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Marine pharmacology in 2005–6: Marine Compounds with Anthelmintic, Antibacterial, Anticoagulant, Antifungal, Anti-inflammatory, Antimalarial, Antiprotozoal, Antituberculosis, and Antiviral Activities; affecting the Cardiovascular, Immune and Nervous Systems, and other Miscellaneous Mechanisms of Action

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Abstract

BACKGROUND—The review presents the 2005–2006 peer-reviewed marine pharmacology literature, and follows a similar format to the authors' 1998–2004 reviews. The preclinical pharmacology of chemically characterized marine compounds isolated from marine animals, algae, fungi and bacteria is systematically presented.

RESULTS—Anthelminthic, antibacterial, anticoagulant, antifungal, antimalarial, antiprotozoal, antituberculosis and antiviral activities were reported for 78 marine chemicals. Additionally 47 marine compounds were reported to affect the cardiovascular, immune and nervous system as well as possess anti-inflammatory effects. Finally, 58 marine compounds were shown to bind to a variety of molecular targets, and thus could potentially contribute to several pharmacological classes.

CONCLUSIONS—Marine pharmacology research during 2005–2006 was truly global in nature, involving investigators from 32 countries, and the United States, and contributed 183 marine chemical leads to the research pipeline aimed at the discovery of novel therapeutic agents.

SIGNIFICANCE—Continued preclinical and clinical research with marine natural products demonstrating a broad spectrum of pharmacological activity and will probably result in novel therapeutic agents for the treatment of multiple disease categories.

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Keywords

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1. Introduction

The current article reviews the 2005–6 preclinical pharmacology of marine natural products using a similar format to the previous reviews on pharmacological research [1–5]. The review of the literature on the pharmacology of antitumor and cytotoxic marine compounds has been reported elsewhere [6–11]. Only those articles reporting on the bioactivity or pharmacology of marine chemicals that were structurally characterized are included in the current article. As in our previous reviews, we used a modification of Schmitz's chemical classification [12] to assign structures to four major chemical classes, namely, polyketides, terpenes, nitrogen-containing compounds or polysaccharides. Those articles that reported anthelminthic, antibacterial, anticoagulant, antifungal, antimalarial, antiprotozoal, antituberculosis and antiviral properties of marine chemicals have been presented in Table 1 with the corresponding structures shown in Fig. 1. The publications describing marine compounds affecting the cardiovascular, immune and nervous systems, as well as those with anti-inflammatory effects are grouped in Table 2, and their structures shown in Fig. 2. Finally, marine compounds with activity towards a series of cellular and molecular targets are exhibited in Table 3, and their structures depicted in Fig. 3. Publications regarding the bioactivity of marine extracts or as yet structurally uncharacterized marine compounds have been excluded from the present review, although several promising reports were published during 2005–6: anti-inflammatory and analgesic effects of Egyptian Red Sea sponge extracts [13]; proangiogenic effects of 15–20 kDa fucoidans on endothelial cells [14]; antioxidative and anti-inflammatory effects of phlorotannin-containing extracts with potential for osteoarthritis from the brown alga *Ecklonia cava* [15]; immunostimulating activity *in vivo* of a novel sulfated exopolysaccharide derived from a red-tide microalga *Gyrodinium impudicum* [16]; antiherpetic activity *in vitro* of sulfated fucans from the marine brown alga *Stoechospermum marginatum* [17]; *in vitro* bioactivity of Brazilian marine sponge extracts against herpes, adenovirus and rotaviruses [18]; antifungal activity of glycolipid fractions from the red alga *Chondria armata* [19]; antiviral and immunoregulatory activity of an exopolysaccharide from the marine *Bacillus licheniformis* [20]; potent anticoagulant activity of a sulfated polysaccharide from the brown alga *Ecklonia cava* [21]; antimicrobial activity of Red Sea coral extracts [22]; a novel broad-spectrum antibacterial protein produced by the bacterium *Marinomonas mediterranea* [23]; antiviral activity of polysaccharide fractions isolated from the cyanobacterium *Arthrospira platensis* (formerly *Spirulina platensis*) [24]; antiangiogenic and antimicrobial activity of sponge-associated bacterial extracts [25], and a β-galactose-specific lectin with anti-HIV-1 activity isolated from the marine worm *Chaetopterus variopedatus* [26].

2. Marine compounds with anthelmintic, antibacterial, anticoagulant, antifungal, antimalarial, antiprotozoal, antituberculosis, and antiviral activities

Table 1 presents new pharmacological findings reported during 2005–6 on the anthelmintic, antibacterial, anticoagulant, antifungal, antimalarial, antiprotozoal, antituberculosis, and antiviral pharmacology of the 78 marine natural products shown in Fig. 1.

2.1 Anthelmintic and antibacterial activity

Three studies contributed to the search of novel *anthelmintic* marine natural products during 2005–6. Capon and colleagues [27,28] described two novel betaines **(−)-echinobetaine A**

(1) and **(+)-echinobetaine B (2),** from the Australian sponge *Echinodictyum* sp. which were nematocidal (LD_{99}=83 and 8.3μg/mL, respectively) to the commercial livestock parasite *Haemonchus contortus*. Although the mechanism of action of these compounds remains undetermined, (+)-echinobetaine B's nematocidal activity was comparable to that of "two commercially available synthetic antihelmintics, closantel and levamisole". Davyt and colleagues [29] reported a novel halogenated **β-bisabolene sesquiterpenoid (3)** from the red alga *Laurencia scoparia* that showed anthelmintic activity (EC_{50}=0.11 mM) against the parasitant stage (L4) of *Nippostrongilus brasiliensis*, a rat gastrointestinal parasite that has a similar lifestyle and morphology to human hookworms.

As part of an ongoing global effort to discover novel antimicrobials to treat infections caused by resistant pathogenic bacteria, during 2005–6, 27 studies contributed novel *antibacterial* marine natural products isolated from marine fungi, bacteria, sponges, soft corals, jellyfish and fish, a considerable increase from our previous reviews [1–5]. Only two reports provided detailed mechanism of action studies. Linington and colleagues [30] discovered that the novel **caminosides B (4) and D (5)** glycolipids, isolated from the Caribbean marine sponge *Caminus sphaeroconia*, were inhibitors of pathogenic *E.coli* type III secretion system. Both caminosides were observed to "possess a number of structural features not found in sponge glycolipids" and were also noted to be effective against Gram-positive methicillin-resistant *S. aureus* and vancomycin–resistant *Enteroccocus* (MIC=3.1–6.3 μg/disk). Oh and colleagues [31] reported that the bis(indole) alkaloids **deoxytopsentin (6)** and **hamacanthin A (7)** isolated from the marine sponge *Spongosorites* sp. exhibited potent antibacterial activity against *S. aureus (*MIC=3.12–6.35 μg/mL*).* Interestingly, both alkaloids inhibited the enzyme sortase A (IC_{50}=15.7 & 86.3 μg/mL, respectively), a membrane-associated transpeptidases that plays a key role in Gram-positive pathogenic bacterial invasion of host cells.

As shown in Table 1, several potent marine antibacterials were also reported in 2005–6 (Fig 1), with MICs less than 10 μg/mL against several antibiotic-resistant bacterial strains, but unfortunately the articles did not include data on putative mechanisms of action: **aurelin (8)** [32]; **batzellaside A (9)** [33]; **dendridine A (10)** [34]; **6-oxo-de-*O*-methyllasiodiplodin (11)** [35]; **grammistins (12)** [36]; **halichonadin C (13)** [37]**; lajollamycin (14)** [38]; **marinomycins** A **(15)**, B **(16)**, C **(17)** and D **(18)** [39]; **resistoflavin methyl ether (19)** [40]; ***Streptomyces* anthraquinones (20–21)** [41]; ***Streptomycetaceae* quinone (22)** [42] and, **xeniolide I (23)** [43].

Furthermore, novel structurally characterized marine molecules with MICs greater than 10 μg/mL were also isolated during this period, but are not included in Table 1 or Fig. 1 because of their weaker antibacterial activity: **agelasidine** A, (MIC=50 μg/mL) [44], **alkylpyridinium** (MIC<25 μg/mL) [45]; **diaporthelactone** (MIC=50 μg/mL) [46]; ***Geniculosporium* sp. botryanes** [47]; **guangomide A & B** (MIC=100 μg/mL) [48]; **latrunculins** (MIC=14.7–17.8 μg/mL) [49]; **norresistomycin** (MIC=16 μg/mL) [50]; **perinadine A** (MIC=33–66.7 μg/mL) [51]; ***Pseudomonas aeruginosa* quinoline** (MIC=50–100 μg/mL) [52]; **rifamycin B & SV** [53]; **sarasinoside A_1 and J** [54]; **scalusamide A** (MIC=33 μg/mL) [55], and ***Thorectandra* sp. alkaloid** (MIC=12.5 μg/mL) [56]. Although these marine compounds demonstrated weaker antimicrobial activity, they highlight the fact that novel antimicrobial leads may result from further research into the chemical biodiversity present in marine bacteria, fungi and sponges.

2.2 Anticoagulant activity

As shown in Table 1, during 2005–6, 5 articles reported *anticoagulant* marine natural products isolated from algae, fish and clams, an increase from our previous reviews [1–5]. Rajapakse and colleagues [57] characterized a 12.01 kDa single-chain monomeric **protein** from the marine yellowfin sole (*Limanda aspera*) which inhibited the blood coagulation serine endopeptidase factor XII (IC_{50}<1 μM) by forming an inactive complex, and also triggered

platelet aggregation by binding to a membrane glycoprotein integrin. Drozd and colleagues [58] extended the pharmacology of the **fucoidans (24)** from the marine algae *Fucus evanescens* and *Laminaria cichorioides*, showing that these sulfated polysaccharides inhibited both thrombin and factor Xa with potency comparable to non-fractioned and low-molecular weight heparins, although with considerable variability attributed to the "degree of sulfation and various types of glycoside bonds". Luppi and colleagues [59] reported the purification and structural characterization of an unusual low-sulfated **heparin (25)** from the marine Italian bivalve mollusk *Callista chione* that decreased anti-factor Xa and activated partial thromboplastin time activity (IC_{50}=52–97 IU/mg), probably as the result of a specific decrease in sulfation at position 2 of the uronic acid units. Pereira and colleagues [60] using an approach that combined structural analysis with specific biological assays, investigated the anticoagulant pharmacology of **sulfated galactans (26,27)** isolated from the red marine alga *Gelidium crinale*. Their detailed mechanistic studies demonstrated that 2,3-disulfated a-galactose units along the galactan chain were of major significance for the sulfated galactans's anticoagulant activity, because the chains modulated interactions of the polysaccharides with "target proteases and coagulation inhibitors". Rocha and colleagues [61] described a novel **sulfated galactofucan (28)** isolated from the marine brown alga *Spatoglossum schroederi* with a unique structure composed of a central core of 4-linked, partially 3-sulfated *β*-galactose units. Remarkably, the polysaccharide had no anticoagulant activity, yet showed potent antithrombotic activity resulting from the synthesis of heparan sulfate by vascular endothelial cells.

2.3 Antifungal activity

As shown in Table 1, sixteen studies during 2005–6 reported on the *antifungal* activity of several novel marine natural products isolated from marine algae, fungi, bacteria, sponges and sea stars, a substantial increase from our 1998–2004 reviews [1–5].

Four reports extended the molecular pharmacology of novel antifungal marine chemicals. Li and colleagues [62] discovered that the **capisterones A and B (29,30)** from the green alga *Penicillus capitatus* reversed drug resistance to clinically relevant azole-resistant fungal strains. Interestingly, although both compounds had no inherent antifungal activity, they enhanced fluconazole activity in efflux pump-overexpressing *Candida albicans* strains, suggesting their utility in protocols for resistant fungal infections. Sionov and colleagues [63] observed that a **phenol compound (31)** from the marine sponge *Dysidea herbacea* had significant activity against the human fungal pathogens *C. albicans* and *Aspergillus fumigatus* (MIC=1.95–7.8 μg/mL) which compared well with the clinically used antifungal amphotericin B (MIC=1–2 μg/mL). The phenol compound caused significant concentration-dependent changes in fungal cell morphology and cell membrane, resulting in K^+ ion leakage. Pettit and colleagues [64] extended the *in vitro* and *in vivo* pharmacology of the marine **spongistatin 1 (32)** isolated from the marine sponge *Hyrios erecta*, a previously described anticancer agent [65]. The macrocyclic lactone polyether was shown to be fungicidal to 74 reference strains and clinical isolates (MIC=1–32 μg/mL), including several fungal strains resistant to the clinically used drugs flucytosine, ketoconazole and fluconazole. Furthermore, mechanism of action studies revealed that spongistatin 1 disrupted cytoplasmatic and spindle microtubules in *Cryptococcus neoformans* in a time- and concentration-dependent manner, preventing nuclear migration, and both nuclear and cellular cell division. Jang and colleagues [66] found that a synthetic analogue of **halocidin (33),** a previously reported antimicrobial peptide isolated from the hemocytes of a marine ascidian, had potent antifungal activity (MIC=1–4 μg/mL). The synthetic Di-K19Hc peptide derivative of **33** was shown to bind to *C. albicans* very rapidly (30 seconds) via an interaction with β-1,3-glucan, a component of the fungal cell wall, and concomitantly inducing ion channel formation, K^+ efflux, and death of the fungal cell.

Additionally, and as shown in Table 1, several marine chemicals showed significant antifungal activity (i.e. MICs that were less than 10 μg/mL (Fig 1; **34–43**), but unfortunately mechanism of action studies were lacking at the time of publication: the lipopeptide **hassallidin A (34),** (MIC=4.8 μM) [67], the polyketide **latrunculins (35–42),** (MIC=2.5–19 μM) [49], and the fatty acid **majusculoic acid (43),** (MIC=8 μM) [68]. Further investigation of the molecular pharmacology of these compounds will be required to determine their mechanism of action.

Finally, additional novel structurally-characterized marine molecules demonstrated MICs greater than 10 μg/mL, and therefore because of the weaker antifungal activity they have been excluded from Table 1 and Fig. 1: **amphidinols** (IC_{50}=10–58 μM) [69,70], **callipeltins F–I** (IC_{50}=100 μM) [71], ***Lamellodysidea herbacea* sterols** [72], **minutosides A and B** [73], **oceanalin A** (IC_{50}=30 μM) [74], **sokodoside A and B** [75], and **sterigmatocyn** [76]. Although these marine chemicals showed weaker antifungal activity, they represent potential pharmacological leads perhaps possessing novel and uncharacterized mechanisms of action that might ultimately benefit the ongoing global search for clinically useful antifungal agents.

2.4 Antimalarial, antiprotozoal, and antituberculosis activity

As shown in Table 1, in 2005–6 nine studies were reported in the area of *antimalarial, antiprotozoal and antituberculosis* pharmacology of structurally characterized marine natural products, a significant increase from our previous 1998–2004 reviews [1–5].

Wright and Lan-Unnasch [77] reported that **pycnidione (44)** isolated from the marine fungus *Phoma* sp., had significant antiplasmodial activity against three strains of *Plasmodium falciparum* (IC_{50}=0.15–0.4 μM). Because of structural similarities between pycnidione and atovaquone, an ingredient of the antimalarial medication Malarone®, the investigators proposed that the antiplasmodial activity of pycnidione was “significant in terms of lead structure development”. Campagnuolo and colleagues [78] identified antimalarial activity in novel polyketide cycloperoxides isolated from the marine sponge *Plakortis simplex*. The known **plakortide Q (45)** demonstrated the highest inhibition of *P. falciparum* chloroquine-sensitive and chloroquine-resistant strains (IC_{50}=0.52–1 μM), suggesting that the configuration at C-3 exerted a significant effect on antimalarial activity of these compounds. Laurent and colleagues [79] proved that the known **xestoquinone (46)** isolated from the Pacific Ocean sponge *Xestospongia* sp. had significant *in vitro* antiplasmodial activity (IC_{50}=3μM), and inhibited Pfnek-1(IC_{50}=1 μM), a protein kinase of *P. falciparum* that plays a yet undetermined role in its biochemistry. Rao and colleagues [80] highlighted the bioactivity of four new manzamine-type alkaloids, as well as that of 13 known manzamine alkaloids isolated from Indonesian sponges of the genus *Acanthostrongylophora* against the chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum.* Although less potent than artemisinin, used as a control in these studies (IC_{50}=10 & 6.3 ng/mL, respectively), the higher bioactivity of **manzamine Y (47)** against *P. falciparum* (IC_{50}=0.42–0.85 μg/mL) demonstrated the importance of hydroxy and the 8-membered ring in the aliphatic region of this molecule for the antimalarial activity.

