *Spongia*, 21-hydroxy derivatives of petrosaspongiolides K (44a) and P (48a) were isolated in addition to four other pyridinium alkaloids named spongidines A–D (51–54) [61]. Spongidines were found to be structurally related to petrosaspongiolide L (45) particularly in the presence of pyridine ring.

Petrosaspongiolides A–L were subjected to *in vitro* cytotoxicity assay against the human bronchopulmonary NSCLC-N6 carcinoma cell line. They revealed IC$_{50}$ values ranging between 1.0–32.2 µM [59]. Petrosaspongiolides C (43) and K (44) exhibited the highest potency with IC$_{50}$ values of 1.0 and 3.5 µM, respectively. However, petrosaspongiolides A (41) and B (42) were the least cytotoxic congeners *in vitro* with IC$_{50}$ values of 28 and 32.2 µM, respectively. 41 inhibited tumoral proliferation *in vivo* at 20 mg/Kg without significant toxicity when tested on immunosuppressed rats carrying a bronchopulmonary tumor (NSCLC-N6) [59].

Petrosaspongiolides M–R (46–50) revealed the presence of a γ-hydroxybutenolide moiety and a hemiacetal function. Due to these structural similarities to manoalide (1), petrosaspongiolides M–R have received special attention from the scientific community to study their inhibitory activity against PLA$_2$ from different resources to point out their specificity. Two main groups of PLA$_2$ enzymes have been reported [62], the secretory PLA$_2$ (sPLA$_2$ groups I, II, III, V, IX, and X with relatively small molecular weights) and the cytosolic PLA$_2$ (cPLA$_2$ groups IV, VI, VII, and VIII with higher molecular weights). Inhibition of specific PLA$_2$ 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 [61].

Petrosaspongiolides M–R (46–50) together with 21-hydroxy derivatives of petrosaspongiolides K (44a) and P (48a), and spongidines A–D (51–54) were tested on five different sPLA$_2$s 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) [60,61].
Among petrosaspongiolide derivatives, 46 and 48a inhibited mainly human synovial PLA2 with IC_{50} values of 1.6 and 5.8 µM, respectively, compared to manoalide (1) (IC_{50} = 3.9 µM) [60,61]. Petrosaspongiolide M (46) also inhibited bee venom PLA2 enzyme with IC_{50} of 0.6 µM, compared to 1 (IC_{50} of 7.5 µM) [60].

The mechanism of action of petrosaspongiolides M–R (46–50) as anti-inflammatory marine metabolites has been the topic for many research articles [63–68]. The covalent binding of 46 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 petrosaspongiolide M γ-hydroxybutenolide ring [63]. The molecular mechanism of inactivating the bee venom and the human type IIA secretory PLA2s by petrosaspongiolides R (50) [67], and M (46) [68], respectively, has been investigated. In both cases, either covalent (imine formation) and/or non-covalent (van der Waals) interactions contributed to the inhibitory activity against PLA2 enzymes [67,68]. Due to potent anti-inflammatory properties of petrosaspongiolides, their chemical synthesis has been interestingly investigated. Recently, the first enantioselective synthesis of petrosaspongiolide R (50) has been successfully performed [69].

3. Triterpenes (C_{30})

Steroidal triterpenes were the first marine isoprenes to be discovered in the 1930s. Scientific interest has been driven towards these metabolites due to the isolation of biosynthetically unprecedented derivatives possessing a broad spectrum of bioactivities. 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.

3.1. Isomalabaricane triterpenes

Malabaricol (55) 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 [70–72]. Malabaricane, the trivial name of this group of compounds, was given to the hydrocarbon system (3S*,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 [71,72].
The malabaricanes are structurally characterized by a tricyclic triterpenoid core and a conjugated polyene side chain [70–72], 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 [73,74].

Isomalabaricane triterpenes were first reported from a Fijian collection of the sponge *Jaspis stelligera* [73] and the Somalian marine sponge *Stelletta* sp. [74]. Since then, they have been isolated from several genera of marine sponges belonging to the order Astrophorida including members of the genera *Rhabdastrella* [75,80,82,86,93,94,96,100], *Stelletta* [77–79,85,88,92], *Jaspis* [81,87,89,98,99,101,102], and *Geodia* [83,90,95].

Isomalabaricane triterpenoids having polyene conjugated functionality can be classified into three groups: (1) stelletins principally possessing the γ-pyrene 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 been also 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 [78–80,88,89,98,99]. Nevertheless, these compounds continue to gain a great deal of attention because of their significant cytotoxic activity [79,89], 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 [86].

Stelletins comprise the first group of isomalabaricane-type triterpenoids. Stelletin A (56) was recognized in 1981 as a yellow triterpenoidal pigment from the Fijian marine sponge *Jaspis stelligera* [73]. Later, it was obtained together with its E isomer, stelletin B (57), from the marine sponge *Stelletta tenuis* collected off Hainan Island, China [77]. Stelletin A (56) revealed significant cytotoxicity against murine leukemia P388 cell line with IC_{50} of 2.1 nM [77].

56: R,R’ = O, Δ^{13(14)} = Z
57: R,R’ = O, Δ^{13(14)} = E
58: R = OCOCH₃, R’ = H, Δ^{13(14)} = E
59: R = OCOCH₃, R’ = H, Δ^{13(14)} = Z
60: Δ^{13(14)} = Z, Δ^{24(25)} = E
61: Δ^{13(14)} = E, Δ^{24(25)} = Z
62: Δ^{13(14)} , Δ^{24(25)} = Z
63: Δ^{13(14)} , Δ^{24(25)} = E
Stelletin G (62), with an opened γ-pyrone and featuring terminal -COOH and -CH₃ functionalities, was isolated together with 56 from *J. stellifera* [73]. Later, stelletins G (62) was reported from the Australian marine sponge *Stelletta* sp. together with stelletins E (60) and F (61) [78]. The E isomer of stelletin G (62) was isolated from the marine sponge *Rhabdastrella globostellata* collected from the South China Sea and it was given the trivial name rhabdastrellic acid–A (63) [75,76].

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 [78–80,82,85], in addition to 22,23-dihydrostelletin D [81].

Rhabdastrellins A–F (64–69), along with stelletins L (70) and M (71), were obtained from the marine sponge *Rhabdastrella* aff. *distinca* collected from a coral reef off Hainan, in the South China Sea [86]. Four of the rhabdastrellins (64–67) exhibited a primary alcohol moiety at C-29 instead of a methyl group as for the stelletins and the other two rhabdastrellins E (68) and F (69). While all rhabdastrellins and stelletins L and M share a hydroxyl group at C-3 instead of a carbonyl group as in other stelletins [86].

The antiproliferative profile of stelletins A–F (56–61) 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(58)/D(59) pair was the most potent derivative with a mean panel GI₅₀ of 0.09 µM. The stelletin E(60)/F(61) pair was approximately 10-times less potent (mean GI₅₀ of 0.98 µM) [79].

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 pro-apoptotic Bax protein to the mitochondria, thereby resulting in a dissipation of mitochondrial membrane potential, activation of caspase-3, and execution of the apoptotic machinery [84].

Stelletin A (56) demonstrated a differential cytotoxicity against human leukemia HL-60 cells (IC$_{50}$ 0.9 µM) compared to human prostate cancer LNCaP cells (IC$_{50}$ 260 µM) by activation of NADPH oxidase, which induces oxidative cell death through a FasL–caspase-3-apoptotic pathway [83]. Stelletins B (57) and E (60) revealed selective cytotoxicity toward p21-deficient human colon tumor HCT-116 cells with IC$_{50}$ values of 0.043 and 0.039 µM, respectively [80]. Stelletins L (70) and M (71) exhibited selective cytotoxicity against stomach cancer AGS cells with IC$_{50}$ values of 3.9 and 2.1 µM, respectively [85]. Rhabdastrellin A–E (63) also inhibited proliferation of human leukemia HL-60 cells with an IC$_{50}$ value of 1.5 µM through inhibition of the PI3K/Akt pathway and induction of caspase-3 dependent-apoptosis [76]. Only rhabdastrellin A (64) possessed moderate inhibitory activity toward human leukemia HL-60 cells (IC$_{50}$ = 8.7 µM) while other rhabdastrellins were inactive (IC$_{50}$ > 20 µM) [86].