Several additional marine chemicals were reported in 2005–6 to possess antimalarial activity, but their bioactivity appeared to be less significant, i.e. MIC >10μM: The diterpenes **caucanolides A and D (48,49)** from the Colombian gorgonian coral *Pseudopterogorgia bipinnata*, (IC_{50}=17 μg/mL) [81], **sesquiterpenoid metabolites (50–54)** from a Caribbean gorgonian coral *Eunicea sp.*, (IC_{50}=10–18 μg/mL) [82], the diterpene **kallolide D (55)** from a Colombian *Pseudopterogorgia* species, (IC_{50}=30.6 μM) [83], the furanocembranolide diterpenes **leptolide (56)** and **deoxypseudopterolide (57)** from the Panamanianoctocorals *Leptogorgia alba* and *Leptogorgia rigida*, (IC_{50}= 50 & 74 μM, respectively)[84], and a **tyramine derivative (58)** from the Panamanian octocoral *Muricea austera* (IC_{50}=36 μM) [85].

Three marine compounds were reported to possess *antiprotozoal* activity. Lim and colleagues [86] found that **ent-plakortide P (59),** a new natural product from the sponge *Plakortis* sp., inhibited *Leishmania mexicana* proliferation (IC_{50}=1 μg/mL), although it appeared to be less potent than ketoconazole (IC_{50}=0.06 μg/mL). Washida and colleagues [87] examined a novel polyol compound **karatungiol A (60)** isolated from the symbiotic Indonesian marine dinoflagellate *Amphidinium* sp., and observed antiprotozoal activity against *Trichomonas foetus* (IC_{50}=1 μg/mL). This constitutes an important observation in view of the fact that this flagellated protozoan parasite of both the bovine and feline reproductive tract appears to show increasing resistance to the anthelmintics fenbendazole and metronidazole. Gray and colleagues [88] discovered a new disulfated meroterpenoid, **isoakaterpin (61)**, from extracts of the Brazilian marine sponge *Callyspongia* sp. that inhibited *Leishmania* spp. adenine phosphoribosyl transferase (IC_{50}=1.05 μM), an enzyme that is part of the purine salvage pathway in the parasite, and "should compromise parasite but not mammal metabolism".

Three novel marine compounds were contributed to the global search for novel *antituberculosis* agents. De Oliveira and colleagues [89] reported that (+)-**fistularin -3 (62)** and **11-deoxy-fistularin-3 (63)** isolated from the Brazilian sponge *Aplysina cauliformis* inhibited growth of *Mycobacterium tuberculosis* H37Rv (MIC=7.1–7.3 μM, respectively), thus extending previous observations on the antituberculosis activity of fistularin-3 **(62)**[90]. Because these compounds evidenced very low toxicity to macrophages (IC_{50}=200 and 630 μM, respectively), there is definite potential for these compounds to become leads for antituberculosis drug development. As part of the investigation of the extensive chemodiversity of the Caribbean sea whip *Pseudopterogorgia elisabethae*, Rodriguez and colleagues [91] noted that at the concentration range of 128-64 mg/mL the novel benzoxazole alkaloid **ileabethoxazole (64)** inhibited *M. tuberculosis* (H_{37}Rv, MIC=61 μg/mL), with a potency that "lies within the same range as that of the very active rifampin". As a result of an ongoing investigation to identify new manzamines from the Indo-Pacific sponge, *Acanthostrongylophora* sp., Rao and colleagues [80] identified two of the alkaloids, namely **(+)-8-hydroxymanzamine A (66)** and **manzamine F (73)**, that inhibited *M. tuberculosis* (H_{37}Rv, MIC=0.9 & 0.4 μg/mL, respectively), results which compared very favorably with rifampicin (MIC=0.5 μg/mL), a first-line antituberculosis drug.

2.5 Antiviral activity

As shown in Table 1, interest in the *antiviral* pharmacology of novel marine natural products remained high during 2005–6. Four studies reported novel marine chemicals with antiviral activity against herpes simplex, measles and cytomegalovirus. Rodriguez and colleagues [92] isolated three galactan **polysaccharide fractions** from the Argentinian marine algae *Callophyllis variegata* which showed potent antiviral activity against herpes simplex types 1 (HSV-1) and 2 (HSV-2) (IC_{50}=0.16–2.19 μg/mL) and dengue type 2 (IC_{50}=0.1–0.41 μg/mL), together with low cytotoxicity, suggesting that these compounds might become "promising antiviral agents". Lee and colleagues [93] described a sulfated polysaccharide **naviculan** from *Navicula directa*, a diatom collected from deep-sea water in Toyama Bay, Japan, which inhibited HSV-1 and HSV-2 (IC_{50}=7–14 μg/mL) by interferring with early stages of viral replication, probably affecting viral binding, adsorption and penetration into host cells. Matsuhiro and colleagues [94] reported the structural analysis and antiviral activity of a **sulfated galactan** isolated from the marine red seaweed *Schizymenia binderi*. The sulfated galactan exhibited highly selective antiviral activity against HSV-1 and HSV-2 (IC_{50}=0.18–0.76 μg/mL), very low cytotoxicity, appeared to inhibit viral adsorption to host cells and was thus considered to be superior to "other previously reported sulfated galactans of algal origin". Iwashima and colleagues [95] discovered that three **plastoquinone**s **(74–76)** isolated from the marine alga *Sargassum micracanthum* inhibited cytomegalovirus (IC_{50}=0.49–2.6 μM) and

measles virus (IC_{50}=2.7–3.1 μM), suggesting that the compounds could become "lead compounds in an anti-human cytomegalovirus drug" development.

Two reports contributed additional pharmacology against human immunodeficiency virus type-1 (HIV-1), the causative agent of the acquired immunodeficiency disease syndrome (AIDS), a disease that infects more than 40 milion people worldwide. In a detailed mechanistic study De Souza and colleagues [96] described the biochemical pharmacology of two **diterpenes (77–78)** isolated from a Brazilian marine alga *Dictyota menstrualis* on HIV-1 reverse transcriptase enzyme. Both diterpenes were shown to behave as classical non-competitive reversible inhibitors of the RNA-dependent DNA polymerase activity of HIV-1 reverse transcriptase (K_i=10 and 35 μM, respectively). Mori and colleagues [97] contributed the characterization of a novel and potent HIV-inactivating protein **griffithsin** from the red alga *Griffithsia* sp. Griffithsin, a new type of lectin, displayed potent antiviral activity against laboratory strains and primary isolates of HIV-1 (IC_{50}=0.043–0.63 nM), by a mechanism that required binding to viral glycoproteins (eg. gp120, gp41 and gp160) in a monosaccharide-dependent manner. Furthermore, the authors noted griffithsin was a potential "candidate microbicide to prevent the sexual transmission of HIV and AIDS".

3. Marine compounds with anti-inflammatory effects and affecting the cardiovascular, immune and nervous system

Table 2 summarizes the preclinical pharmacological research completed during 2005–2006 with the 47 marine secondary metabolites shown in Fig. 2.

3.1 Anti-inflammatory compounds

The anti-inflammatory pharmacology of marine compounds reported during 2005–6 showed a considerable increase from our previous reviews [1–5].

Busserolles and colleagues [98] tested the hypothesis that oral administration of **bolinaquinone (79)** and **petrosiaspongiolide M (80)**, two marine terpenes isolated from the sponges *Dysidea* sp. and *Petrosaspongia nigra*, could inhibit inflammation and oxidative stress in an *in vivo* murine model of inflammatory bowel disease in humans. The observation that both compounds inhibited neutrophilic infiltration, interleukin-1β, prostaglandin E_2 levels and cyclooxygenase 2 protein expression *in vivo*, supports further development of these compounds for "protective strategies" against intestinal inflammatory diseases. Miyaoka and colleagues [99] contributed to the pharmacology of phospholipase A_2 inhibitors by investigating two sesterterpenoids, **cladocorans A (81)** and **B (82)** from the coral *Cladocora cespitosa*, which possess a -hydroxy-butenolide moiety. Cladocorans A and B were observed to potently inhibit secretory phospholipase A_2 (IC_{50}=0.8–1.9 μM), with a potency similar to manoalide (IC_{50}=0.6 μM). McNamara and colleagues [100] reported the isolation of a novel **isozonarone derivative** (**83**) and of **isozonarol (84)** from the New Zealand sponge *Dysidea* cf. *cristagalli*. *In vitro* studies with human neutrophils demonstrated a concentration-dependent reduction of superoxide anion release (IC_{50}=3–11 μM) by a mechanism hypothesized to involve the accumulation of the lipophilic sesquiterpene moiety in cell membranes, where it could interfere with superoxide production. Mayer and colleagues [101] conducted a structure-activity relationship (SAR) study to investigate the anti-neuroinflammatory properties of the indole-derived alkaloids **manzamines** A **(65)**, B **(69)**, C **(85)**, D **(86)**, E **(71)** and F **(73),** isolated from the marine sponges *Haliclona* sp., *Amphimedon* sp., and *Xestospongia* sp. Manzamine A's potent inhibition of both superoxide anion (IC_{50}=0.1 μM) and thromboxane B_2 (IC_{50}=0.016 μM) release by activated brain microglia cells, suggested that the "solubility or ionic forms of manzamine A as well as changes such as saturation or oxidation of the β carboline or 8-membered amine ring" played a critical role in the observed SAR results. Sawant and

colleagues [102] investigated both the marine cembranoid diterpene **sarcophine (87)** and a semisynthetic sulfur-containing derivative **(88)** in an *in vitro* anti-neuroinflammatory assay [103]. Only compound **(87) s**ignificantly inhibited both generation of superoxide anion and thromboxane B_2 (IC_{50}=1 μM) from activated rat brain macrophages, demonstrating that "targeting the epoxide ring of sarcophine" enhanced sarcophine's anti-inflammatory activity. Mandeau and colleagues [104] showed that a new steroid, **3β-hydroxy-26-norcampest-5-en-25-oic acid (89)** from the sponge *Euryspongia n.* sp. reduced 6KPGF1α production by human keratinocytes by 41% at 10 μg/mL. Interestingly, Ahmed and colleagues [105] reported that the known steroid **gibberoketosterol (90),** isolated from the Formosan soft coral *Sinularia gibberosa*, significantly reduced proinflammatory iNOS and COX-2 proteins in lipopolysaccharide-stimulated murine macrophages at a concentration of 10 μM to 44.5 % and 68.3 % of control values, respectively. Tziveleka and colleagues [106] submitted anti-inflammatory studies with the known **chromenol (91)** isolated from the marine Greek sponge *Ircinia spinosula*. The authors noted that the compound's potent inhibition of leukotriene B4 generation by stimulated porcine leukocytes (IC_{50}=1.9 μM), was related to the "*absence of a side chain OH group as well as the reduced number of prenyl moieties*" on the sponge metabolite. Huang and colleagues [107] described a novel sesquiterpenoid **isoparalemnone (92)** from the Formosan soft coral *Paralemnalia thyrsoides* that significantly inhibited inflammatory iNOS protein expression (70% at 10 μM) in activated RAW 264.7 cells. Sugiura and colleagues [108] reported that a **phlorofucofuroeckol-B (93)** from an edible Japanese marine brown alga, *Eisenia arborea*, inhibited histamine release (IC_{50}=7.8 μM) from a rat basophilic leukemia in a concentration-dependent manner, an observation which compared favorably with a clinically used antihistamine Tranilast (IC_{50}=46.6 μM). Kita and colleagues [109] discovered a novel amphoteric iminium metabolite, **symbioimine (94)** in a dinoflagellate *Symbiodinium* sp. isolated from the marine flatworm *Amphiscolops* sp., and showed that it inhibited the cyclooxygenase 2 enzyme by 32% at 10 μM. The authors suggested that symbioimine might become a useful lead to develop new nonsteroidal anti-inflammatory drugs.

3.2 Cardiovascular compounds

Sauviate and colleagues [110] reported novel studies on the mechanism of action of **lepadiformines A and B (95,96)**, previously described marine alkaloids from the tunicate *Clavelina moluccensis*. Lepadiformines A and B dose-dependently inhibited the background inward rectifying K^+ current (IC_{50}=1.42 μM) by blocking the cardiac muscle K_{ir} channel, and putatively interacting with "one of the negatively charged aminoacids located in the inner vicinity of the narrow K^+ selectivity filter, candidates being residues D172, E224 or E229. Onodera and colleagues [111] isolated **zooxanthellamide Cs (97)** from cultures of the marine dinoflagellate *Symbiodinium* sp., and showed they were vasoconstrictive to rat blood vessels (EC_{50}= 0.39 μM). The structure-activity relationship study suggested that the "*huge macrolactone structure*" played an as yet undetermined but critical role in the vasoconstrictive activity.

3.3 Compounds affecting the immune system

As a significant contribution to the discovery of novel indoleamine 2,3-dioxygenase (INDO) inhibitors, agents shown to prevent immunological rejection of tumors, Pereira and colleagues [112], reported that the polyketides **annulins A, B, and C (98–100)** purified from the marine Northeastern Pacific hydroid *Garveia annulata,* potently inhibited INDO *in vitro* (K*i*= 0.12–0.68 μM). Interestingly, the annulins were more potent than 1-methyltryptophan (K*i*=6.6 μM), one of the most potent agents currently available. Aminin and colleagues [113] investigated the immunomodulatory properties of a "medical lead" named cumaside, which consisted of a complex of cholesterol with monosulfated **cucumariosides (101)**, triterpene oligoglycosides from the Far-Eastern edible sea cucumber *Cucumaria japonica*. The investigators observed that cumaside, while lowering the membranolytic activity of the cucumariosides, appeared to

significantly enhance their immunomodulatory properties on both human and murine macrophages and lymphocytes. Costantino and colleagues [114] contributed a new α-galactoglycosphingolipid, **damicoside (102)**, isolated from the marine sponge *Axinella damicornis*. Damicoside exhibited concentration-dependent stimulatory activity in a murine spleen proliferation assay, showing that a free galactose 2-OH and 3-OH are critical for activity, while in contrast, a free galactose 4-OH is not required for the immunostimulatory activity of these bioactive glycosphingolipids compounds. Kim and colleagues [115] investigated the antiapoptotic activity of **laminarin polysaccharides** isolated from the alga *Laminaria japonica*. A detailed pharmacological investigation revealed that the laminarin polysaccharides suppressed mouse thymocyte apoptosis, while also significantly inducing the upregulation of 33 immunomodulatory genes from a total of 7,410 genes which were examined using a cDNA microarray. Xia and colleagues [116] extended the pharmacology of a **sulfated polymannuroguluronate (SPMG) (103),** a polysaccharide with an average molecular weight of 8.0 kDa isolated from the brown alga *Laminaria japonica*, which recently entered Phase II clinical trials in China as an anti-AIDS drug candidate. Although SPMG appeared to exert immunopotentiation by direct activation of T cell proliferation, and the concomitant modulation of cytokines, namely enhancement of interleukin-2 and interferon- generation and inhibition of tumor necrosis factor-α release, the authors concluded that “much remains, however, unknown about the immunomodulation mechanism of SPMG”. Oda and colleagues [117] described the pharmacology of **verrucarin A** (**104**), a compound isolated from the culture broth of the Palauan marine fungus *Myrothecium roridum*. Verrucarin A significantly inhibited interleukin-8 production from human promyelocytic leukemia cells, by a mechanism that involved inhibition of the activation of the mitogen activated kinases c-JUN and p38.

3.4 Compounds affecting the nervous system

Pharmacological studies with marine compounds affecting the nervous system during 2005–6 focused on three main areas of neuropharmacology: the stimulation of neurogenesis, the targeting of receptors, and other miscellaneous activities on the nervous system.

Biologically active molecules which stimulate neurogenesis and rescue damaged neuronal cells are potentially promising therapeutic strategies to treat neurodegenerative diseases [118]. As shown in Table 2, the enhancement of the neuritogenic properties of nerve growth factor (NGF), a chemical that has a critical role in differentiation, survival and neuronal regeneration, was reported for several marine natural compounds isolated from sea cucumbers, sea stars, brown algae and a fungus, respectively.

Nandini and colleagues [119] isolated a novel 70-kDa **chondroitin sulfate/dermatan sulfate** hybrid chain from the skin of the blue shark *Prionace glauca* which exhibited neuritogenic activity of both an axonic and a dendritic nature, as well as binding activities for various growth factors and two neurotrophic factors. The unique structure and biological activity of the proteoglycans demonstrated that shark skin has “immense potential to be exploited for pharmaceutical purposes”. Although it is clear that the harvest of sharks for either food or pharmaceutical purposes is highly questionable, from a sustainability point of view the characterization of biological metabolites from these animals is extremely interesting and significant. Kisa and colleagues [120,121] contributed two new monosialo- and disialo-gangliosides **CEG-3 (105)** and **CEG-6 (106)** from the Japanese sea cucumber *Cucumaria echinata.* Although the molecular mechanism of action remains undetermined, both gangliosides induced neurite outgrowth in 42–50% of rat pheochromocytoma PC12 cells at 10 μM in the presence of NGF, suggesting the “isolation and characterization of such neuritogenically active ganglosides” will require considerable further study. Inagaki and colleagues [122] contributed the first isolation and characterization of a **trisialo-ganglioside LLG-5 (107)** from the sea star *Linckia laevigata*. LLG-5 proved to be more neuritogenic (59.3

% at 10 μM) to rat pheochromocytoma PC12 cells than CEG-3 and CEG-6. Higuchi and colleagues [123] isolated a biologically active **glycoside GP-3 (108)** from the starfish *Asterina pectinifera* which proved to be slightly less neuritogenic (38.2 % at 10 μM) to rat pheochromocytoma PC12 cells than CEG-3, CEG-6 and LLG-5. Han and colleagues [124] reported a structure-activity relationship with new steroid glycosides, namely **linckosides (109–111)** isolated from the Okinawan sea star *Linckia laevigata*. All linckosides enhanced the neuritogenic activity of NGF by 40–98%, with a SAR study revealing the "importance of the carbon branch modified by a pentose at the side chain" in the neuritogenic activity. Wei and colleagues [125] investigated a novel polyketide **shimalactone A (112)** isolated from the cultured marine-derived fungus *Emericella variecolor* GF10. Shimalactone A induced neuritogenesis in a neuroblastoma Neuro 2A cell line at 10 μg/mL by an as yet undetermined mechanism. Tsang and colleagues [118] described **sargachromenol (113)** from the marine brown alga *Sargassum macroca*rpum. Sargachromenol was shown to "markedly" promote NGF-dependent neurogenesis in PC12D cells (ED_{50}=9 μM). Interestingly, mechanistic studies demonstrated that both the cyclic AMP-mediated protein kinase and mitogen-activated protein kinase 1/2 signal transduction pathways were required for neurite growth stimulated by sargachromenol. Tsang's detailed molecular studies clearly suggests that additional mechanism of action investigations with the gangliosides, linckosides and shimalactones might possibly help develop these chemicals as potentially new medicines for the treatment of neurodegenerative diseases.

As shown in Table 2, the conotoxins αD-VxXIIA, αD-VxXIIB, and αD-VxXIIC, conopeptide SO-3 and dysiherbaine, were shown to target receptors present in the nervous system.

Loughnan and colleagues [126] reported three novel **conotoxins αD-VxXIIA, αD-VxXIIB, and αD-VxXIIC (114–116)**, purified from the venom of the marine snail *Conus vexillum*. A detailed series of mechanistic studies revealed that the three post-translationally modified conotoxins were non-competitive inhibitors of nicotinic acetylcholine receptors with selectivity towards *α7* and *β*-containing neuronal receptor subtypes, and with αD-VxXIIB conotoxin being the most potent (IC_{50}=0.4 nM for *α7*). Wen and colleagues [127] described a new O-superfamily **conopeptide SO-3 (117)**, derived from the marine snail *Conus striatus*. Because the new conopeptide was shown to selectively target N-type voltage-sensitive calcium currents in cultured hippocampal neurons (IC_{50}=0.16 μM), the authors suggested that it may have "therapeutic potential as a novel analgesic agent". Sanders and colleagues [128,129] extended the pharmacology of **dysiherbaines (118,119)**, potent kainate receptor agonists derived from the marine sponge *Dysidea herbacea.* Detailed molecular studies revealed the site residues responsible for subunit selectivity of the two compounds on kainate receptors, observations which could aid in the rational design of "selective ligands with distinct pharmacological properties". Tsuneki and colleagues [130] investigated the preclinical pharmacology of the marine quinolizidine alkaloid (−) **pictamine (120)**, isolated from the ascidian *Clavelina picta*. Pictamine irreversibly blocked *α4β2* and *α7* nicotinic acetylcholine receptors (IC_{50}= 1.5 μM), and thus could become a valuable tool to study neuronal activity mediated by these two major types of nicotinic receptors.

As shown in Table 2, during 2005–6, additional marine compounds were reported to exhibit pharmacological effects on the nervous system. Aiello and colleagues [131] established the molecular pharmacology of a novel **bromopyrrole alkaloid (121)**, isolated from the Mediterranean sponge *Axinella verrucosa.* In a series of *in vitro* studies, the alkaloid was observed to display potent neuroprotective activity against the agonists serotonin and glutamate. Aiello and colleagues [132] also reported another marine natural product, namely the alkaloid **daminin (122)** isolated from the Mediterranean sponge *Axinella damicornis* that was observed to reduce Ca^{2+} levels in neuronal cells *in vitro* stimulated with either glutamic acid or n-methyl-D-aspartate, agents that cause a strong rise in Ca^{2+} in these cells. Bringmann

and colleagues [133] isolated a novel angucyclinone **gephyromycin (123)** from the bacterium *Streptomyces griseus*. Gephyromcyin appeared to "represent a new potent glutamate agonist" towards neuronal cells, and at 3 μg/mL caused significant increase in intracellular Ca^{2+} concentration, a response comparable to the potent glutamate agonist DCG-IV. To and colleagues [134] while studying the mechanisms involved in neuronal outgrowth observed that the alkaloid **motuporamine C (124)**, isolated from the Papua New Guinea marine sponge *Xestospongia exigua*, stimulated concentration-dependent neuronal growth cone collapse. The intracellular signaling mechanisms involved significant upregulation of the Rho-Rho- kinase collapse pathway, suggesting this compound might be useful to examine mechanisms "utilized by neurons for outgrowth". Temraz and colleagues [135] noted that Red Sea soft corals *Sarcophyton glaucum* and *Lobophyton crassum* contained natural products which include **trigonelline (125)**, that increased the electrophysiological excitability of rat cultured dorsal root ganglion neurons. The increased excitability was associated with enhanced KCl-evoked Ca^{2+} influx consistent with an increase in action potential firing, perhaps contributing to "chemical defenses".

4. Marine Compounds with Miscellaneous Mechanisms of Action

Table 3 lists 58 marine compounds with miscellaneous pharmacological mechanisms of action, and with their respective structures presented in Fig. 3. Because during 2005–2006 additional pharmacological data were unavailable, it was not possible to assign these compounds to a particular drug class as was the case for the compounds included in Tables 1 and 2.

As shown in Table 3, the pharmacological activity, respective IC_{50}s, and a molecular mechanism of action have been reported for 23 marine natural products: *Agelas* sp. **dibromopyrrole (126), adociaquinone B (127), barrettins (128** and **129), bromoageliferins (130** and **131), chlorolissoclimide (132), fascaplysin analogue CA224 (133), hippuristanol (134), liphagal (135), lukianol B (136), rubrolide (137), micropeptins (138** and **139), pateamine (140), phlorofucofuroeckol A (141), purealin (142),** *Spongia* **sesterterpenoids (143–145), squalamine** analog **(146), and xestospongin B (147)** and **C (148)**.

In contrast, although a pharmacological activity was described, and an IC_{50} for inhibition of an enzyme or receptor determined, detailed molecular mechanism of action studies were unavailable for the following 35 marine compounds included in Table 3: **actiniarin B (149), amphezonol A (150), ascochitine (151), briaexcavatin E** and **G (152** and **153), brunsvicamides B** and **C (154** and **155), caulerpin (156), cortistatin A (157), cyanopeptolin 954 (158), dehydroluffariellolide diacid (159), *O*-methyl nakafuran-8-lactone (160), 2*β*, 3*α*-epitaondiol (161), fascaplysin (162), gorgosterols (163–165), hexylitaconic acid (166), himeic acid A (167), kalihinol A (168), largamides D–G 169–172, peribysins E–G (173–175), petrosamine B (176), phrygiasterol (177),** *Portieria hornemannii* **monoterpenes (178** and **179),** *Sargassum micracanthum* **plastoquinone (180), scalaradial (181), secomycalolide A (182),** and *Symphyocladia latiuscula* **bromophenol (183)**.

5. Reviews on marine pharmacology

Several reviews covering both general and specific subject areas of marine pharmacology were published during 2005–6: (a) *general marine pharmacology*: biodiversity as a continuing source of novel drug leads [136]; international collaboration in drug discovery and development [137]; indole alkaloid marine natural products as a promising source of new drug leads for multiple disease categories [138]; the biopotential of marine actinomycete diversity and natural product discovery [139]; the renaissance of natural products as drug candidates [140]; bioactive compounds from cyanobacteria and microalgae [141]; drug discovery from natural sources [142]; a new resource for drug discovery: marine actinomycete bacteria [143]; bioactive compounds from marine processing byproducts [144]; implications of marine

biotechnology on drug discovery [145]; (b) *antimicrobial marine pharmacology:* advances in antimicrobial and antiangiogenic pharmacology of squalamine [146]; marine natural products as anti-infective agents [147]; chemotyping/metabolomics use for metabolite profiling in microbial drug discovery [148]; the status of natural products from fungi and their potential as anti-infective agents [149]; (c) *cardiovascular pharmacology*: dietary long-chain omega-3 fatty acids of marine origin and their protective cardiovascular effects [150]; (d) *antituberculosis, antimalarial and antifungal marine pharmacology:* compounds for infectious diseases [151]; marine natural products against tuberculosis [152]; (e) *antiviral marine pharmacology:* antiviral activities of polysaccharides from natural sources [153]; antiplasmodial marine natural products in the perspective of current chemotherapy and prevention of malaria [154]; (f) *anti-inflammatory marine pharmacology*: therapeutic potential of the antioxidative properties of coelenterazine, a marine bioluminescent substrate [155]; chemistry and biology of anti-inflammatory marine phospholipase A_2 inhibitors [156]; the structures, biosynthesis and pharmacology of the marine natural products of *Pseudopterogoria elisabethae* [157]; chemistry and biology of anti-inflammatory marine natural products [158]; marine sponge metabolites for the control of inflammatory diseases [159]; antioxidant metabolites from marine derived fungi [160]; (g) *nervous system marine pharmacology*: marine compounds for the treatment of neurological disorders [161]; potential candidates for Alzheimer's disease [151]; novel pain relief via marine snails [162]; bryostatin-1: pharmacology and therapeutic potential as a CNS drug [163], and (h) *miscellaneous molecular targets*: V-ATPases as drug targets [164]; topoisomerase inhibitors of marine origin [165]; enzyme inhibitors from marine actinomycetes [166]; marine compounds as a new source for glycogen kinase 3 inhibitors [167].

6. Conclusion

Four years after the approval of the marine compound ziconotide (Prialt®) by the U.S. Food and Drug Administration [168], global research focused on the therapeutic potential of marine natural products remains very active and sustained. The latest update on the clinical pipeline of marine-derived agents is available at http://marinepharmacology.midwestern.edu/clinDev.htm.

The current contribution to the marine pharmacology reviews series which was begun in 1998 [1–5], demonstrates that marine pharmacology research continued to proceed at a sustained pace in 2005–2006, as a result of the active participation of natural product chemists and pharmacologists from Argentina, Australia, Brazil, Canada, Chile, China, Colombia, Costa Rica, Egypt, Finland, France, Germany, Greece, India, Indonesia, Israel, Italy, Japan, the Netherlands, New Caledonia, New Zealand, Panama, Portugal, Russia, Slovenia, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, Uruguay, and the United States. Thus, if the rate of preclinical and clinical pharmacological research continues, we anticipate that more marine natural products will probably become potential leads for clinical development as novel therapeutic agents for the treatment of multiple disease categories.

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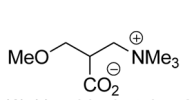
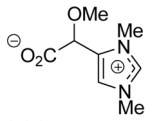
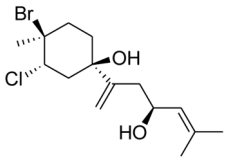


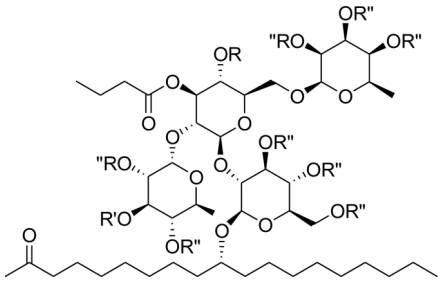
(**1**) (-)-echinobetaine A



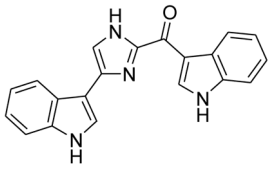
(**2**) (+)-echinobetaine B



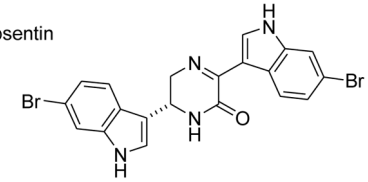
(**3**) *Laurencia scoparia* terpene



(**4**) caminoside B, R=Bu, R'=H, R"=H
(**5**) caminoside D, R=Bu, R'=Bu, R"=H



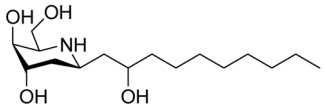
(**6**) deoxytopsentin



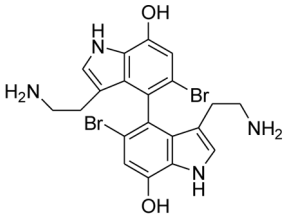
(**7**) hamacanthin A

AACSDRAHGHICESFKSFCKDSGRNGVKLRANCKKTCGLC

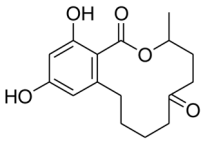
(**8**) aurelin



(**9**) batzellaside A



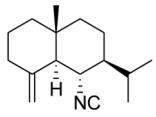
(**10**) dendridine A



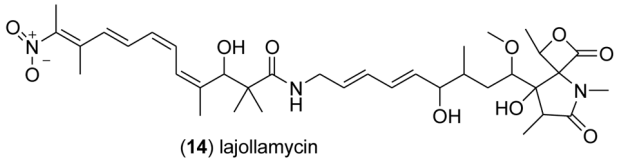
(**11**) 6-oxo-de-O-methyllasiodiplodin

GsF LFGFLI KLI PSLFGALSNI GRNRNQ
GsG LFGFLI PLLPHI I GAI PQVI GAI R
Pp 4b LFGFLI PLLPHLI GAI PQVI GAI R
GsB I GGI I SFFKRLF
GsD FI GGI I SFFKRLF
GsE FI GGI I SFI KKLF
Pp2a FIGGI I SLI KKLF
GsA WWRELLKKLAFTAAGHLGSVLAAKQSGW
GsC NWRKI LGKI AKVAAGLLGSMLAGYQV

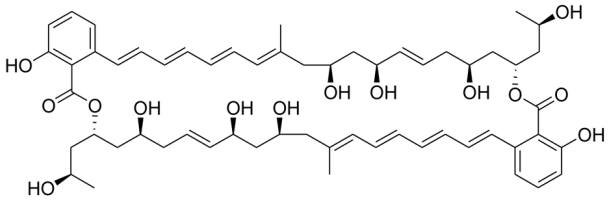
(**12**) grammistins



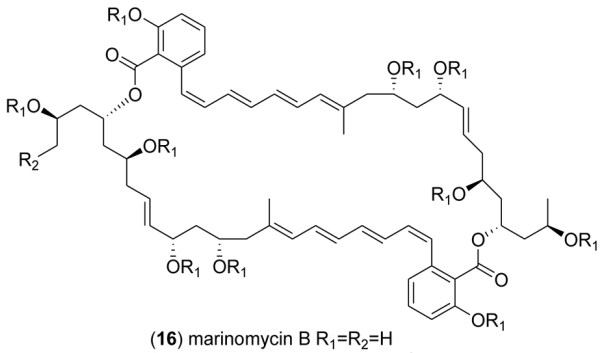
(**13**) halichonadin C



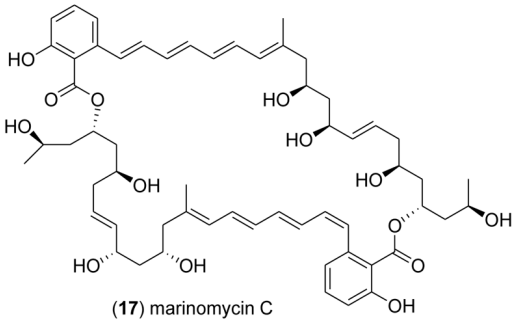
(**14**) lajollamycin



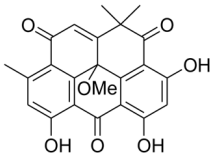
(**15**) marinomycin A



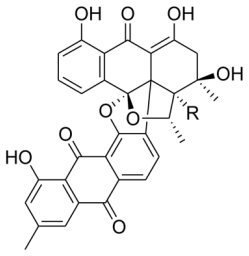
(**16**) marinomycin B R_1=R_2=H
(**18**) marinomycin D R_1=H, R_2=CH_3