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 (72–77), which have been isolated from the Okinawan marine sponge Jaspis stellifera [87], stelliferin G (78) and 29-hydroxy derivatives of stelliferins A (79) and E (80) have been isolated from an unidentified species of the genus Jaspis collected near Tonga [89].

The 29-hydroxy derivative of stelliferin D (81) together with 3-epimeric isomers of 79 and 80 were reported from the marine sponge Stelletta globostellata collected by SCUBA off Mage-jima Island, Japan [88]. Whereas stelliferin riboside (72a), the first example of a glycosylated stelliferin, was isolated from the Fijian sponge Geodia globostellata [90].
Stelliferins A–F (72–77) 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) [87], while the isomeric mixture of stelliferin G (78) and 29-hydroxystelliferin A (79) showed the highest inhibitory activity against the melanoma MALME-3M cell line with IC\(_{50}\) values of 0.2 and 0.4 µM, respectively [89]. Stelliferin riboside (72a) displayed moderate cytotoxicity against ovarian A2780 cancer cells (IC\(_{50}\) = 60 µM) [90].

Due to the significant antiproliferative activity exhibited by stelletins and stelliferins, research efforts have been directed towards their chemical synthesis. In 1999, Raeppe\_l 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 [91].

Globostellatic acid (82) 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 Stelleta globostellata collected off Mage Island near Kagoshima, Japan [92].

Other globostellatic acid congeners, F–M, and X methyl esters, have been reported from different collections of the Indonesian marine sponge Rhabdastrella globostellata [93,94].

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 [92].

For cytotoxicity toward mouse lymphoma L5178Y cells, the 3-O-deacetyl congeners, globostellatic acids H/I (83/84) 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 (85/86), with an IC\(_{50}\) of 8.28 nM. The reverse was found for the 13Z isomer of stelliferin riboside (72a) that revealed higher activity than its 3-O-deacetyl congener with IC\(_{50}\) values of 0.22 and 2.40 nM, respectively [93].

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 [93]. Two globostellatic acid X methyl esters (87 and 88), 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 inhibiting angiogenesis which if pathologically uncontrolled, accompanies several diseases such as atherosclerosis, arthritis, diabetic retinopathy, and cancer.

\[ \text{R} \]

82

\[ \text{R} \]

83: \( H \), \( \Delta^{13(14)} = E \)
84: \( H \), \( \Delta^{13(14)} = Z \)
85: \( \text{OCOCH}_3 \), \( \Delta^{13(14)} = E \)
86: \( \text{OCOCH}_3 \), \( \Delta^{13(14)} = Z \)

87: \( \Delta^{17(20)} = E \)
88: \( \Delta^{17(20)} = Z \)

13E,17E- Globostellatic acid X methyl ester (87) also inhibited basic fibroblast growth factor (bFGF)-induced tubular formation and vascular endothelial growth factor (VEGF)-induced migration of HUVECs. In addition, 87 induced apoptosis of HUVECs without affecting their VEGF-induced phosphorylation of ERK1/2 kinases [94].

Geoditins, which are stelliferin-related isomalabaricane triterpenoids, are mainly oxygenated at both C-22 and C-25. Five geoditins (89–93) were obtained from the marine sponges Geodia japonica [95] and Rhabdastrella aff. distinca [96] collected at different locations in the South China Sea.

89: \( \text{R, R'} = \text{O} \), \( \Delta^{13(14)} = Z \), \( \Delta^{23(24)} = E \)
90: \( \text{R} = \text{H} \), \( \text{R'} = \text{OCOCH}_3 \), \( \Delta^{13(14)} = Z \), \( \Delta^{23(24)} = E \)
91: \( \text{R, R'} = \text{O} \), \( \Delta^{13(14)} \), \( \Delta^{23(24)} = Z \)
92: \( \text{R, R'} = \text{O} \), \( \Delta^{13(14)} \), \( \Delta^{23(24)} = Z \)
93: \( \text{R} = \text{H} \), \( \text{R'} = \text{OCOCH}_3 \), \( \Delta^{13(14)} \), \( \Delta^{23(24)} = Z \)
Geoditins (89–93) 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 (91) showed significant cytotoxicity towards the former three cell lines with IC₅₀ values of 0.3, 0.2 and 1.0 µM, respectively. While 13E-isogeoditin A (92) revealed no cytotoxic activity, implying that the Z-geometry at C-13 enhances antiproliferative activity compared to the E-form [96]. Geoditin A (89) proved to be cytotoxic against HL-60 cells [IC₅₀ = 6.7 µM] while geoditin B (90) exhibited relatively weak cytotoxicity. Mechanistically, geoditin A (89) markedly induced reactive oxygen species (ROS), decreased mitochondrial membrane potential and mediated a caspase-3 apoptosis pathway [97].

Jaspiferals (94–103) and aurorals (104–107) are isomalabaricane-type terpenoids differentiated into nortriterpenoids, norsesterterpenoids and norditerpenes possessing a 3α-hydroxy group. Jaspiferals A–G (94–100) were purified from the Okinawan marine sponge Jaspis stellifera [98] while the 3-O-acetyl and methyl ester derivatives of jaspiferals B (101), D (102) and E (103) were obtained from a new species of Jaspis collected at the Vanuatu Islands [99]. Aurorals (104–107) have been isolated from the New Caledonian marine sponge Rhabdastrella globostellata [100].

Jaspiferals A–G (94–100) exhibited in vitro cytotoxicity against murine lymphoma L1210 cells with IC₅₀ values of 1.6–10.4 µM, whereas only jaspiferals E–G (98–100) revealed antineoplastic
activity against human epidermoid carcinoma KB cells (IC$_{50}$ of 5.2–14.7 µM) [98]. Jaspiferal G (100) 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 jaspiferal E (98) and F (99) showed antifungal activity against T. mentagrophytes (MIC, 134 µM) [98]. On the other hand, the 3-O-acetyl, methyl ester derivatives of jaspiferal B (101), D (102) and E (103) revealed weak cytotoxicity against L1220 cells (IC$_{50}$ > 8.8 µM) [99].

Aurorals (104–107), which differ from jaspiferal C–F (96–99) by the presence of a primary alcohol group at the C-4 position, exhibited stronger cytotoxicity against KB cells. The isomeric mixtures of aurorals (104/105), (106/107) and jaspiferal C/D (96/97) showed IC$_{50}$ values of 0.5, 22.2 and 13.3 µM, respectively, while jaspiferal E/F (98/99) were inactive up to 27 µM [100].

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 (108) and B (109); sesterterpene, jaspolide F (113); diterpenes, jaspolides C (110) and D (111); and nortriterpene, jaspolide E (112) which were all isolated from the marine sponge Jaspis sp. collected from the South China Sea [101].

**Figure 2.** Proposed biogenetic transformation of jaspolides A–F (108–113) [101].
A presumable biogenetic transformation scheme of jaspolides A–F (108–113) (Figure 2), revealed that light-induced isomerization is responsible for the jaspolides A/B (108/109) and C/D (110/111) isomeric pairs. In addition it substantiated jaspolide D (111) as a precursor to jaspolide F (113), formed through condensation with an isoprenyl pyrophosphate (IPP) followed by oxidation at a terminal methyl group [101]. Jaspolides G (114) and H (115) are dimeric isomalabaricane congeners which were isolated from the same Chinese sponge Jaspis sp. and their proposed biogenetic pathway (Figure 3) suggested that they were derived from stelletin A (56) yielding the left moiety, and the nortriterpene, geoditin A (89) yielding the right moiety [102].