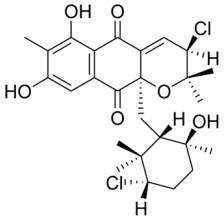
(**17**) marinomycin C



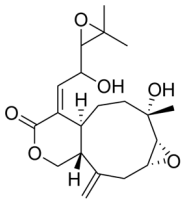
(**19**) resistoflavin methyl ether



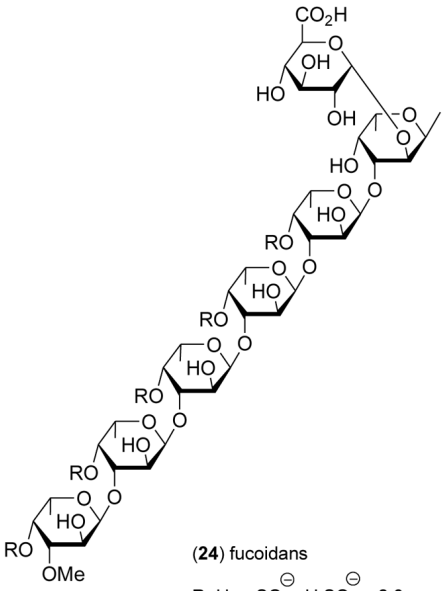
Streptomyces anthraquinones
(**20**) R=H; (**21**) R=OH



(**22**) *Streptomycetaceae* quinone

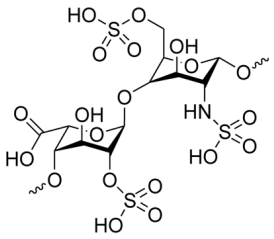


(**23**) xeniolide I

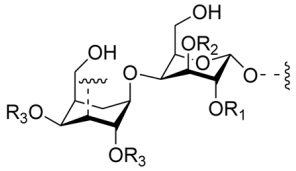


(**24**) fucoidans

R=H or $SO_3^{\ominus}$, H:$SO_3^{\ominus}$ = 2:3



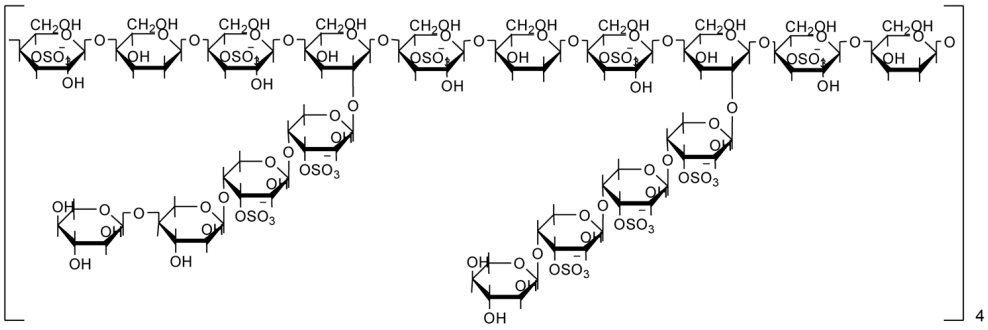
(**25**) heparin



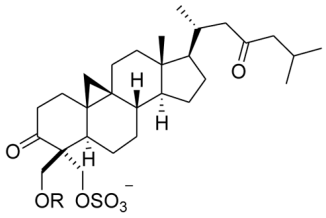
sulfated galactans, R_1,R_2,and R_3=H or $SO_3^{\ominus}$

(**26**) *occidentalis*, R_1 as $SO_3^{\ominus}$-66%, R_2 as $SO_3^{\ominus}$-33%

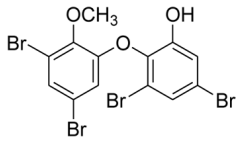
(**27**) *crinale*, R_1 as $SO_3^{\ominus}$-60%, R_2 as $SO_3^{\ominus}$-15%



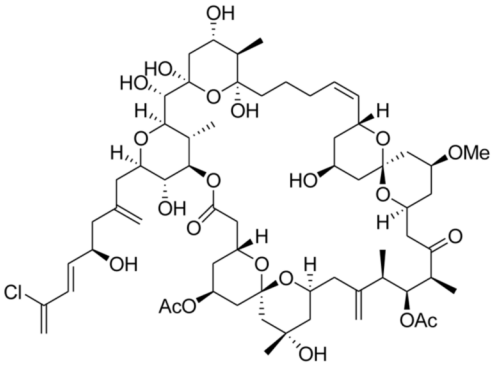
(**28**) sulfated galactofucan from *S.schroederi*



(**29**) capisterone A, R=Ac
(**30**) capisterone B, R=H



(**31**) *Dysidea herbacea* phenol

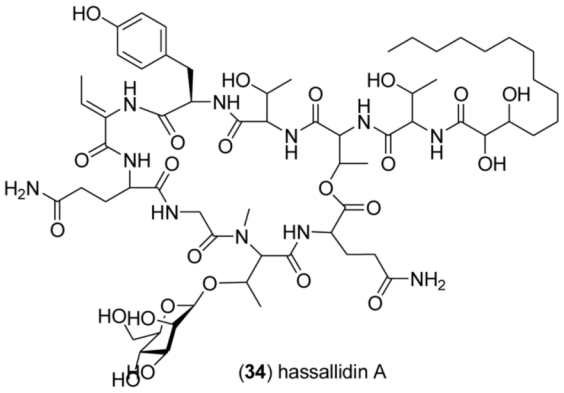


(**32**) spongistatin 1

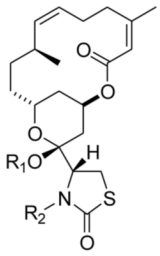
WLNALLHHGLNCAKGVLA*

ALLHHGLNCAKGVLA*

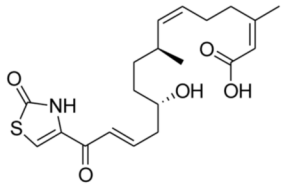
(**33**) halocidin, * signify C-terminus amidation



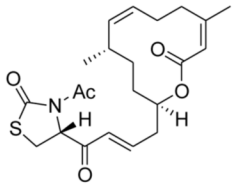
(**34**) hassallidin A



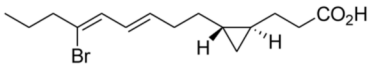
(**35**) latrunculin B (R_1=H, R_2=H)
(**36**) *N*-acetyllatrunculin B (R_1=H, R_2=CH_3CO)
(**37**) 15-*O*-methyllatrunculin B (R_1=CH_3, R_2=H)
(**38**) 15-*O*-butyllatrunculin B (R_1=C_4H_9, R_2=H)
(**39**) 15-*O*-octyllatrunculin B (R_1=C_8H_{17}, R_2=H)
(**40**) *N*-hydroxymethyllatrunculin B
(R_1=H, R_2=CH_2OH)



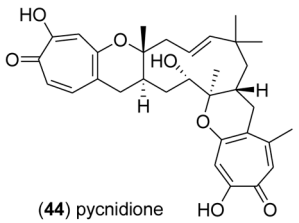
(**41**) latrunculin T

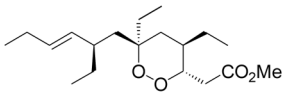


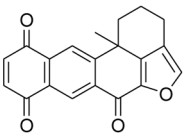
(**42**) acetylation product of latrunculin

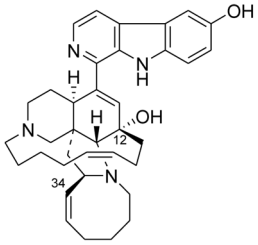


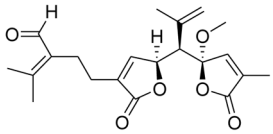
(**43**) majusculoic acid

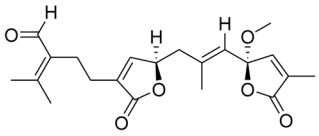

(**44**) pycnidione

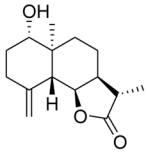

(**45**) plakortide Q

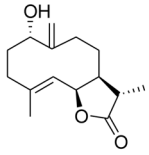

(**46**) xestoquinone

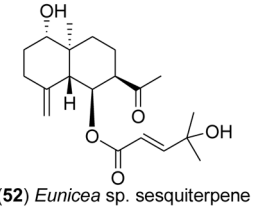

(**47**) manzamine Y

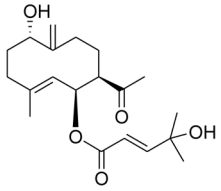

(**48**) caucanolide A

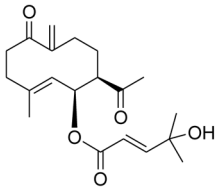

(**49**) caucanolide D

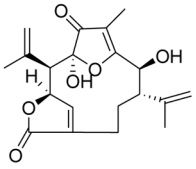

(**50**) *Eunicea* sp. sesquiterpene 2

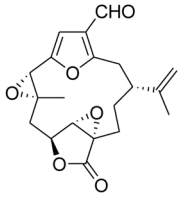

(**51**) *Eunicea* sp. sesquiterpene 3

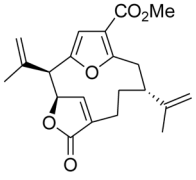

(**52**) *Eunicea* sp. sesquiterpene 5


(**53**) *Eunicea* sp. sesquiterpene 6


(**54**) *Eunicea* sp. sesquiterpene 7


(**55**) kallolide D


(**56**) leptolide


(**57**) deoxypseudopterolide

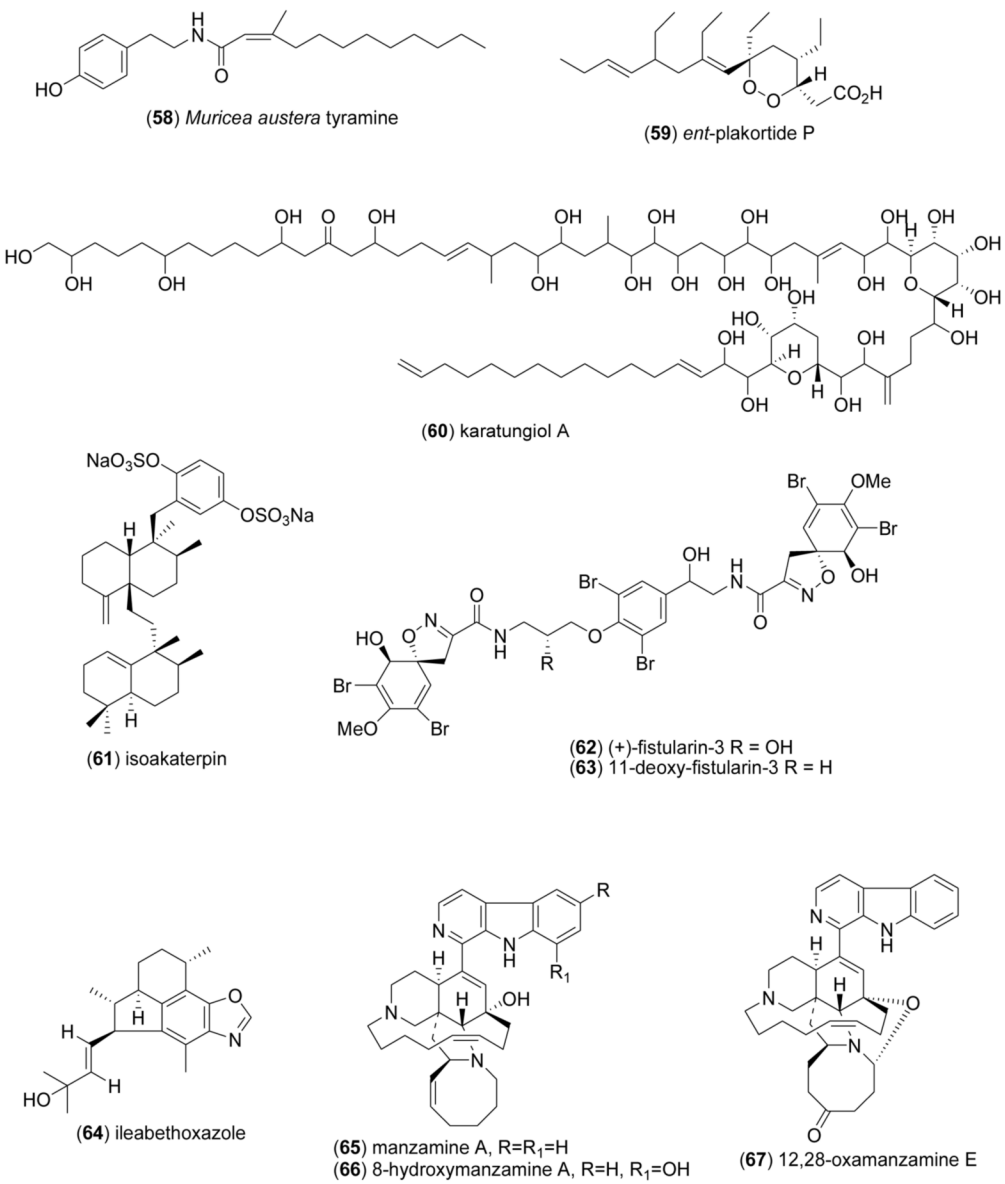
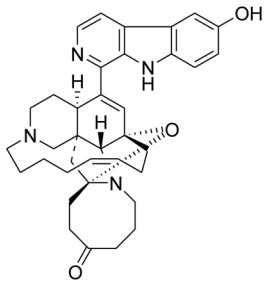
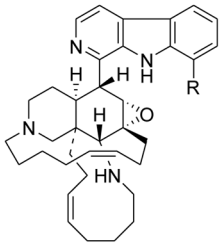


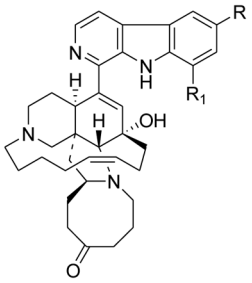
Figure 1.



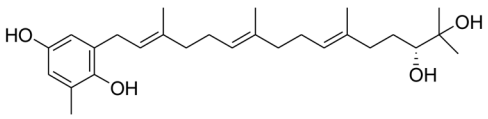
(**68**) 12,34-oxa-6-hydroxymanzamine E



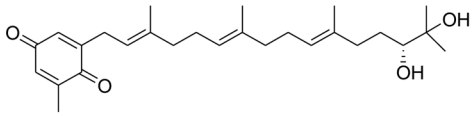
(**69**) manzamine B, R=H
(**70**) 8-hydroxymanzamine B, R=OH



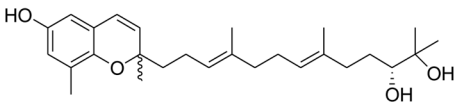
(**71**) manzamine E, R=R_1=H
(**72**) 6-hydroxymanzamine E, R=OH, R_1=H
(**73**) manzamine F, R=H, R_1=OH



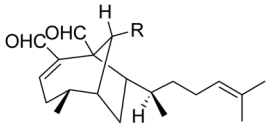
(**74**) *Sargassum* plastoquinone 1



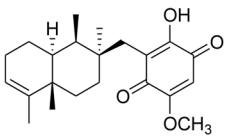
(**75**) *Sargassum* plastoquinone 2



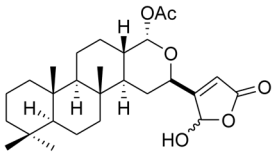
(**76**) chromene derivative from *Sargassum micracanthum*



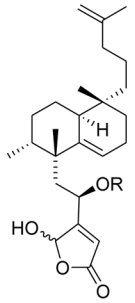
(**77**) *Dictyota* diterpene 1 R = OH
(**78**) *Dictyota* diterpene 2 R = OAc



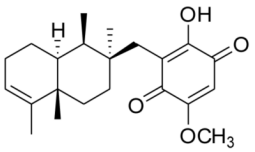
(**79**) bolinaquinone



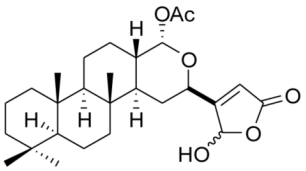
(**80**) petrosiaspongiolide M



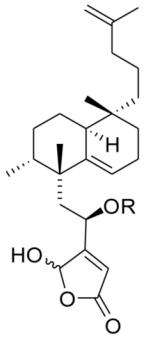
(**81**) cladocoran A R = Ac
(**82**) cladocoran B R = H



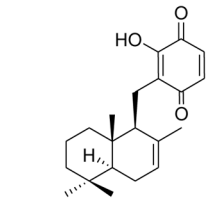
(**79**) bolinaquinone



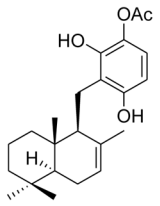
(**80**) petrosiaspongiolide M



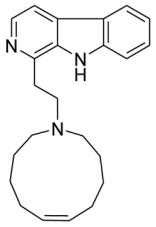
(**81**) cladocoran A R = Ac
(**82**) cladocoran B R = H



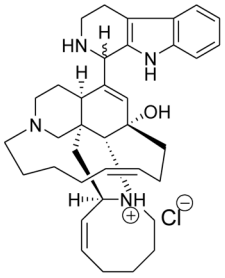
(**83**) 21-hydroxy-*ent*-isozonarone



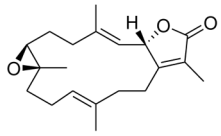
(**84**) 20-*O*-acetyl-21-hydroxy-*ent*-isozonarol



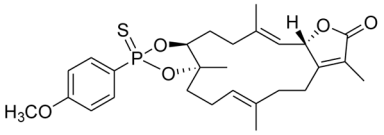
(**85**) manzamine C



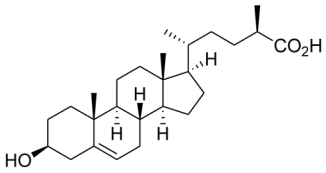
(**86**) manzamine D hydrochloride



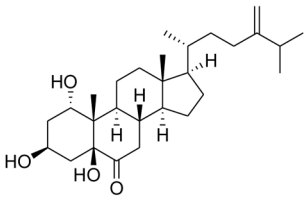
(**87**) sarcophine



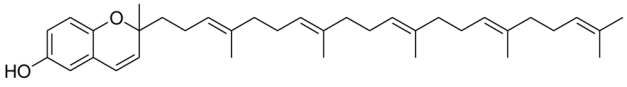
(**88**) sulfur-containing derivative of sarcophine



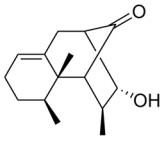
(**89**) 3β-hydroxy-26-norcampest-5-en-25-oic acid



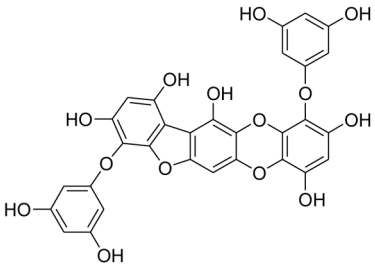
(**90**) gibberoketosterol



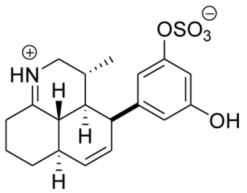
(**91**) chromenol derivative



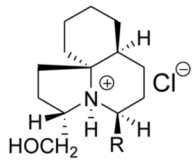
(**92**) isoparalemnone



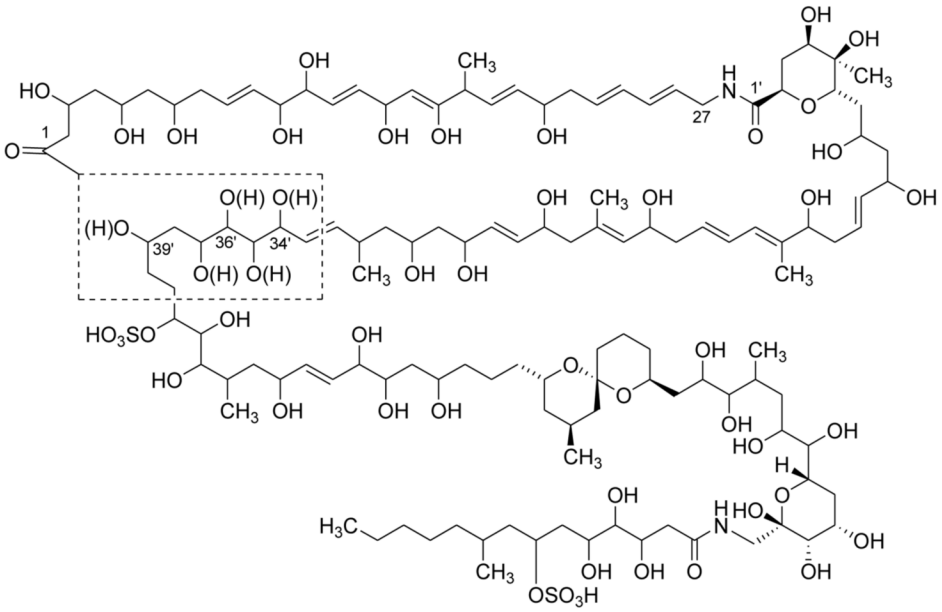
(**93**) phlorofucofuroeckol-B



(**94**) symbioimine

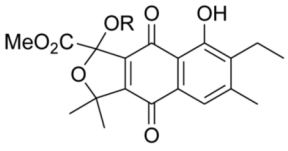


(**95**) lepadiformine A R = C_6H_{13}
(**96**) lepadiformine B R = C_4H_9

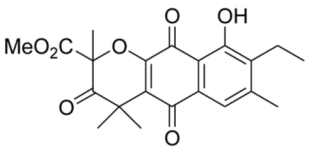


(**97**) zooxanthellamide Cs (ZAD-Cs)

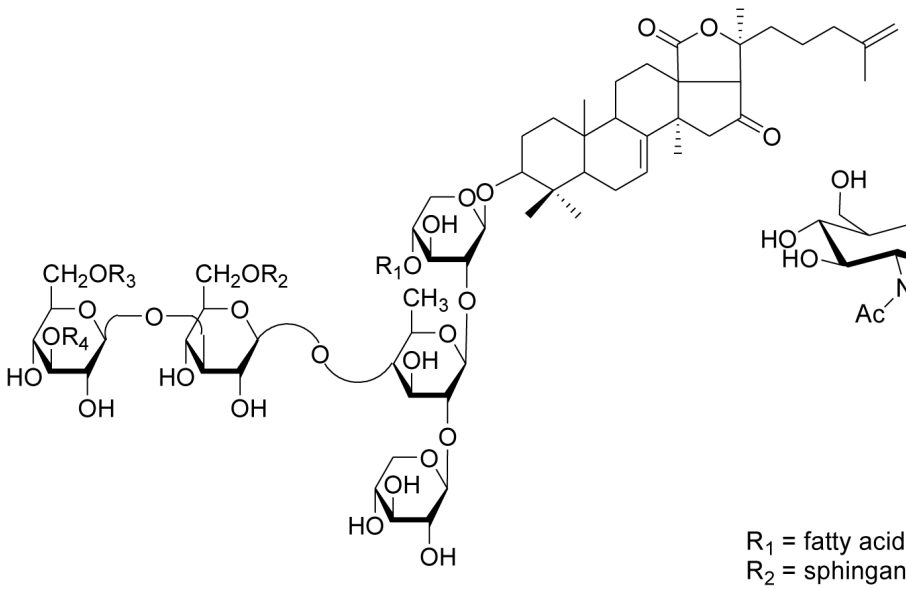
Note: ZAD–C1 to C5 are the isomeric constituents lactonized at positions 34', 35', 36', 37', and 39', respectively.



(**98**) annulin A R = H
(**99**) annulin C R = Me

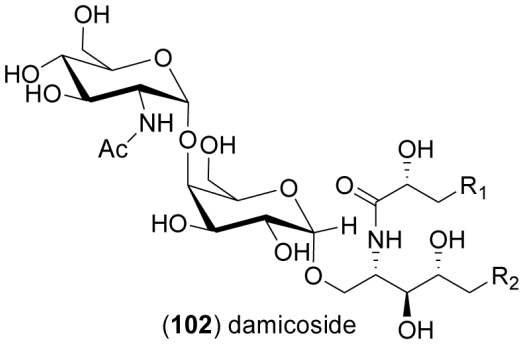


(**100**) annulin B



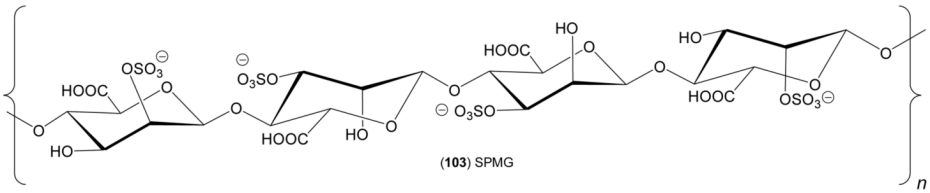
(**101**) cucumariosides

$R_1 = SO_3Na$, $R_2 = R_3 = H$, $R_4 = CH_3$
$R_1 = SO_3Na$, $R_2 = R_3 = R_4 = H$
$R_1 = R_2 = SO_3Na$, $R_3 = H$, $R_4 = CH_3$
$R_1 = SO_3Na$, $R_2 = H$, $R_3 = SO_3Na$, $R_4 = CH_3$
$R_1 = R_2 = R_3 = SO_3Na$, $R_4 = CH_3$
$R_1 = R_2 = R_3 = H$, $R_4 = CH_3$
$R_1 = R_2 = R_3 = R_4 = H$

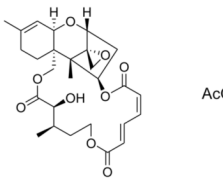


(**102**) damicoside

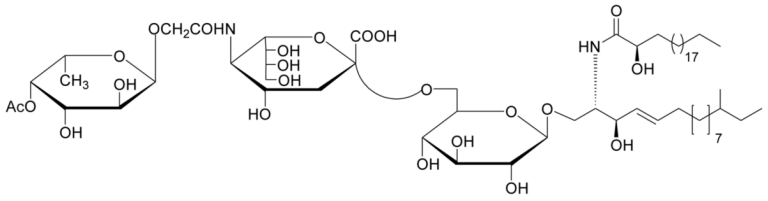
R_1 = fatty acid methyl esters of varying composition
R_2 = sphinganines of varying composition



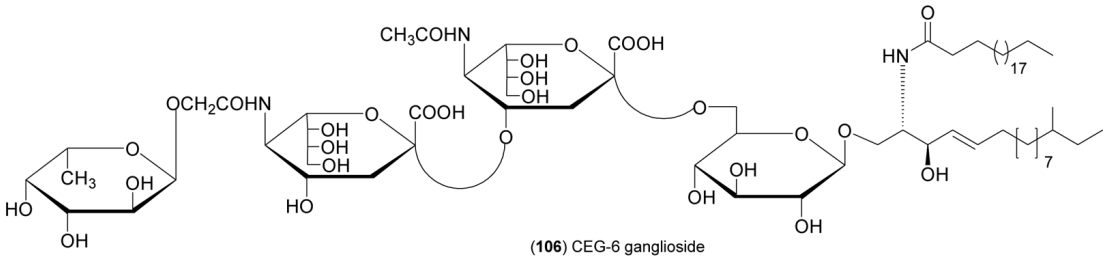
(**103**) SPMG



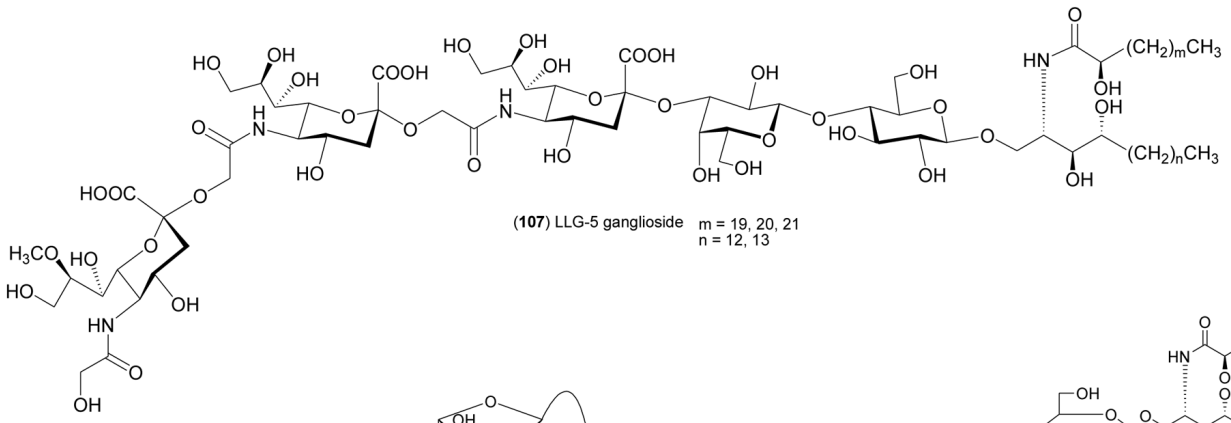
(**104**) verrucarin A



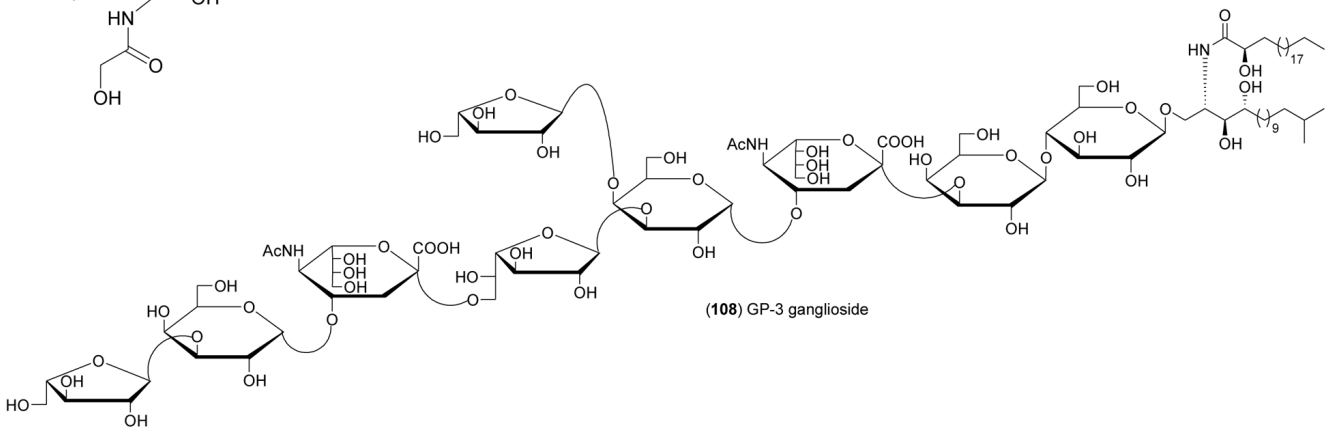
(**105**) CEG-3 ganglioside



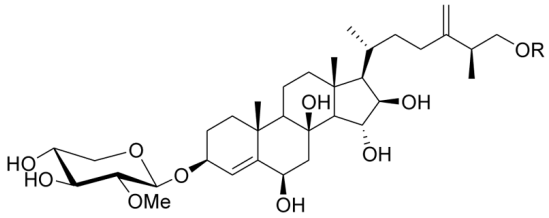
(**106**) CEG-6 ganglioside



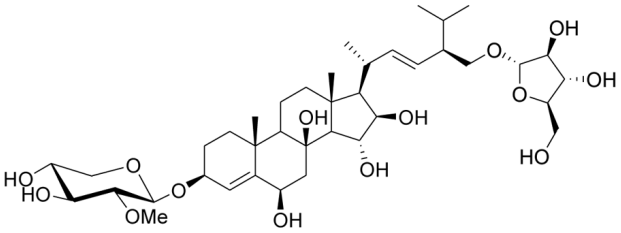
(**107**) LLG-5 ganglioside m = 19, 20, 21
n = 12, 13



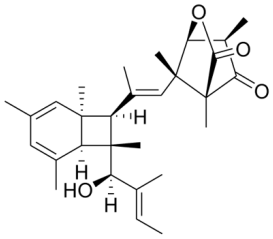
(**108**) GP-3 ganglioside



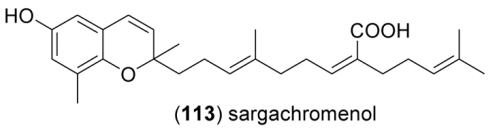
(**109**) linckoside F R = H
(**110**) linckoside I R = β-Xyl



(**111**) linckoside K



(**112**) shimalactone A

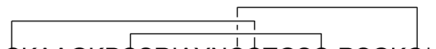


(**113**) sargachromenol

DVQD–CQVSTOGSKWGRCCLNRVCGPMCCPASHCYCVYHRGRGHGCSC#
(**114**) conotoxin VxXIIA

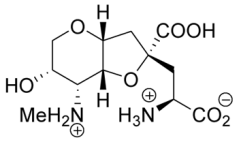
DDJSJCIINTRDSPWGRCCRTRMCGSMCCPRNGCTCVYHWRRGHGCSCPG#
(**115**) conotoxin VxXIIB

DLRQ–CTRNAPGSTWGRCCLNPMCGNFCCPRSGCTCAYNWRRGIYCSC#
(**116**) conotoxin VxXIIC

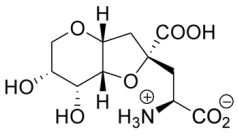


(**117**) conopeptide SO-3

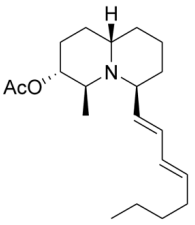
Note: The asterisk represents an amidated C-terminus.