Jaspolide B (109) arrested HL-60 cells in the G2/M phase of the cell cycle and induced apoptosis in a dose- and time-dependent manner. Jaspolide B with an IC50 value of 0.61 µM exhibited a comparable efficacy as that of paclitaxel (IC50 = 0.78 µM). These results suggested 109 to be a promising anticancer agent for chemotherapy of leukemia by prohibiting cell cycle progression at the G2/M phase and triggering apoptosis [103].

**Figure 3.** Postulated biogenetic pathway of jaspolides G (114) and H (115) [102].

In a further study with human hepatoma cells, jaspolide B (109) inhibited the growth of Bel-7402 and HepG2 cells with IC50 values of 29.1 and 29.5 µM, respectively. Incubation with 0.5 µM of 109 caused time-dependent induction of 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 colchicine, a well-known microtubule-disassembly agent [104]. 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, Stelleta, 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) [80]. However, it could not be ascertained for the isomalabaricane producing *Stelletta* sp. from Somalia [74] and *Stelletta tenuis* from China [77]. The latter, collected from an identical location (Hainan Island), was taxonomically recognized as *R. globostellata* [75].

3.2. Steroidal saponins

In the Kingdom Animalia, steroidal and triterpene glycosides are predominant metabolites of starfishes and sea cucumbers, respectively [108]. In addition, these types of glycosides have also been isolated from marine sponges. To the best of our knowledge, around 80 sponge triterpenoidal glycosides have been reported to date, including erylosides [107–114], formosides [115,116], nobiloside [117], and sokodosides [118] from different sponge species of the genus *Erylus*; sarasinosides from the marine sponges *Asteropus sarasinosum* [120–123], *Melophlus isis* [124], and *M. sarassinorum* [125]; mycalosides from *Mycale laxissima* [126–128]; ectyoplasides and feroxosides from the Caribbean marine sponge *Ectyoplasia ferox* [129,130]; ulososides from *Ulosa* sp. [131,132]; wondosterols from a two-sponge association [133]; and pachastrelloside A from a marine sponge of the genus *Pachastrella* [134]. 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 (116), an acidic steroidal metabolite closely related to lanosterol (117) and possessing potent antileukemic activity, was originally isolated from the Okinawan marine sponge *Penares* sp. in 1988 [105]. Penasterol together with its analogs penasterone and acetylpenasterol, isolated from the Okinawan marine sponge *Penares incrustans*, inhibit IgE-dependent histamine release from rat mast cells [106].

Eryloside A (118) was the first eryloside congener isolated from the Red Sea sponge *Erylus lendenfeldi* (class Demospongiae; order Choristida; family Geodiidae) [107]. Twenty eight additional erylosides (A–F, F₁–F₇, G–V) have been reported from different species of the genus *Erylus* including *E. goffrilleri* [109,114], *E. formosus* [110,113], *E. nobilis* [111], in addition to another collection of *E. lendenfeldi* [112].
For eryloside A (118), antitumor activity against murine leukemia P388 cells with an IC$_{50}$ = 5.7 µM and antifungal activity against *Candida albicans* (MIC = 21.1 µM) have been reported [107]. Eryloside E (119), 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* [109]. It revealed immunosuppressive activity with an EC$_{50}$ 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 [109].

Eryloside F (120) was reported from two collections of the marine sponge *E. formosus* [110] and exhibited potent thrombin receptor antagonistic activity. Furthermore, it inhibited platelet aggregation *in vitro*. Against hepatocyte HepG2 cells, 120 possessed little activity [110]. Erylosides F$_1$ (121) and F$_3$ (122) were isolated along with nine other congeners from the Caribbean sponge *E. formosus* [113]. In contrast to its 24-epimer, eryloside F$_3$ (122) induced early apoptosis in Ehrlich carcinoma cells at 130 µM, while erylosides F (120) and F$_1$ (121) activated the Ca$^{2+}$ influx into mouse spleenocytes at the same doses [113].

Erylosides K (123) and L (124) have been obtained together with 118 from another collection of the Red Sea marine sponge *Erylus lendenfeldi* [112]. While 123 was identified as the 24,25-didehydro congener of eryloside A, eryloside L (124) incorporated a naturally unprecedented 8α,9α-epoxy-4α-methyl-8,9-secocholesta-7,9(11),14-triene skeleton [112]. Erylosides A (118) and K (123) led to a 50% mortality rate in the brine shrimp assay at a concentration of 0.14 mM. Whereas, eryloside L (124) was inactive at the same concentration [112].

In addition to erylosides, the marine sponges *E. formosus* and *E. nobilis* produced other steroidal saponins identified as formosides A (125) [115] and B (126) [116]; and nobiloside (127) [117],
respectively, whilst sokodosides A (128) and B (129) have been obtained from the marine sponge Erylus placenta [118]. A convergent synthesis of the trisaccharides of 129 has been successfully performed [119].

Formoside A (125) was first reported by Jaspars and Crews in 1994 from the Caribbean marine sponge Erylus formosus [115]. Later, it was isolated together with formoside B (126) from another collection of the same sponge from the Bahamas [116]. Formoside A (125) and its N-acetyl galactosamine derivative, formoside B (126) 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 [116].

Nobiloside (127), a penasterol saponin, was reported from the marine sponge E. nobilis collected off Shikine-jima Island, Japan [117] and revealed the presence of a carboxylic group at C-30 in addition to uronic acid moieties. Nobiloside (127) inhibited neuraminidase from the bacterium Clostridium perfringens with an IC₅₀ of 0.5 µM [117].

Sokodosides A (128) and B (129) were obtained from the marine sponge E. placenta collected off Hachijo Island, Japan [118]. 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 (129) exhibited double bonds at unusual positions Δ⁸(9),14(15),16(17).
Both sokodosides displayed moderate antifungal activity against the fungus Mortierella rammanniana and the yeast Saccharomyces cerevisiae, but no antibacterial activity was found. Additionally, sokodosides A (128) and B (129) exhibited cytotoxic activity against P388 cells with IC50 values of 103 and 62 μM, respectively [118].

Sarasinosides follow erylosides in the number of isolated metabolites. To date, 21 sarasinoside congeners have been reported, which all featured a carbonyl group at C-23 position. Sarasinoside A1 (130) was the first steroidal saponin reported in the literature, even before eryloside A (118), from the Palauan marine sponge Asteropus sarasinsum, together with other eight new congeners [120–122]. Then, from the same sponge collected in the Solomon Islands, four additional sarasinosides D–G were reported [123]. From each of the marine sponges Melophlus isis (Guam) [124] and M. sarasinorum (Indonesia) [125], four sarasinoside congeners were isolated.

Among the sarasinoside congeners known to date, sarasinoside A1 (130) and B1 (131) exhibited piscidical activity against Poecilia reticulata with LD50 values (48 h) of 0.3 and 0.6 μM, respectively [120,122].
Sarasinoside A₁ is known to possess moderate cytotoxicity in vitro against leukemia P388 [121] and K562 [124] cell lines with IC₅₀ values of 2.2 and 5.0 µM, respectively. Sarasinoside A₃, which differs from A₁ (130) in having Δ⁸(9),¹⁴(15) instead of Δ⁸(9) unsaturation, exhibited mild cytotoxic activity with an IC₅₀ of 13.3 µM [124].

In the agar diffusion antimicrobial assay (10 µg/disc), 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 (132) was active against *S. cerevisiae* and showed moderate antibacterial activity against *B. subtilis* and *E. coli* [125].

Mycalosides include eleven 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 [126–128]. They were all characterized by having oxygenated C-4, C-15, and C-21 positions.

Mycaloside A (133) and G (134) 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) [127].