(**118**) dysiherbaine



(**119**) neodysiherbaine A



(**120**) (–)-pictamine

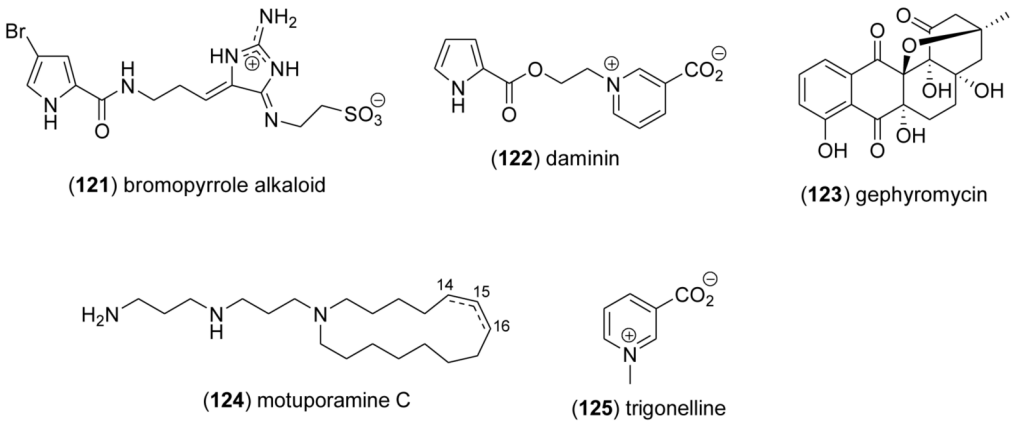
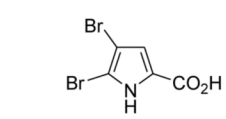
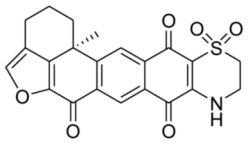


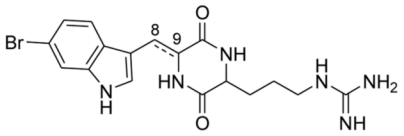
Figure 2.



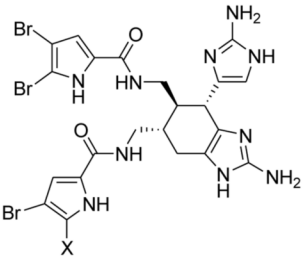
(**126**) *Agelas* sp. dibromopyrrole



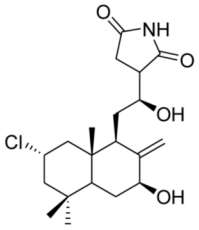
(**127**) adociaquinone B



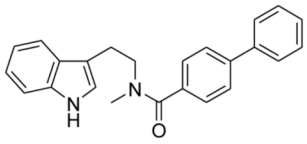
(**128**) barettin: $\Delta^{8,9}$
(**129**) 8,9-dihydrobarettin



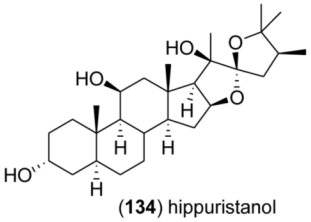
(**130**) bromoageliferin X = H
(**131**) dibromoageliferin X = Br



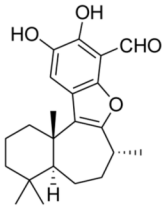
(**132**) chlorolissoclimide



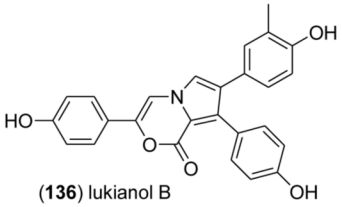
(**133**) CA224



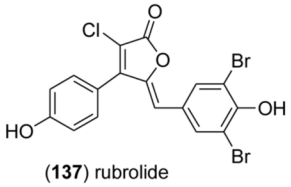
(**134**) hippuristanol



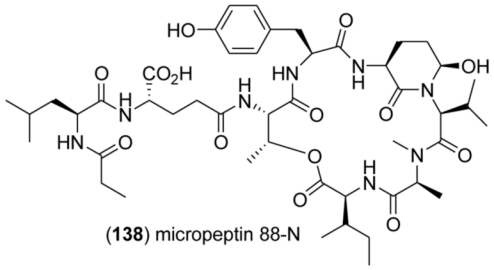
(**135**) liphagal



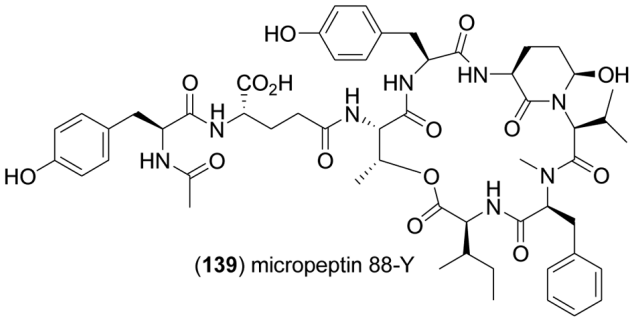
(**136**) lukianol B



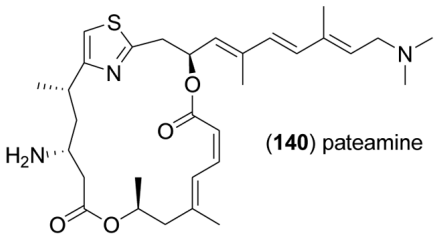
(**137**) rubrolide



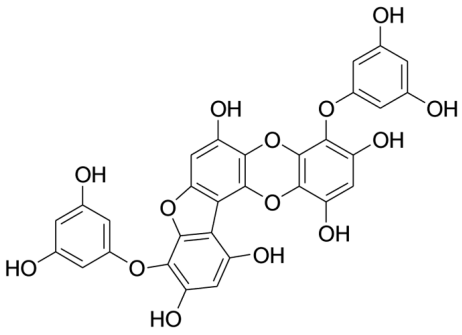
(**138**) micropeptin 88-N



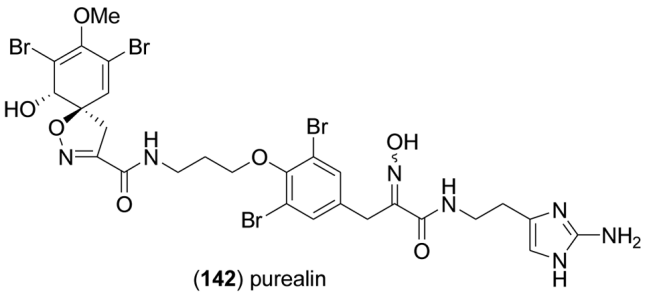
(**139**) micropeptin 88-Y



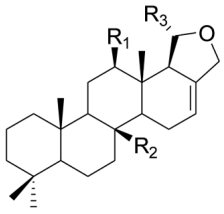
(**140**) pateamine



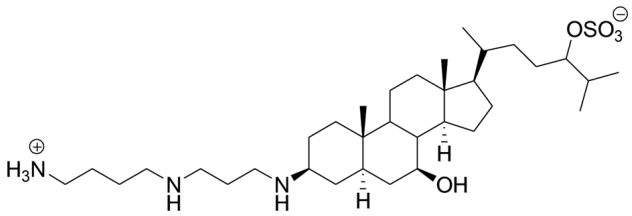
(**141**) phlorofucofuroeckol A



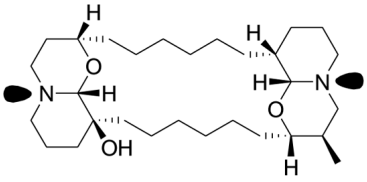
(**142**) purealin



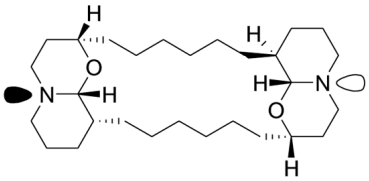
scalarane diterpenes
(**143**) R_1 = OAc, R_2 = CH_2OAc, R_3 = OH
(**144**) R_1 = OH, R_2 = CH_2OH, R_3 = H
(**145**) R_1 = OH, R_2 = Me, R_3 = OMe



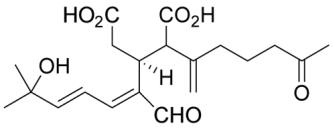
(**146**) squalamine analog



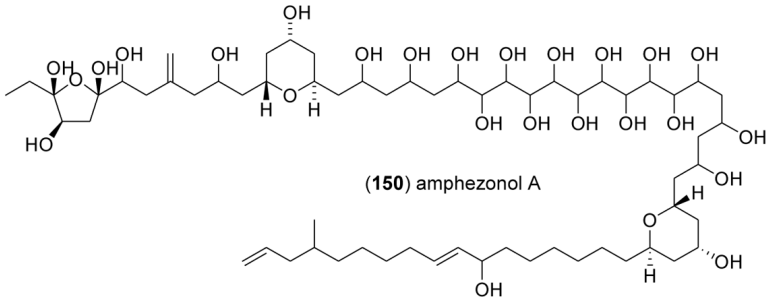
(**147**) xestospongin B



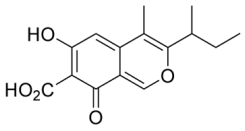
(**148**) xestospongin C



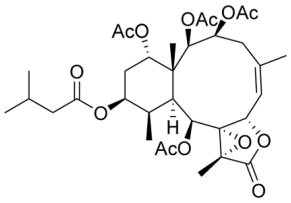
(**149**) actiniarin B



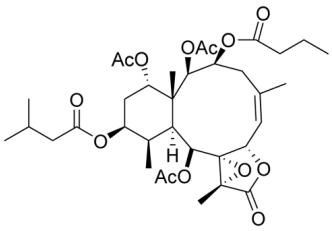
(**150**) amphezonol A



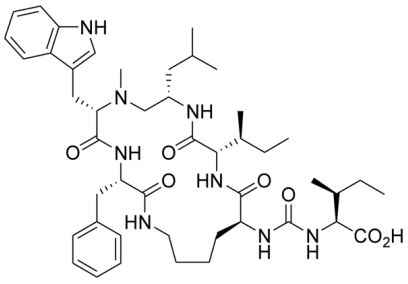
(**151**) ascochitine



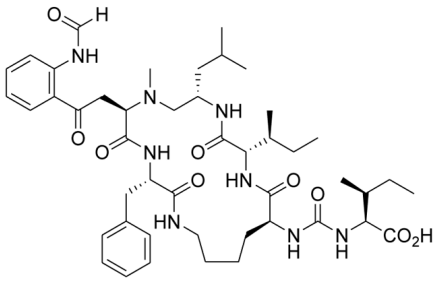
(**152**) briaexcavatin E



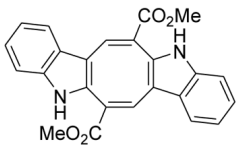
(**153**) briaexcavatin G



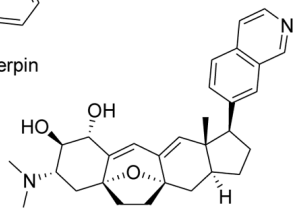
(**154**) brunsvicamide B



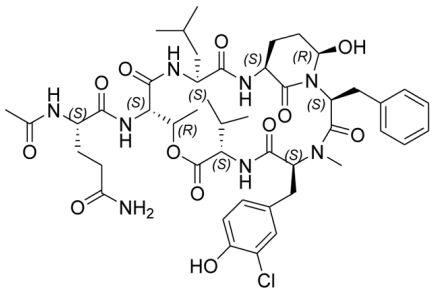
(**155**) brunsvicamide C



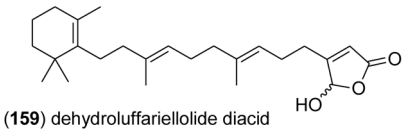
(**156**) caulerpin



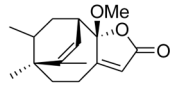
(**157**) cortistatin A



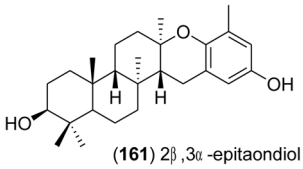
(**158**) cyanopeptolin 954



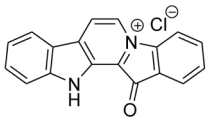
(**159**) dehydroluffariellolide diacid



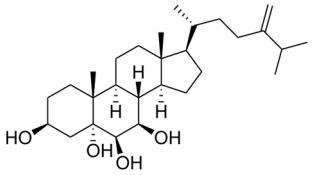
O-methyl nakafuran-8 lactone
(**160**)



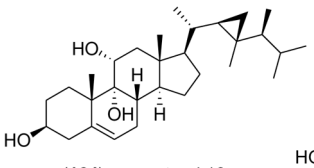
(**161**) 2β,3α-epitaondiol



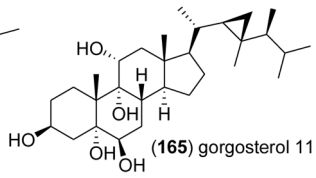
(**162**) fascaplysin



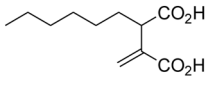
(**163**) gorgosterol 9



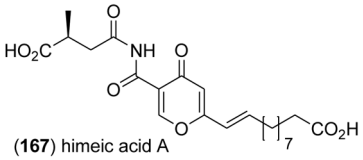
(**164**) gorgosterol 10



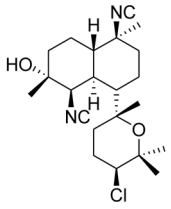
(**165**) gorgosterol 11



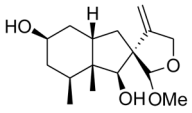
(**166**) hexylitaconic acid



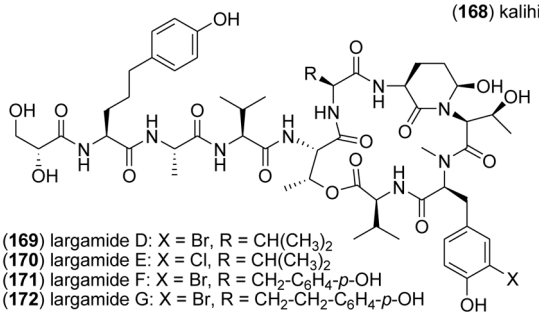
(**167**) himeic acid A



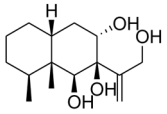
(**168**) kalihinol A



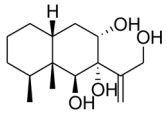
(**173**) peribysin E



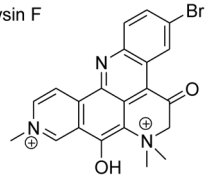
(**169**) largamide D: X = Br, R = $CH(CH_3)_2$
(**170**) largamide E: X = Cl, R = $CH(CH_3)_2$
(**171**) largamide F: X = Br, R = CH_2-C_6H_4-*p*-OH
(**172**) largamide G: X = Br, R = CH_2-CH_2-C_6H_4-*p*-OH



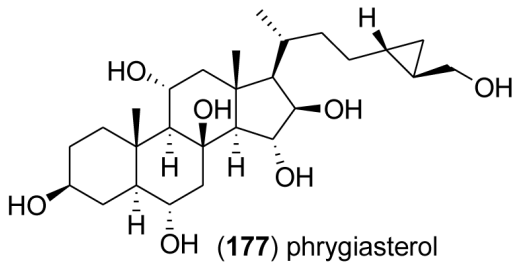
(**174**) peribysin F



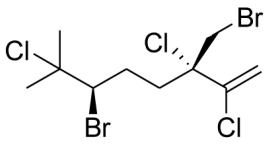
(**175**) peribysin G

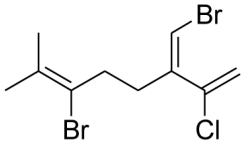


(**176**) petrosamine B

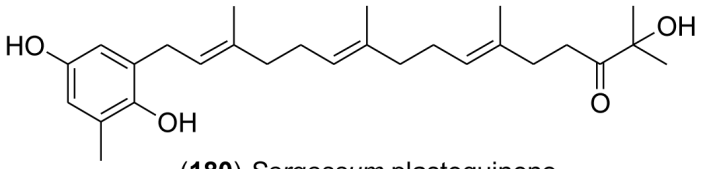


(**177**) phrygiasterol

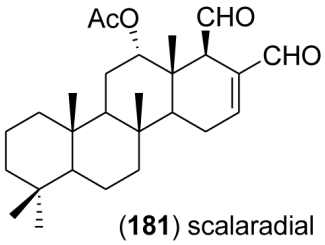




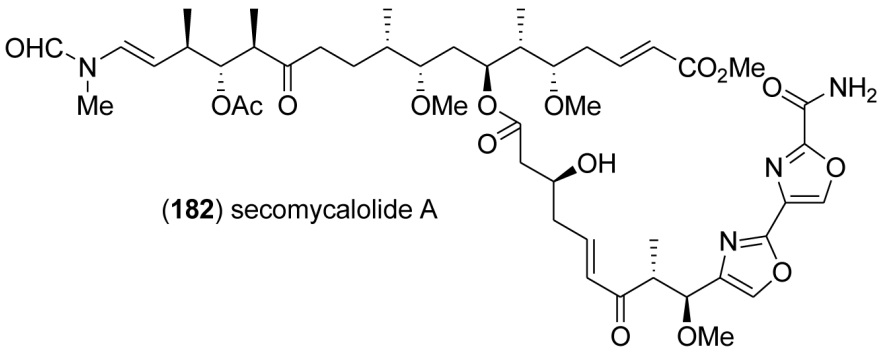
(**178**, **179**) halogenated monoterpenes



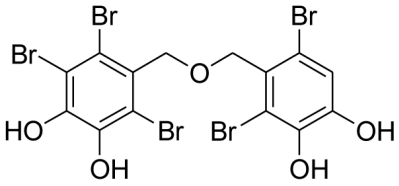
(**180**) *Sargassum* plastoquinone



(**181**) scalaradial



(**182**) secomycalolide A



(**183**) *Symphyocladia* bromophenol

Figure 3.

Table 1

Marine Pharmacology in 2005–6: Marine Compounds with Anthelmintic, Antibacterial, Anticoagulant, Antifungal, Antimalarial, Antiprotozoal, Antituberculosis, and Antiviral Activities

Class	Compound/Organism[a]	Chemistry	Pharmacologic Activity	IC_{50}[b]	MMOA[b]	Country[c]	References
elmintic	**(−)-echinobetaine A & (+)-B (1,2)**/sponge	Alkaloid[f]	Activity against nematode *Haemonchus contortus*	8.3–83 μg/mL^{++}	Undetermined	AUS	[27,28]
elmintic	***Laurencia scoparia* terpene (3)**/alga	Sesquiterpene[e]	Activity against nematode *Nippostrongylus brasiliensis*	0.11 mM	Undetermined	URY, BRA	[29]
acterial	**canthosides B & D (4,5)**/sponge	Polysaccharide[g]	Methicillin-resistant *S. aureus* & vancomicin- resistant *Enterococcus* inhibition	3.1–6.3 μg/disk^{+}	*E. coli* Type III secretion inhibition	CAN, NLD, USA	[30]
acterial	***Spongosorites* sp. alkaloids (6,7)**/sponge	Alkaloid[f]	*S. aureus* inhibition	3.12–6.25	Sortase A inhibition	S.KOR	[31]
acterial	**aurelin (8)**/jellyfish	Peptide[f]	*E. Coli* inhibition	7.7 μg/mL^{+}	Undetermined	RUS	[32]
acterial	**batzellaside A (9)**/sponge	Alkaloid[f]	*S. epidermidis* inhibition	≤ 6.3 μg/mL^{+}	Undetermined	USA	[33]
acterial	**dendridine A (10)**/sponge	Alkaloid[f]	*B. subtilis* & *M. luteus* inhibition	4.2–8.3 μg/mL^{+}	Undetermined	AUS, JPN	[34]
acterial	**6-oxo-de-*O*-methyllasiodiplodi n (11)**/fungus	Polyketide[d]	*B. subtilis, S. aureus* & *S. enteritidis* inhibition	6.25–12.5 μg/mL^{+}	Undetermined	CHN	[35]
acterial	**grammistins (12)**/fish	Peptide[f]	*B. subtilis, S. aureus* & *E. coli* inhibition	3.13–12.5 μg/mL^{+}	Undetermined	JPN	[36]
acterial	**halichonadin C (13)**/sponge	Sesquiterpene[e]	*M. luteus* inhibition	0.52 μg/mL^{+}	Undetermined	JPN	[37]
acterial	**lajollamycin (14)**/bacterium	Polyketide[d]	*S. aureus* & *S. pneumoniae* inhibition	1.5–4 μg/mL^{+}	Undetermined	USA	[38]
acterial	**marinomycins A–D (15–18)**/bacterium	Polyketide[d]	*S. aureus* & *E. faceium* inhibition	0.1–0.6 μM	Undetermined	USA	[39]
acterial	**resistoflavin methyl ether(19)**/bacteria	Polyketide[d]	*B. subtilis* inhibition	3.1 μg/mL^{+}	Undetermined	DEU	[40]
acterial	***Streptomyces* anthraquinones (20,21)**/bacterium	Polyketide[d]	Methicillin-resistant *S. aureus* inhibition	0.15–0.36	Undetermined	USA	[41]
acterial	***Streptomycetaceae* quinone (22)**/bacterium	Polyketide[d]	Methicillin-resistant *S. aureus* & vancomicin-resistant *Enterococcus* inhibition	1.95–3.90 μg/mL^{+}	Undetermined	USA	[42]
acterial	**xeniolide I (23)**/soft coral	Terpene[e]	*E. coli* & *B. subtilis* inhibition	1.2 μg/mL^{+}	Undetermined	ISR	[43]
coagulant	***Limandra aspera* protein**/fish	Peptide[f]	Factor XIIa and platelet integrins inhibition	< 1 μM	Formation of inactive complex with XIIa	KOR	[57]
coagulant	**fucoidans (24)**/alga	Polysaccharide[g]	Thrombin and factor Xa inhibition *in vitro* and *in vivo*	ND		RUS	[58]
coagulant	**heparin (25)**/clam	Polysaccharide[g]	Activated partial thromboplastin time & Xa inhibition *in vitro*	52–97 IU/mg	Lower activity than bovine mucosal heparin	ITA	[59]
coagulant	**sulfated galactans (26,27)**/alga	Polysaccharide[g]	Thrombin and factor Xa inhibition *in vitro*	ND	2,3-disulfated a- galactose units critical motif	BRA	[60]

Class	Compound/Organism[a]	Chemistry	Pharmacologic Activity	IC_{50}[b]	MMOA[b]	Country[c]	References
coagulant	**sulfated galactofucan** (28)/alga	Polysaccharide[g]	Endothelial cell heparan sulfate synthesis stimulation	ND	Factor Xa inhibition *in vitro*	BRA	[61]
ungal	**capisterones A & B (29,30)**/alga	Steroid[e]	Enhancement of fluconazole activity	ND	CDR1 & MDR1 efflux pump reversal activity	USA	[62]
ungal	***Dysidea herbacea*** phenol (31)/sponge	Polyketide[d]	*C. albicans* & *A. niger* inhibition	1.95–7.8 μg/mL$^+$	Leakage of K^+ from fungal cells	ISR	[63]
ungal	**spongistatin (32)**/sponge	Polyketide[d]	Broad panel of yeasts and filamentous fungi	1–32 μg/mL$^+$	Disruption of microtubule network	USA	[64]
ungal	**halocidin (33)**/ascidian	Peptide[f]	*C. albicans* inhibition	1–4 μg/mL$^+$	Membrane pore formation	KOR	[66]
ungal	**hassallidin A (34)**/bacterium	Lipopeptide[f]	*C. albicans* & *A. fumigatus* inhibition	4.8 μM$^+$	Undetermined	DEU	[67]
ungal	**latrunculins (35–42)**/sponge	Polyketide[d]	*C. albicans* inhibition comparable to clotrimazole	2.5–19 μM$^+$	Undetermined	EGY, USA	[49]
ungal	**majusculoic acid (43)**/bacterium	Polyketide[d]	*C. albicans* inhibition, less potent than fluconazole	8 μM$^+$	Undetermined	USA	[68]
nalarial	**pycnidione (44)**/fungus	Polyketide[d]	*P. falciparum* W2 & D6 strain inhibition	0.2–0.4 ng/mL	Undetermined	AUS, USA	[77]
nalarial	**plakortide Q (45)**/sponge	Polyketide[d]	*P. falciparum* D10 & W2 strain inhibition	0.5–1 μM	Undetermined	ITA	[78]
nalarial	***Xestospongia* sp. xestoquinone (46)**/sponge	Polyketide[d]	FCB1 *P. falciparum* inhibition	3 μM	Pfnek-1 kinase inhibition	FRA	[79]
nalarial	**manzamine Y (47)**/sponge	Alkaloid[f]	*P. falciparum* D6 & W2 strain inhibition	0.4–0.85 μg/mL	Undetermined	IDN, ESP, USA	[80]
nalarial	**caucanolides A & D (48,49)**/soft coral	Diterpene[e]	*P. falciparum* W2 inhibition	17 μg/mL	Undetermined	COL, PAN, USA	[81]
nalarial	***Eunicea* sp. sesquiterpenoids (50–54)**/coral	Sesquiterpene[e]	*P. falciparum* W2 strain inhibition	10–18 μg/mL	Undetermined	COL, PAN, USA	[82]
nalarial	**kallolide D (55)**/sea whip	Diterpene[e]	*P. falciparum* inhibition	30.6 μM	Undetermined	PAN, USA	[83]
nalarial	**leptolide & deoxypseudopter olide (56,57)**/coral	Diterpene[e]	*P. falciparum* W2 strain inhibition	50 & 74 μM	Undetermined	ESP, PAN	[84]
nalarial	***Muricea austera* tyramine (58)**/coral	Tyramine	*P. falciparum* W2 strain inhibition	36 μM	Undetermined	ESP, PAN	[85]
rotozoal	***ent*-plakortide P (59)**/sponge	Polyketide[d]	*Leishmania mexicana* inhibition	1 μg/mL	Undetermined	KOR	[86]
rotozoal	**karatungiol A (60)**/alga	Polyketide[d]	*Trichomonas foetus* inhibition	1 μg/mL$^+$	Undetermined	JPN	[87]
rotozoal	**isoakaterpin (61)**/sponge	Meroterpenoid[e]	*Leishmania* spp. adenosine phosphoribosyl transferase inhibition	1.05 μM	Undetermined	CAN, BRA	[88]
uberculosi s	**fistularin-3 & 11- deoxyfistularin-3 (62,63)**/ sponge	Tyrosine	*M. tuberculosis* inhibition	7.1–7.3 μM$^+$	Undetermined	BRA	[89]

Class	Compound/Organism[a]	Chemistry	Pharmacologic Activity	IC_{50}[b]	MMOA[b]	Country[c]	References
uberculosi s	**ileabethoxazole (64)**/soft coral	Diterpene[e]	*M. tuberculosis* inhibition	61 μg/mL[+]	Undetermined	USA	[91]
uberculosi s	**manzamine alkaloid (65- 73)**/sponge	Alkaloids[f]	*M. tuberculosis* inhibition	0.4–5.2 μg/mL[+]	Undetermined	IDN, ESP, USA	[80]
viral	***Callophylis variegata*** galactans/alga	Polysaccharide[g]	Herpes simplex & dengue type 2 inhibition	0.1–2.2 μg/mL	Undetermined	ARG	[92]
viral	**naviculan**/diatom	Polysaccharide[g]	Herpes simplex 1 & 2 inhibition	7.4–14 μM	Undetermined	JPN	[93]
viral	***Schizymenia binderi* sulfated galactan**/alga	Polysaccharide[g]	Herpes simplex 1 & 2 inhibition	0.18–0.76 μg/mL	Interference with HSV-heparan sulfate cellular residues	ARG, CHL	[94]
viral	***Sargassum* plastoquinones (74–76)**/alga	Terpenoid[e]	Measles & cytomegalovirus inhibition	0.49–3.1 μM	Lipid peroxidation observed	JPN	[95]
viral	***Dictyota* diterpenes (77,78)**/alga	Diterpene[e]	Inhibition of HIV-1 reverse transcriptase	10–35 μM[**]	RNA-dependent DNA-polymerase activity inhibition	BRA	[96]
viral	**griffithsin**/alga	Protein[f]	T- & M-tropic HIV-1 inhibition	0.043–0.63 nM	Inhibition of CD4-dependent gp120 binding	USA	[97]

nism, *Kingdom Animalia*: fish and ascidian (Phylum Chordata); sea star (Phylum Echinodermata), clam (Phylum Mollusca), sponges (Phylum Porifera); corals, sea whips and jellyfish (Phylum ria); *Kingdom Monera*: bacteria (Phylum Cyanobacteria); *Kingdom Fungi*: fungus; *Kingdom Plantae:* diatom, alga;

: concentration of a compound required for 50% inhibition *in vitro*,

nated IC_{50},

inhibition constant for a drug,

: concentration at which 50% of ligand binding sites are occupied, ND: not determined;

: minimum inhibitory concentration,

99: dose required to kill 99% of test population;

OA: molecular mechanism of action

ntry: ARG: Argentina; AUS: Australia; BRA: Brazil; CAN: Canada; CHN: China; CHL: Chile; COL: Colombia; DEU: Germany; EGY: Egypt; ESP: Spain; FRA: France; IDN: Indonesia; IND: ISR: Israel; ITA: Italy; JPN: Japan; NLD: The Netherlands; NZL: New Zealand; PAN: Panama; PRT: Portugal; RUS: Russia; SVN: Slovenia; URY: Uruguay;

ketide;

ene;

gen-containing compound;

Biochim Biophys Acta. Author manuscript; available in PMC 2010 May 1.

[g] Polysaccharide.