Ectyoplasides A (135) and B (136) were first isolated from the Caribbean sponge *E. ferox* (class Demospongiae; order Axinellida; family Raspaliidae) collected along the coasts of San Salvador Island, Bahamas [129]. The compounds are C-4 norpenasterol triterpenoidal derivatives. Later, ectyoplasides were reisolated together with feroxosides A (137) and B (138) from the same sponge collected along the coasts of Grand Bahama Island [130]. 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 (135 and 136) exhibited moderate in vitro cytotoxic activity with IC₅₀ values ranging from 9.0 to 11.4 μM [129], whilst against the latter cell line, feroxosides (137 and 138) were mildly cytotoxic (IC₅₀ = 17.6 μM) [130].

Pachastrelloside A (139) 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 [134].

A Korean sponge-association composed of Poecyllastra wondoensis and Jaspis wondoensis resulted in the isolation of wondosteroles A–C (140–142), which are structurally related to 139 [133]. Wondosteroles 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.

Wondosteroles A–C (140–142) were weakly cytotoxic against P388 cells (IC₅₀ = 63 μM) and at a concentration of 10 μg/disk only 140 and 142 showed antibacterial activities against P. aeruginosa and E. coli [133]. Pachastrelloside A (139) inhibited cell division of fertilized starfish (Asterina pectinifera) eggs at 35 μM [134].
4. Future Aspects

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 [135]. 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 with this strategy such as the conus toxin ziconotide [136]. 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 [137]. 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 harbour within the tissues of marine invertebrates.

If bacterial or other associated microorganisms proved 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 [138]. 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.

Acknowledgements

Preparation of this review was supported by a grant of BMBF (to P.P.). A scholarship granted and financed by the Egyptian government (predoctoral fellowship for S.S.E.) is gratefully acknowledged.
References and Notes

1. Braekman, J.C.; Daloze, D. Chemical defence in sponges. Pure Appl. Chem. 1986, 58, 357–364.
2. Ruzicka, Z.L. The isoprene rule and the biogenesis of terpenic compounds. Experientia 1953, 9, 357–367.
3. Bergmann, W.; Johnson, T.B. The chemistry of marine animals. I. The sponge Microciona pralifera. Z. Physiol. Chem. 1933, 222, 220–226.
4. Fusetani, N. Biofouling and antifouling. Nat. Prod. Rep. 2004, 21, 94–104.
5. De Silva, E.D.; Scheuer, P.J. Manoalide, an antibiotic sesterterpenoid from the marine sponge Luffariella variabilis (Polejaeff). Tetrahedron Lett. 1980, 21, 1611–1614.
6. De Silva, E.D.; Scheuer, P.J. Three new sesterterpenoid antibiotics from the marine sponge Luffariella variabilis (Polejaeff). Tetrahedron Lett. 1981, 22, 3147–3150.
7. Kernan, M.R.; Faulkner, D.J.; Jacobs, R.S. The luffariellins, novel anti-inflammatory sesterterpenes of chemotaxonomic importance from the marine sponge Luffariella variabilis. J. Org. Chem. 1987, 52, 3081–3083.
8. Albigati, K.F.; Holman, T.; Faulkner, D.J.; Glaser, K.B.; Jacobs, R.S. Luffariellolide, an anti-inflammatory sesterpene from the marine sponge Luffariella sp. Experientia 1987, 43, 949–950.
9. Kernan, M.R.; Faulkner, D.J.; Parkanyi, L.; Clardy, J.; de Carvalho, M.S.; Jacobs, R.S. Luffolide, a novel anti-inflammatory terpene from the sponge Luffariella sp. Experientia 1989, 45, 388–390.
10. König, G.M.; Wright, A.D.; Sticher, O. Four new antibacterial sesterterpenes from a marine sponge of the genus Luffariella. J. Nat. Prod. 1992, 55, 174–178.
11. Potts, B.C.M.; Capon, R.J.; Faulkner, D.J. Luffactalactone and (4E,6E)-dehydromanoalide from the sponge Luffariella variabilis. J. Org. Chem. 1992, 57, 2965–2967.
12. Butler, M.S.; Capon, R.J. The luffarins (A–Z), novel terpenes from an Australian marine sponge, Luffariella geometrica. Aust. J. Chem. 1992, 45, 1705–1743.
13. Tsuda, M.; Shigemori, H.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. Luffariolides A–E, new cytotoxic sesterterpenes from the Okinawan marine sponge Luffariella sp. J. Org. Chem. 1992, 57, 3503–3507.
14. Kobayashi, J.; Zeng, C.M.; Ishibashi, M.; Sasaki, T. Luffariolides F and G, new manoalide derivatives from the Okinawan marine sponge Luffariella sp. J. Nat. Prod. 1993, 56, 436–439.
15. Reddy, M.V.R.; Harper, M.K.; Faulkner, D.J. Luffasterols A–C, 9,11-secoesters from the Palauan marine sponge Luffariella sp. J. Nat. Prod. 1997, 60, 41–43.
16. Tsuda, M.; Endo, T.; Mikami, Y.; Fromont, J.; Kobayashi, J. Luffariolides H and J, new sesterterpenes from a marine sponge Luffariella. J. Nat. Prod. 2002, 65, 1507–1508.
17. Namikoshi, M.; Suzuki, S.; Meguro, S.; Nagai, H.; Koike, Y.; Kitazawa, A.; Kobayashi, H.; Oda, T.; Yamada, J. Manoalide derivatives from a marine sponge Luffariella sp. collected in Palau. Fish. Sci. 2004, 70, 152–158.
18. Ettinger-Epstein, P.; Motti, C.A.; de Nys, R.; Wright, A.D.; Battershill, C.N.; Tapiolas, D.M. Acetylated sesterterpenes from the Great Barrier reef sponge Luffariella variabilis. J. Nat. Prod. 2007, 70, 648–651.
19. Gauvin-Bialecki, A.; Aknin, M.; Smadja, J. 24-O-Ethylmanoalide, a manoalide-related sesterterpene from the marine sponge *Luffariella* cf. *variabilis*. *Molecules* 2008, 13, 3184–3191.

20. Kobayashi, M.; Okamoto, T.; Hayashi, K.; Yokoyama, N.; Sasaki, T.; Kitagawa, I. Marine natural products. XXXII. Absolute configurations of C-4 of the manoalide family, biologically active sesterterpenes from the marine sponge *Hyrtios erecta*. *Chem. Pharm. Bull.* 1994, 42, 265–270.

21. Bourguet-Kondracki, M.L.; Debitus, C.; Guyot, M. Biologically active sesterterpenes from a new Caledonian marine sponge *Hyrtios erecta*. *Chem. Pharm. Bull.* 1994, 42, 265–270.

22. Cambie, R.C.; Craw, P.A.; Bergquist, P.R.; Karuso, P. Chemistry of sponges, III. Manoalide monoacetate and thorectolide monoacetate, two new sesterterpenoids from *Thorectandra excavatus*. *J. Nat. Prod.* 1988, 51, 331–334.

23. De Rosa, S.; de Stefano, S.; Zavodnik, N. Cacospongionolide: a new antitumoral sesterterpene, from the marine sponge *Cacospongia mollior*. *J. Org. Chem.* 1988, 53, 5020–5023.

24. Tasdemir, D.; Concepción, G.P.; Mangalindan, G.C.; Harper, M.K.; Hajdu, E.; Ireland, C.M. New terpenoids from a *Cacospongia* sp. from the Philippines. *Tetrahedron* 2000, 56, 9025–9030.

25. Montagnac, A.; Pais, M.; Debitus, C. Fasciospongides A, B and C, new manoalide derivatives from the sponge *Fasciospongia cavernosa*. *J. Nat. Prod.* 1994, 57, 186–190.

26. De Rosa, S.; Crispino, A.; de Giulio, A.; Iodice, C.; Pronzato, R.; Zavodnik, N. Cacospongionolide B, a new sesterterpene from the sponge *Fasciospongia cavernosa*. *J. Nat. Prod.* 1995, 58, 1776–1780.

27. De Rosa, S.; Crispino, A.; de Giulio, A.; Iodice, C.; Tommonaro, G. Cavernosolide, a new sesterterpene from a Tyrrhenian sponge. *J. Nat. Prod.* 1997, 60, 844–846.

28. De Rosa, S.; Carbonelli, S. Two new luffarin derivatives from the Adriatic Sea sponge *Fasciospongia cavernosa*. *Tetrahedron* 2006, 62, 2845–2849.

29. Elkhayat, E.; Edrada, R.A.; Ebel, R.; Wray, V.; van Soest, R.W.M.; Mohamed, M.H.; Müller, W.E.G.; Proksch, P. New luffariellolide derivatives from the Indonesian sponge *Acanthodendrilla* sp. *J. Nat. Prod.* 2004, 67, 1809–1817.

30. Ueoka, R.; Nakao, Y.; Fujii, S.; van Soest, R.W.M.; Matsunaga, S. Aplysinoplides A–C, cytotoxic sesterterpenes from the marine sponge *Aplysinopsis digitata*. *J. Nat. Prod.* 2008, 71, 1089–1091.

31. De Freitas, J.C.; Blankemeier, L.A.; Jacobs, R.S. *In vitro* inactivation of the neurotoxic action of β-bungarotoxin by the marine natural product, manoalide. *Experientia* 1984, 40, 864–865.

32. Lombardo, D.; Dennis, E.A. Cobra venom phospholipase A₂ inhibition by manoalide. A novel type of phospholipase inhibitor. *J. Biol. Chem.* 1985, 260, 7234–7240.

33. Glaser, K.B.; Jacobs, R.S. Molecular pharmacology of manoalide. Inactivation of bee venom phospholipase A₂. *Biochem. Pharmacol.* 1986, 35, 449–453.

34. Glaser, K.B.; Jacobs, R.S. Inactivation of bee venom phospholipase A₂ by manoalide. A model based on the reactivity of manoalide with amino acids and peptide sequences. *Biochem. Pharmacol.* 1987, 36, 2079–2086.

35. Bennett, C.F.; Mong, S.; Clarke, M.A.; Kruse, L.I.; Crooke, S.T. Differential effects of manoalide on secreted and intracellular phospholipases. *Biochem. Pharmacol.* 1987, 36, 733–740.
36. Glaser, K.B.; de Carvalho, M.S.; Jacobs, R.S.; Kernan, M.R.; Faulkner, D.J. Manoalide: structure-activity studies and definition of the pharmacophore for phospholipase A_2 inactivation. *Mol. Pharmacol.* **1989**, *36*, 782–788.

37. Jacobson, P.B.; Marshall, L.A.; Sung, A.; Jacobs, R.S. Inactivation of human synovial fluid phospholipase A_2 by the marine natural product, manoalide. *Biochem. Pharmacol.* **1990**, *39*, 1557–1564.

38. Ortiz, A.R.; Pisabarro, M.T.; Gago, F. Molecular model of the interaction of bee venom phospholipase A_2 with manoalide. *J. Med. Chem.* **1993**, *36*, 1866–1879.

39. Deems, R.A.; Lombardo, D.; Morgan, B.P.; Mihelich, E.D.; Dennis, E.A. The inhibition of phospholipase A_2 by manoalide and manoalide analogues. *Biochim. Biophys. Acta* **1987**, *917*, 258–268.

40. Reynolds, L.J.; Morgan, B.P.; Hite, G.A.; Mihelich, E.D.; Dennis, E.A. Phospholipase A_2 inhibition and modification by manoalogue. *J. Am. Chem. Soc.* **1988**, *110*, 5172–5177.

41. Potts, B.C.M.; Faulkner, D.J.; Jacobs, R.S. Phospholipase A_2 inhibitors from marine organisms. *J. Nat. Prod.* **1992**, *55*, 1701–1717.

42. Reynolds, L.J.; Mihelich, E.D.; Dennis, E.A. Inhibition of venom phospholipase A_2 by manoalide and manoalide analogue. *J. Biol. Chem.* **1991**, *266*, 16512–16517.

43. Potts, B.C.M.; Faulkner, D.J.; de Carvalho, M.S.; Jacobs, R.S. Chemical mechanism of inactivation of bee venom phospholipase A_2 by the marine natural products manoalide, luffariellolide, and scalaradial. *J. Am. Chem. Soc.* **1992**, *114*, 5093–5100.

44. De Rosa, M.; Giordano, S.; Scettti, A.; Sodano, G.; Soriante, A.; Pastor, P.G.; Alcaraz, M.J.; Payá, M. Synthesis and comparison of the anti-inflammatory activity of manoalide and cacospongionolide B analogues. *J. Med. Chem.* **1998**, *41*, 3232–3238.

45. Mann, J. Sponges to wipe away pain. *Nature* **1992**, *358*, 540.

46. Blanchard, J.L.; Epstein, D.M.; Boisclair, M.D.; Rudolph, J.; Pal, K. Dysidiolide and related γ-hydroxybutenolide compounds as inhibitors of the protein tyrosine phosphatase, CDC25. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2537–2538.

47. Charan, R.D.; McKee, T.C.; Boyd, M.R. Thorectandrols A and B, new cytotoxic sesterterpenes from the marine sponge *Thorectandra* species. *J. Nat. Prod.* **2001**, *64*, 661–663.

48. Charan, R.D.; McKee, T.C.; Boyd, M.R. Thorectandols C, D, and E, new sesterterpenes from the marine sponge *Thorectandra* sp. *J. Nat. Prod.* **2002**, *65*, 492–495.

49. De Rosa, S.; de Giulio, A.; Crispino, A.; Iodice, C.; Tommonaro, G. Further bioactive sesterterpenes from the Tyrrenian sponge *Fasciospongia cavernosa*. *Nat. Prod. Res.* **1997**, *10*, 267–274.

50. Barrero, A.F.; Alvarez-Manzaneda, E.J.; Chahboun, R.; Cuerva, J.M.; Segovia, A. Synthetic applications of the thermal rearrangement of ozonides: first enantiospecific synthesis of marine metabolite Luffarin *W*. *Synlett* **2000**, *9*, 1269–1272.

51. Boukouvalas, J.; Robichaud, J.; Maltais, F. A unified strategy for the regiospecific assembly of homoallayl-substituted butenolides and γ-hydroxybutenolides: first synthesis of luffariellolide. *Synlett* **2006**, *16*, 2480–2482.

52. Gross, H.; König, G.M. Terpenoids from marine organisms: unique structures and their pharmacological potential. *Phytochem. Rev.* **2006**, *5*, 115–141.
53. Kernan, M.R.; Barrabee, E.B.; Faulkner, D.J. Variation of the metabolites of Chromodoris funerea: comparison of specimens from a Palauan marine lake with those from adjacent waters. *Comp. Biochem. Physiol.* 1988, 89B, 275–278.

54. Sullivan, B.; Faulkner, D.J. An antimicrobial sesterterpene from a Palauan sponge. *Tetrahedron Lett.* 1982, 23, 907–910.

55. Schmidt, E.W.; Faulkner, D.J. Palauolol, a new anti-inflammatory sesterterpene from the sponge Fascaplysinopsis sp. from Palau. *Tetrahedron Lett.* 1996, 37, 3951–3954.

56. De Rosa, S.; Puliti, R.; Crispino, A.; de Giulio, A.; de Sena, C.; Iodice, C.; Mattia, C.A. 25-Deoxyacacospiongonolide B and cacospiongonolide C, two new terpenoids from the sponge Fasciospongia cavernosa. *Tetrahedron* 1995, 51, 10731–10736.