Table 2

Marine Pharmacology in 2005–6: Marine Compounds with Anti-inflammatory activity, and affecting the Cardiovascular, Immune and Nervous System

Drug Class	Compound/organism[a+]	Chemistry	Pharmacological activity	IC_{50}[b]	MMOA[c]	Country[d]	References
nti-inflammatory	**bolinaquinone (79)** & **petrosias pongiolid e M (80)**/sponge	Merosesquiterpene[f] & Sesterterpene[f]	Inhibition of colonic inflammation *in vivo*	ND	iNOS, NO, IL-1β & PGE_2 inhibition	ESP, ITA	[98]
nti-inflammatory	**cladocorans A & B (81,82)**/coral	Sesterterpene[f]	Secretory phospholipase A_2 inhibition	0.8–1.95 μM	Undetermined	JPN	[99]
nti-inflammatory	***Dysidea* quinones (83,84)**/sponge	Sesquiterpene-quinone[f]	Human neutrophil free radical release inhibition *in vitro*	3–11 μM	Superoxide anion inhibition	NZL	[100]
nti-inflammatory	**manzamines A–F (65,69,71,73, 85,86)/sponge**	Indole-derived alkaloid[g]	Modulation of LPS-activated brain microglia *in vitro*	0.016–10 μM	TXB_2 and superoxide anion inhibition	USA	[101]
nti-inflammatory	**sarcophines (87,88)**/soft coral	Diterpene[f]	Modulation of LPS-activated brain microglia *in vitro*	1 μM	TXB_2 and superoxide anion inhibition	EGY, USA	[102]
nti-inflammatory	***Euryspongia* n. sp. sterol (89)**/sponge	Steroid[f]	HU keratinocyte 6-keto-PGF1α inhibition	10 μg/mL*	Undetermined	FRA	[104]
nti-inflammatory	**gibberoketosterol (90)**/soft coral	Steroid[f]	iNOS and COX-2 protein inhibition	10 μM*	Undetermined	EGY, TAIW	[105]
nti-inflammatory	***Ircinia spinosula* chromenol (91)**/ sponge	Triterpene-polyketide[e]	Porcine leukocyte LTB_4 inhibition	1.9 μM	Undetermined	GRC, DEU	[106]
nti-inflammatory	**isoparalemnone (92)**/soft coral	Sesquiterpene[f]	Inhibition of iNOS protein	10 μM*	Undetermined	EGY, TAIW	[107]
nti-inflammatory	**PFF-B (93)**/alga	Shikimate-derivative[e]	Inhibition of histamine release *in vitro*	7.8 μM	Undetermined	JPN	[108]
nti-inflammatory	**symbioimine (94)**/dinoflagellate	Alkaloid[g]	COX-2 protein inhibition	> 10 μM*	Undetermined	JPN	[109]
ardiovascular	**lepadiformines A & B (95,96)**/ ascidian	Alkaloid[g]	Cardiac inward rectifying K^+ current inhibition	1.4–1.6 μM***	Voltage-dependent block	FRA	[110]
ardiovascular	**zooxanthellamide Cs (97)**/alga	Polyketide[e]	Vasoconstriction of rat blood vessels	0.39 μM	Undetermined	JPN	[111]
mmune system	**annulins A–C (98–100)**/hydroid	Polyketide[e]	Indoleamine 2,3-dioxygenase inhibition	0.1–1.1μM**	Undetermined	CAN	[112]
mmune system	**cucumariosides (101)**/sea cucumber	Triterpene- oligoglycoside[f]	Stimulation of lymphocytes & neutrophils	ND	IL-6 & TNF-α increase	RUS	[113]
mmune system	**damicoside (102)**/sponge	Glycosphingolipid	Stimulation of spleen cell proliferation	0.001 μg/m L*	Free galactose group required for activity	ITA	[114]
mmune system	**laminarin**/alga	Polysaccharide[h]	Inhibition of lymphocyte apoptosis	1–4 mg/mL	Induction of 33 immune response genes	S.KOR	[115]
mmune system	**sulfated SPMG (103)**/alga	Polysaccharide[h]	*In vivo* activation of T cells	10 mg/kg	IL-2, IFN-γincrease; TNF-α decrease	CHN	[116]

rug Class	Compound/organism[a+]	Chemistry	Pharmacological activity	IC_{50}[b]	MMOA[c]	Country[d]	References
mmune system	**verrucarin A** (**104**)/fungus	Polyketide[e]	Interleukin-8 inhibition	> 10 ng/mL*	p38 & JNK MAP kinase inhibition	JPN	[117]
ervous system	**CEG-3 ganglioside** (**105**)/sea cucumber	Glycolipid	Induction of neurite outgrowth	10 μM*	Undetermined	JPN	[120]
ervous system	**CEG-6 ganglioside** (**106**)/sea cucumber	Glycolipid	Induction of neurite outgrowth	<10 μM*	Undetermined	JPN	[121]
ervous system	**LLG-5 g**anglioside (**107**)/sea star	Ganglioside	Induction of neurite outgrowth	< 10 μM*	Undetermined	JPN	[122]
ervous system	**GP-3 ganglioside** (**108**)/sea star	Ganglioside	Induction of neurite outgrowth	> 10 μM*	Undetermined	JPN	[123]
ervous system	**inckosides F, I, K** (**109–111**)/sea star	Steroid[f]	Induction of neurite outgrowth	ND	Dependent on pentose modified C branch	JPN	[124]
ervous system	**shimalactone A** (**112**)/fungus	Polyketide[e]	Induction of neuritogenesis	10 μg/mL*	Undetermined	JPN	[125]
ervous system	**sargachromenol** (**113**)/alga	Diterpene-polyketide[e]	Promotion of NGF-stimulated neurite outgrowth	9 μM	cAMP & MAP kinase pathways required	JPN	[118]
ervous system	***Conus vexillum* conotoxins** (**114–116**)/snail	Peptide[g]	Non-competitive nicotinic receptor antagonists	0.4–8.4 nM	Slow block of agr;7 & α3β2 nicotinic receptor	AUS, DEU	[126]
ervous system	**SO-3 conopeptide** (**117**)/snail	Peptide[g]	N-type neuronal Ca^{2+} current inhibition	0.16 μM	Selective N-type voltage-sensitive Ca channel blocker	CHN	[127]
ervous system	**dysiherbaines** (**118**,**119**)/sponge	Aminoacid[g]	Ionotropic glutamate receptor binding	0.5–4.3 nM**	GluR5, GluR6 & KA2 receptor binding	FIN, JPN, GBR, USA	[128,129]
ervous system	**(−)-pictamine** (**120**)/ascidian	Quinolizidine alkaloid[g]	Nicotinic acetylcholine receptor block	1.5 μM	*α4β2* receptor irreversible inhibition	JPN, USA	[130]
ervous system	**bromopyrrole alkaloid** (**121**)/sponge	Bromopyrrole alkaloid[g]	Glutamate and serotonin antagonist	10 μg/mL*	Inhibition of neuronal Ca^{2+} entry	ITA, DEU	[131]
ervous system	**dmanin** (**122**)/sponge	Pyrrole alkaloid[g]	Inhibition of neuronal Ca^{2+} levels	1 μg/mL*	Undetermined	ITA, DEU	[132]
ervous system	**gephyromycin** (**123**)/bacterium	Polyketide[e]	Increase of neuronal Ca^{2+} levels	ND	Undetermined	GBR, DEU	[133]
ervous system	**motuporamine C** (**124**)/sponge	Alkaloid[g]	Neuronal growth collapse	5 μM*	Upregulation of Rho pathway	CAN	[134]
ervous system	**trigonelline** (**125**)/soft coral	Pyridinium alkaloid[g]	Voltage-activated K^+ current inhibition	> 0.1 mM*	Enhanced Ca^{2+} influx	EGY, GBR	[135]

rganism: *Kingdom Animalia*: hydroid, corals (Phylum Cnidaria) ; ascidian, blue shark (Phylum Chordata), sea star, cucumber (Phylum Echinodermata); snail (Phylum Mollusca); sponge (Phylum ifera); *Kingdom Fungi*: fungus; *Kingdom Plantae:* alga; *Kingdom Monera*: bacterium (Phylum Cyanobacteria);

C_{50}: concentration of a compound required for 50% inhibition *in vitro*,

[*] estimated IC_{50},

[**] K*i*: inhibition constant for a drug,

[***] Kd: concentration at which 50% of ligand binding sites are occupied, ND: not determined;

[c] **MMOA**: molecular mechanism of action, NO: nitric oxide;

[d] **Country**: AUS: Australia; CHN: China; DEU: Germany; EGY: Egypt; FIN: Finland; FRA: France; GBR: United Kingdom; GRC: Greece; ITA: Italy; JPN: Japan; NZL: New Zealand; S.KOR: South Korea; TAIW: Taiwan ;

[e] Polyketide;

[f] Terpene;

[g] Nitrogen-containing compound;

[h] Polysaccharide.

Table 3

Marine Pharmacology in 2005–6: Marine Compounds with Miscellaneous Mechanisms of Action.

Compound/Organism[a]	Chemistry	Pharmacological Activity	IC_{50}[b]	MMOA[c]	Country[d]	References
***Agelas* sp. dibromopyrrole (126)**/sponge	Alkaloid[g]	Reduction in Ca^{2+} elevation induced by K^+ depolarization	< 0.3 mM	Voltage-gated calcium channel inhibition	DEU	[169]
adociaquinone B (127)/sponge	Alkaloid[g]	Cdc25B phosphatase inhibition	0.07 μM	Selective oxidation of catalytic cysteine	USA	[170]
barettin (128) & 8,9-dihydrobarettin (129)/sponge	Diketopiperazine[g]	Serotonin uptake inhibition	0.34–4.63 μM	Binding to 5-HT_{2A}, 5-HT_{2C}, 5-HT_4 & 5-HT_{2C}	SWE	[171]
bromoageliferin (130) & dibromoageliferin (131)/sponge	Alkaloid[g]	Inhibition of Ca^{2+} entry	4–6.6 μM	Reduction of voltage-dependent calcium entry	DEU	[172]
chlorolissoclimide (132)/marine slug	Alkaloidal diterpene[f]	Reversible protein synthesis inhibition	0.7 μM	Blocked elongation & ribosome release from polysomes	CAN,	[173]
fascaplysin analogue CA224 (133)/synthetic	Alkaloid	Cyclin-dependent kinase 4 inhibition	5.5 μM	No Cdk2-cyclin A inhibition; no DNA intercalation	GBR	[174]
hippuristanol (134)/coral	Steroid[f]	Translation inhibition *in vitro* & *in vivo*	0.4–2 μM	Translation initiation factor eIF4A RNA-binding inhibition	JPN,	[175]
liphagal (135)/sponge	Meroterpene[f]	Phosphatidylinositol-3-kinase inhibition	0.1 μM	More selectivity to PI3Kα than PI3Kγ	CAN, NLD, USA	[176]
lukianol B (136) & rubrolide (137)/ascidian	Tyrosine derivative[g]	Antidiabetic activity	0.6–0.8 μM	Aldose reductase inhibition	ESP	[177]
micropeptin 88N (138) & 88-Y (139)/bacterium	Depsipeptide[g]	Chemotrypsin inhibition	1.3–15 μM	Attachment to active site of enzyme, no hydrolysis	JPN	[178]
pateamine (140)/sponge	Polyketide[e]	Protein synthesis inhibition	5 nM	Translation initiation factor eIF4A I/II & III inhibition NZL, USA	CAN,	[179]
phlorofucofuroeckol A(141)/alga	Shikimate-derivative	Angiotensin-converting enzyme 1 inhibition	12.7 μM	Reactive oxygen species/peroxynitrite scavenger	S.KOR	[180]
purealin (142)/sponge	Dibromotyrosine derivative[g]	Cytosplamatic dynein heavy chain inhibitor	35 μM	Uncompetitive inhibition, no binding to ATP site	USA	[181]
***Spongia* sesterterpenoid (143–145)**/sponge	Sesterterpene[f]	Hypercholesterolemia antagonist	8.1–64.5 μM	Farnesoid X-activated receptor inhibition	S. KOR	[182]
squalamine analog (146)/shark	Sterol derivative[f]	Activation of bidirectional Cl^- transport	Undetermined	Cl^- transport dependent on IP3-insensitive stores & unidentified receptor	USA	[183]
xestospongin B (147)/sponge	Alkaloid[g]	IP3-induced Ca^{2+} signalling inhibition	27–44 μM	Competitive to IP_3 receptor binding	CHL, FRA, NCL	[184]
xestospongin C (148)/sponge	Alkaloid[g]	IP3-induced Ca^{2+} release inhibition	458 nM	Enhanced rayanodyne receptor activity	USA	[185]

Compound/Organism[a]	Chemistry	Pharmacological Activity	IC_{50}[b]	MMOA[c]	Country[d]	References
actiniarin B (149)/anemone	Polyketide[e]	Cdc25B phosphatase inhibition	1.6 μg/mL	Undetermined	USA	[186]
amphezonol A (150)/alga	Polyketide[e]	DNA polymerase α inhibition	15 μM	Undetermined	JPN	[187]
ascochitine (151)/fungus	Polyketide[e]	*M. tuberculosis* tyrosine phosphatase inhibition	11.5 μM	Undetermined	DEU	[188]
briaexcavatin E (152)/coral	Diterpene[f]	Neutrophil elastase inhibition	5–10 μM	Undetermined	TAIW	[189]
briaexcavatin G (153)/coral	Diterpene[f]	Neutrophil elastase inhibition	ND	Undetermined	TAIW	[190]
brunsvicamides B & C (154, 155)/bacterium	Peptides[g]	*M. tuberculosis* tyrosine phosphatase inhibition	7.3–8 μM	Undetermined	GBR,	[191]
caulerpin (156)/alga	Alkaloid[g]	HU protein tyrosine phosphatase 1 B inhibition	3.77 μM	Undetermined	CHN	[192]
cortistatin A (157)/sponge	Alkaloid[g]	Antiangiogenic	2 nM	Undetermined	IDN, JPN	[193]
cyanopeptolin 954 (158)/bacterium	Depsipeptide[g]	A-chymotrypsin inhibition	54 nM	Undetermined	DEU,	[194]
dehydroluffariellolide diacid (159)/sponge	Sesterterpene[f]	Cdc25B phosphatase inhibition	1.6 μg/mL	Undetermined	USA	[195]
***O*-methyl nakafuran-8-lactone (160)**/sponge	Sesquiterpene[f]	Protein tyrosine phosphatase 1B inhibition	1.58 μM	Undetermined	CHN, S.	[196]
2*β*,3*α*-epitaondiol (161)/alga	Meroterpene[f]	Sodium channel inhibition	0.7 μM	Undetermined	USA	[197]
fascaplysin (162)/sponge	Alkaloid[g]	Cdc25B phosphatase inhibition	1.0 μg/mL	Undetermined	USA	[195]
gorgosterols (163–165)/coral	Sterol[f]	Binding to liver X receptor α	0.07–1.3 μM	Undetermined	CRI,	[198]
hexylitaconic acid (166)/fungus	Polyketide[e]	Inhibition of p53-HDM2 ubiquitin-protein ligase	50 μg/mL	Undetermined	JPN	[199]
himeic acid A (167)/fungus	Polyketide[e]/Peptide	Ubiquitin-activating enzyme inhibition	< 50 μM	Undetermined	JPN	[200]
kalihinol A (168)/sponge	Diterpene[f]	Cyclooxygenase 2 inhibition	1.07 μM	Undetermined	CHN,	[201]
largamides D–G (169–172)/bacterium	Depsipeptide[g]	α-chymotrypsin type II inhibition	4.0–25.0 μM	Undetermined	USA	[202]
peribysins E–G (173–175)/fungus	Sesquiterpene[f]	Cell adhesion inhibition	15–20.1 μM	Undetermined	JPN	[203,204]
petrosamine B (176)/sponge	Alkaloid[g]	Aspartyl semialdehyde dehydrogenase inhibition	306 μM	Undetermined	AUS	[205]
phrygiasterol (177)/starfish	Sterol[f]	Inhibition of Ca^{2+} influx	20 μg/mL	Undetermined	RUS	[206]
***Portieria hornemannii* monoterpenes (178,179)**/alga	Monoterpene[f]	DNA methyl transferase-1 inhibition	1.25–1.65 μM	Undetermined	USA	[207]
***Sargassum micracanthum* plastoquinone (180)**/alga	Meroterpene[f]	Lipid peroxidation inhibition	0.95 μg/m L	Undetermined	JPN	[208]
scalaradial (181)/sponge	Sesterterpene[f]	PI3K/Akt signaling inhibition	2.9 μM	Undetermined, but independent of $sPLA_2$	CHN	[209]
secomycalolide A(182)/sponge	Polyketide[e]/Peptide	Rat proteasome activity inhibition	11 μg/mL	Undetermined	JPN	[210]

Compound/Organism[a]	Chemistry	Pharmacological Activity	IC_{50}[b]	MMOA[c]	Country[d]	References
***Symphyocladia latiuscula* bromophenol (183)**/alga	Polyketide	Aldose reductase inhibition	0.11–1.15 μg/mL	Undetermined	CHN	[211]

[a] **Organism**, *Kingdom Animalia*: ascidians, shark (Phylum Chordata), anemone, corals (Phylum Cnidaria), starfish (Phylum Echinodermata), sea slug (Phylum Mollusca), sponge (Phylum Porifera); *Kingdom Fungi*: fungus; *Kingdom Plantae:* alga;

[b] **IC_{50}**: concentration of a compound required for 50% inhibition *in vitro*;

[c] **MMOA**: molecular mechanism of action;

[d] **Country:** CAN: Canada; CHE: Switzerland; CHL: Chile; CHN: China; CRI: Costa Rica; DEU: Germany; ESP: Spain; FRA: France;GBR: United Kingdom; IDN: Indonesia; ITA: Italy; JPN: Japan; NCL: New Caledonia; NZL: New Zealand; RUS: Russia; S. KOR: South Korea; SWE: Sweden; TAIW: Taiwan;

[e] Polyketide;

[f] Terpene;

[g] Nitrogen-containing compound;

[h] polysaccharide.