57. Lal, A.R.; Cambie, R.C.; Rickard, C.E.F.; Bergquist, P.R. Sesterterpene lactones from a sponge species of the genus Dactylospongia. *Tetrahedron Lett.* 1994, 35, 2603–2606.

58. Cambie, C.R.; Lal, A.R.; Rickard, C.E.F. A sesterterpene lactone from Petrosaspongia nigra sp. nov. *Acta Cryst.* 1996, C52, 709–711.

59. Gomez-Paloma, L.; Randazzo, A.; Minale, L.; Debitus, C.; Roussakis, C. New cytotoxic sesterterpenes from the New Caledonian marine sponge Petrosaspongia nigra (Bergquist). *Tetrahedron* 1997, 53, 10451–10458.

60. Randazzo, A.; Debitus, C.; Minale, L.; Pastor, P.G.; Alcaraz, M.J.; Payá, M.; Gomez-Paloma, L. Petrosaspongiodoles M–R: new potent and selective phospholipase A2 inhibitors from the New Caledonian marine sponge Petrosaspongia nigra. *J. Nat. Prod.* 1998, 61, 571–575.

61. De Marino, S.; Iorizzi, M.; Zollo, F.; Debitus, C.; Menou, J.-L.; Ospina, L.F.; Alcaraz, M.J.; Payá, M. New pyridinium alkaloids from a marine sponge of the genus Spongia with a human phospholipase A2 inhibitor profile. *J. Nat. Prod.* 2000, 63, 322–326.

62. Balsinde, J.; Balboa, M.A.; Insel, P.A.; Dennis, E.A. Regulation and inhibition of phospholipase A2, *Ann. Rev. Pharmacol. Toxicol.* 1999, 39, 175–189.

63. Dal Piaz, F.D.; Casapullo, A.; Randazzo, A.; Riccio, R.; Pucci, P.; Marino, G.; Gomez-Paloma, L. Molecular basis of phospholipase A2 inhibition by petrosaspongiodile M. *ChemBioChem* 2002, 3, 664–671.

64. Monti, M.C.; Casapullo, A.; Riccio, R.; Gomez-Paloma, L. Further insights on the structural aspects of PLA2 inhibition by γ-hydroxybutenolide-containing natural products: a comparative study of petrosaspongiodilides M–R. *Bioorg. Med. Chem.* 2004, 12, 1467–1474.

65. Monti, M.C.; Casapullo, A.; Riccio, R.; Gomez-Paloma, L. PLA2-mediated catalytic activation of its inhibitor 25-acetyl-petrosaspongiodile M: serendipitous identification of a new PLA2 suicide inhibitor. *FEBS Lett.* 2004, 578, 269–274.

66. Gomez-Paloma, L.; Monti, M.C.; Terracciano, S.; Casapullo, A.; Riccio, R. Chemistry and biology of anti-inflammatory marine natural products. Phospholipase A2 inhibitors. *Curr. Org. Chem.* 2005, 9, 1419–1427.

67. Monti, M.C.; Riccio, R.; Casapullo, A. Effects of petrosaspongiodile R on the surface topology of bee venom PLA2: a limited proteolysis and mass spectrometry analysis. *Bioorg. Chem.* 2009, 37, 6–10.

68. Monti, M.C.; Casapullo, A.; Cavasotto, C.N.; Tosco, A.; Dal Piaz, F.; Ziemys, A.; Margarucci, L.; Riccio, R. The binding mode of petrosaspongiodile M to the human group IIA phospholipase
A2: exploring the role of covalent and noncovalent interactions in the inhibition process. \textit{Chem. Eur. J.} 2009, 15, 1155–1163.

69. Ferreiro-Mederos, L.; Lanners, S.; Henchiri, H.; Fekih, A.; Hanquet, G. Hemisynthesis of two marine cheilantane sesterterpenes from (-)-sclareol: first enantioselective synthesis of petrosaspongioleolide. \textit{R. Nat. Prod. Res.} 2009, 23, 256–263.

70. Chawla, A.; Dev, S. A new class of triterpenoids from \textit{Ailanthus malabarica} DC. Derivatives of malabaricane. \textit{Tetrahedron Lett.} 1967, 8, 4837–4843.

71. Sobti, R.R.; Dev, S. A direct correlation of (+)-malabaricol with (+)-ambreinolide. \textit{Tetrahedron Lett.} 1968, 9, 2215–2217.

72. Paton, W.F.; Paul, I.C.; Bajaj, A.G.; Dev, S. The structure of malabaricol. \textit{Tetrahedron Lett.} 1979, 20, 4153–4154.

73. Ravi, B.N.; Wells, R.J.; Croft, K.D. Malabaricane triterpenes from a Fijian collection of the sponge \textit{Jaspis stellifera}. \textit{J. Org. Chem.} 1981, 46, 1998–2001.

74. McCabe, T.; Clardy, J.; Minale, L.; Pizza, C.; Zollo, F.; Riccio, R. A triterpenoid pigment with the isomalabaricane skeleton from the marine sponge \textit{Stelletta} sp. \textit{Tetrahedron Lett.} 1982, 23, 3307–3310.

75. Rao, Z.; Deng, S.; Wu, H.; Jiang, S. Rhabdastrellic acid–A, a novel triterpenoid from the marine sponge \textit{Rhabdastrella globostellata}. \textit{J. Nat. Prod.} 1997, 60, 1163–1164.

76. Guo, J.-F.; Zhou, J.-M.; Zhang, Y.; Deng, R.; Liu, J.-N.; Feng, G.-K.; Liu, Z.-C.; Xiao, D.-J.; Deng, S.-Z.; Zhu, X.-F. Rhabdastrellic acid–A inhibited PI3K/Akt pathway and induced apoptosis in human leukemia HL–60 cells. \textit{Cell Biol. Int.} 2008, 32, 48–54.

77. Su, J.Y.; Meng, Y.H.; Zeng, L.M.; Fu, X.; Schmitz, F.J. Stellettin A, a new triterpenoid pigment from the marine sponge \textit{Stelletta tenuis}. \textit{J. Nat. Prod.} 1994, 57, 1450–1451.

78. McCormick, J.L.; McKee, T.C.; Cardellina II, J.H.; Leid, M.; Boyd, M.R. Cytotoxic triterpenes from a marine sponge, \textit{Stelletta} sp. \textit{Stelletta} sp. \textit{J. Nat. Prod.} 1996, 59, 1047–1050.

79. McKee, T.C.; Bokesch, H.R.; McCormick, J.L.; Rashid, M.A.; Spielvogel, D.; Gustafson, K.R.; Alavanja, M.M.; Cardellina II, J.H.; Boyd, M.R. Isolation and characterization of new anti-HIV and cytotoxic leads from plants, marine, and microbial organisms. \textit{J. Nat. Prod.} 1997, 60, 431–438.

80. Tasdemir, D.; Mangalindan, G.C.; Concepción, G.P.; Verbitski, S.M.; Rabindran, S.; Miranda, M.; Greenstein, M.; Hooper, J.N.A.; Harper, M.K.; Ireland, C.M. Bioactive isomalabaricane triterpenes from the marine sponge \textit{Rhabdastrella globostellata}. \textit{J. Nat. Prod.} 2002, 65, 210–214.

81. Tang, S.A.; Deng, Z.W.; Li, J.; Fu, H.Z.; Pei, Y.H.; Zhang, S.; Lin, W.H. A new isomalabaricane triterpenoid from sponge \textit{Jasplas} sp. \textit{Chin. Chem. Lett.} 2005, 16, 353–355.

82. Clement, J.A.; Li, M.; Hecht, S.M.; Kingston, D.G.I. Bioactive isomalabaricane triterpenoids from \textit{Rhabdastrella globostellata} that stabilize the binding of DNA polymerase β to DNA. \textit{J. Nat. Prod.} 2006, 69, 373–376.

83. Liu, W.K.; Cheung, F.W.K.; Che, C.-T. Stellettin A induces oxidative stress and apoptosis in HL–60 human leukemia and LNCaP prostate cancer cell lines. \textit{J. Nat. Prod.} 2006, 69, 934–937.

84. Krysko, D.V.; Roels, F.; Leybaert, L.; D’Herde K. Mitochondrial transmembrane potential changes support the concept of mitochondrial heterogeneity during apoptosis. \textit{J. Histochem. Cytochem.} 2001, 49, 1277–1284.
Lin, H.-W.; Wang, Z.-L.; Wu, J.-H.; Shi, N.; Zhang, H.-J.; Chen, W.-S.; Morris-Natschke, S.L.; Lin, A.-S. Stellettins L and M, cytotoxic isomalabaricane-type triterpenes, and sterols from the marine sponge *Stelleta tenuis*. *J. Nat. Prod.* 2007, 70, 1114–1117.

Lv, F.; Xu, M.; Deng, Z.; de Voogd, N.J.; van Soest, R.W.M.; Proksch, P.; Lin, W.H. Rhabdastrellins A – F, isomalabaricane triterpenes from the marine sponge *Rhabdastrella* aff. *distinca*. *J. Nat. Prod.* 2008, 71, 1738–1741.

Tsuda, M.; Ishibashi, M.; Agemi, K.; Sasaki, T.; Kobayashi, J. Stelliferins A–F, new antineoplastic isomalabaricane triterpenes from the Okinawan marine sponge *Jaspis stellifera*. *Tetrahedron* 1991, 47, 2181–2194.

Oku, N.; Matsunaga, S.; Wada, S.I.; Watabe, S.; Fusetani, N. New isomalabaricane triterpenes from the marine sponge *Stelletta globostellata* that induce morphological changes in rat fibroblasts. *J. Nat. Prod.* 2000, 63, 205–209.

Meragelman, K.M.; McKee, T.C.; Boyd, M.R. New cytotoxic isomalabaricane triterpenes from the sponge *Jaspis* species. *J. Nat. Prod.* 2001, 64, 389–392.

Tabudravu, J.N.; Jaspars, M. Stelliferin riboside, a triterpene monosaccharide isolated from the Fijian sponge *Geodia globostellifera*. *J. Nat. Prod.* 2001, 64, 813–815.

Raeppe, F.; Weinb, J.-M.; Heissler, D. Synthesis of the trans-syn-trans perhydrobenz[e]indene moiety of the stellettins and the stelliferins. *Tetrahedron Lett.* 1999, 40, 6377–6381.

Ryu, G.; Matsunaga, S.; Fusetani, N. Globostellatic acids A–D, new cytotoxic isomalabaricane triterpenes from the marine sponge *Stelleta globostellata*. *J. Nat. Prod.* 1996, 59, 512–514.

Zhang, W.H.; Che, C.-T. Isomalabaricane-type nortriterpenoids and other constituents of the marine sponge *Geodia japonica*. *J. Nat. Prod.* 2001, 64, 1489–1492.

Lv, F.; Deng, Z.; Li, J.; Fu, H.; van Soest R.W.M.; Proksch, P.; Lin, W.H. Isomalabaricane-type compounds from the marine sponge *Rhabdastrella globostellata*. *J. Nat. Prod.* 2004, 67, 2033–2036.

Liu, W.K.; Ho, J.C.K.; Che, C.T. Apoptotic activity of isomalabaricane triterpenes on human promyelocytic leukemia HL-60 cells. *Cancer Lett.* 2005, 230, 102–110.

Kobayashi, J.; Yuasa, K.; Kobayashi, T.; Sasaki, T.; Tsuda, M. Jaspiferals A–G, new cytotoxic isomalabaricane-type nortriterpenoids from Okinawan marine sponge *Jaspis stellifera*. *Tetrahedron* 1996, 52, 5745–5750.

Zampella, A.; D’Auria, M.V.; Debitus, C.; Menou, J.-L. New isomalabaricane derivatives from a new species of *Jaspis* sponge collected at the Vanuatu Islands. *J. Nat. Prod.* 2000, 63, 943–946.

Bourguet-Kondracki, M.-L.; A.; Debitus, C.; Guyot, M. New cytotoxic isomalabaricane-type sesterterpenes from the new Caledonian marine sponge *Rhabdastrella globostellata*. *Tetrahedron Lett.* 2000, 41, 3087–3090.
101. Tang, S.; Pei, Y.; Fu, H.; Deng, Z.; Li, J.; Proksch, P.; Lin, W.H. Jaspolides A–F, six new isomalabaricane-type terpenoids from the sponge Jaspis sp. Chem. Pharm. Bull. 2006, 54, 4–8.
102. Tang, S.; Deng, Z.; Proksch, P.; Lin, W.H. Jaspolides G and H, unique bisomalabaricanes from the Chinese marine sponge Jaspis sp. Tetrahedron Lett. 2007, 48, 5443–5447.
103. Li, M.; Wei, S.-Y.; Tang, S.-A.; Lin, W.-H.; Cui, J.-R. Antileukemic activity of jaspolide B, an isomalabaricance-type triterpene from marine sponge Jaspis sp. on human promyeloleukemic HL-60 cells. J. Ch. Pharm. Sci. 2008, 17, 11–15.
104. Wei, S.-Y.; Li, M.; Tang, S.A.; Sun, W.; Xu, B.; Cui, J.-R.; Lin, W.-H. Induction of apoptosis accompanying with G1 phase arrest and microtubule disassembly in human hepatoma cells by jaspolide B, a new isomalabaricane-type triterpene. Cancer Lett. 2008, 262, 114–122.
105. Cheng, J.F.; Kobayashi, J.; Nakamura, H.; Ohizumi, Y.; Hirata, Y.; Sasaki, T. Penasterol, a novel antileukemic sterol from the Okinawan marine sponge Penares sp. J. Chem. Soc. Perkin Trans. I 1988, 8, 2403–2406.
106. Shoji, N.; Umeyama, A.; Motoki, S.; Arihara, S.; Ishida, T.; Nomoto, K.; Kobayashi, J.; Takei, M. Potent inhibitors of histamine release, two novel triterpenoids from the Okinawan marine sponge Penares incrustans. J. Nat. Prod. 1992, 55, 1682–1685.
107. Carmely, S.; Roll, M.; Loya, Y.; Kashmir, Y. The structure of eryloside A, a new antitumor and antifungal 4-methylated steroidal glycoside from the sponge Erylus lendenfeldi. J. Nat. Prod. 1989, 52, 167–170.
108. D’Auria, M.V.; Paloma, L.G.; Minale, L.; Riccio, R.; Debitus, C. Structure characterization by two-dimensional NMR spectroscopy, of two marine triterpene oligosaccharides from a Pacific sponge of the genus Erylus. Tetrahedron 1992, 48, 491–498.
109. Gulavita, N.K.; Wright, A.E.; Kelly-Borges, M.; Longley, R.E.; Yarwood, D.; Sills, M.A. Eryloside E from an Atlantic sponge Erylus goffrilleri. Tetrahedron Lett. 1994, 35, 4299–4302.
110. Stead, P.; Hiscox, S.; Robinson, P.S.; Pike, N.B.; Sidebottom, P.; Roberts, A.D.; Taylor, N.L.; Wright, A.E.; Pomponi, S.A.; Langely, D. Eryloside F, a novel penasterol disaccharide possessing potent thrombin receptor antagonist activity. Bioorg. Med. Chem. Lett. 2000, 10, 661–664.
111. Shin, J.; Lee, H.-S.; Woo, L.; Rho, J.-R.; Seo, Y.; Cho, K.W.; Sim, C.J. New triterpenoid saponins from the sponge Erylus nobilis. J. Nat. Prod. 2001, 64, 767–771.
112. Fouad, M.; Al-Trabeen, K.; Badran, M.; Wray, V.; Edrada, R.; Proksch, P.; Ebel, R. New steroidal saponins from the sponge Erylus lendenfeldi. ARKIVOC 2004, xiii, 17–27.
113. Antonov, A.S.; Kalinovsky, A.I.; Stonik, V.A.; Afiyatulloev, S.S.; Aminin, D.L.; Dmitrenok, P.S.; Mollo, E.; Cimino, G. Isolation and structures of erylosides from the Caribbean sponge Erylus formosus. J. Nat. Prod. 2007, 70, 169–178.
114. Afiyatulloev, S.S.; Kalinovsky, A.I.; Antonov, A.S.; Ponomarenko, L.P.; Dmitrenok, P.S.; Aminin, D.L.; Krasokhin, V.B.; Nosova, V.M.; Kisin, A.V. Isolation and structures of erylosides from the Caribbean sponge Erylus goffrilleri. J. Nat. Prod. 2007, 70, 1871–1877.
115. Jaspars, M.; Crews, P. A triterpene tetrasaccharide, formoside, from the Caribbean Choristida sponge Erylus formosus. Tetrahedron Lett. 1994, 35, 7501–7504.
116. Kabanek, J.; Pawlik, J.R.; Eve, T.M.; Fenical, W. Triterpene glycosides defend the Caribbean reef sponge Erylus formosus from predatory fishes. Mar. Ecol. Prog. Ser. 2000, 207, 69–77.
117. Takada, K.; Nakao, Y.; Matsunaga, S.; van Soest, R.W.M.; Fusetani, N. Nobiloside, a new neuraminidase inhibitory triterpenoidal saponin from the marine sponge Erylus nobilis. J. Nat. Prod. 2002, 65, 411–413.

118. Okada, Y.; Matsunaga, S.; van Soest, R.W.M.; Fusetani, N. Sokodosides, steroid glycosides with an isopropyl side chain, from the marine sponge Erylus placenta. J. Org. Chem. 2006, 71, 4884–4888.

119. Dasgupta, S.; Pramanik, K.; Mukhopadhyay, B. Oligosaccarides through reactivity tuning: convergent synthesis of the trisaccharides of the steroid glycoside sokodoside B isolated from marine sponge Erylus placenta. Tetrahedron 2007, 63, 12310–12316.

120. Kitagawa, I.; Kobayashi, M.; Okamoto, Y.; Yoshikawa, M.; Hamamoto, Y. Structures of sarasinosides A1, B1, and C1; new norlanostane-triterpenoid oligosaccharides from the Palauan marine sponge Asteropus sarasinosum. Chem. Pharm. Bull. 1987, 35, 5036–5039.

121. Schmitz, F.J.; Ksebati, M.B.; Gunasekera, S.P., Agarwal, S. Sarasinoside A1: A saponin containing amino sugars isolated from a sponge. J. Org. Chem. 1988, 53, 5941–5947.

122. Kobayashi, M.; Okamoto, Y.; Kitagawa, I. Marine natural products. XXVIII. The structures of sarasinosides A1, A2, A3, B1, B2, B3, C1, C2, and C3, nine new norlanostane-triterpenoidal oligosaccharides from the Palauan marine sponge Asteropus sarasinosum. Chem. Pharm. Bull. 1991, 39, 2867–2877.

123. Espada, A.; Jiménez, C.; Rodríguez, J.; Crews, P.; Riguera, R. Sarasinosides D–G: four new triterpenoid saponins from the sponge Asteropus sarasinosum. Tetrahedron 1992, 48, 8685–8696.

124. Lee, H.-S.; Seo, Y.; Cho, K.W.; Rho, J.-R.; Shin, J.; Paul, V.J. New triterpenoid saponins from the sponge Melophlus isis. J. Nat. Prod. 2000, 63, 915–919.

125. Dai, H.-F.; Edrada, R.A.; Ebel, R.; Nimtz, M.; Wray, V.; Proksch, P. Norlanostane triterpenoidal saponins from the marine sponge Melophlus sarassinorum. J. Nat. Prod. 2005, 68, 1231–1237.

126. Kalinovsky, A.I.; Antonov, A.S.; Afiyatullov, S.S.; Dmitrenok, P.S.; Evtuschenko, E.V.; Stonik, V.A. Mycaloside A, a new steroid oligoglycoside with an unprecedented structure from the Caribbean sponge Mycale laxissima. Tetrahedron Lett. 2002, 43, 523–525.

127. Antonov, A.S.; Afiyatullov, S.S.; Kalinovsky, A.I.; Ponomarenko, L.P.; Dmitrenok, P.S.; Aminin, D.L.; Agafonosa, I.G.; Stonik, V.A. Mycalosides B–I, eight new spermostatic steroid oligoglycosides from the sponge Mycale laxissima. J. Nat. Prod. 2003, 66, 1082–1088.

128. Afiyatullov, S.S.; Antonov, A.S.; Kalinovsky, A.I.; Dmitrenok, P.S. Two new steroid oligoglycosides from the Caribbean sponge Mycale laxissima. Nat. Prod. Commun. 2008, 3, 1581–1586.

129. Cafieri, F.; Fattorusso, E.; Taglialatela-Scafati, O. Ectyoplasides A–B – unique triterpene oligoglycosides from the Caribbean sponge Ectyoplasia ferox. Eur. J. Org. Chem. 1999, 231–238.

130. Campagnuolo, C.; Fattorusso, E.; Taglialatela-Scafati, O. Feroxosides A–B, two norlanostane tetruglycosides from the Caribbean sponge Ectyoplasia ferox. Tetrahedron 2001, 57, 4049–4055.

131. Antonov, A.S.; Kalinovsky, A.I.; Stonik, V.A. Ulososide B, a new unusual norlanostane-triterpene glycoside and its genuine aglycone from the Madagascar sponge Ulosa sp. Tetrahedron Lett. 1998, 39, 3807–3808.
132. Antonov, A.S.; Kalinovskii, A.I.; Dmitrenok, P.S.; Stonik, V.A. New triterpene glycosides from *Ulosa* sp. sponge. *Russ. J. Bioorg. Chem.* 2002, 28, 183–188.

133. Ryu, G.; Choi, B.W.; Lee, B.H.; Hwang, K.-H.; Lee, U.C.; Jeong, D.S.; Lee, N.H. Wondosterols A–C, three steroidal glycosides from a Korean marine two-sponge association. *Tetrahedron* 1999, 55, 13171–13178.

134. Hirota, H.; Takayama, S.; Miyashiro, S.; Ozaki, Y.; Ikegami, S. Structure of a novel steroidal saponin, pachastrelloside A, obtained from a marine sponge of the genus *Pachastrella*. *Tetrahedron Lett.* 1990, 31, 3321–3324.

135. Proksch, P.; Edrada, R.A.; Ebel, R. Drugs from the sea: current status and microbiological applications. *Appl. Micobiol. Biotechnol.* 2002, 59, 125–134.

136. Olivera, B.M. *ω*-Conotoxin MVIIA: from marine snail venom to analgesic drug. In *Drugs from the Sea*; Fusetani, N.; Basel: Karger, Switzerland, 2000; pp. 74–85.

137. Mendola, D. Aquacultural production of bryostatin 1 and ecteinascidin 743. In *Drugs from the Sea*; Fusetani, N., Ed.; Karger: Basel, Switzerland, 2000; pp. 74–85.

138. Fenical, W. Chemical studies of marine bacteria: developing a new resource. *Chem. Rev.* 1993, 93, 1673–1683.

*Samples Availability:* Available from the authors.

© 2010 by the authors; licensee Molecular Diversity Preservation International, Basel, Switzerland. This article is an open-access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0/).