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Marine pharmacology in 2003-4: Marine Compounds with Anthelminthic, Antibacterial, Anticoagulant, Antifungal, Anti-inflammatory, Antimalarial, Antiplatelet, Antiprotozoal, Antituberculosis, and Antiviral Activities; affecting the Cardiovascular, Immune and Nervous Systems, and other Miscellaneous Mechanisms of Action

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Abstract

The current marine pharmacology review that covers the peer-reviewed literature during 2003 and 2004 is a sequel to the authors' 1998-2002 reviews, and highlights the preclinical pharmacology of 166 marine chemicals derived from a diverse group of marine animals, algae, fungi and bacteria. Anthelminthic, antibacterial, anticoagulant, antifungal, antimalarial, antiplatelet, antiprotozoal, antituberculosis or antiviral activities were reported for 67 marine chemicals. Additionally 45 marine compounds were shown to have significant effects on the cardiovascular, immune and nervous system as well as possessing anti-inflammatory effects. Finally, 54 marine compounds were reported to act on a variety of molecular targets and thus may potentially contribute to several pharmacological classes. Thus, during 2003-2004, research on the pharmacology of marine natural products which involved investigators from Argentina, Australia, Brazil, Belgium, Canada, China, France, Germany, India, Indonesia, Israel, Italy, Japan, Mexico, Morocco, the Netherlands, New Zealand, Norway, Panama, the Philippines, Portugal, Russia, Slovenia, South Korea, Spain, Thailand, Turkey, United Kingdom, and the United States, contributed numerous chemical leads for the continued global search for novel therapeutic agents with broad spectrum activity.

Keywords

drug-leads; marine; metabolites; natural products; pharmacology; review; toxicology

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1. Introduction

The purpose of this article is to review the 2003-4 primary literature on pharmacological studies with marine natural products using the same format as in our previous reviews of the marine pharmacology peer-reviewed literature (Mayer and Lehmann, 2000), (Mayer and Hamann, 2002, 2004, 2005). Consistent with our previous reviews, only those articles reporting on the bioactivity or pharmacology of 166 marine chemicals whose structures have been established are included in the present review. As in our previous reviews, we have used Schmitz's chemical classification (Schmitz et al., 1993) to assign each marine compound to a major chemical class, namely, polyketides, terpenes, nitrogen-containing compounds or polysaccharides. Those publications reporting anthelminthic, antibacterial, anticoagulant, antifungal, antimalarial, antiplatelet, antiprotozoal, antituberculosis or antiviral properties of 67 marine chemicals have been tabulated in Table 1 with the corresponding structures shown in Fig.1. The articles reporting on 45 marine compounds affecting the cardiovascular, immune and nervous systems, as well as those with anti-inflammatory effects are grouped in Table 2 and the structures presented in Fig. 2. Finally 54 marine compounds targeting a number of distinct cellular and molecular targets and mechanisms are shown in Table 3 and their structures depicted in Fig. 3. Publications on the biological or pharmacological activity of marine extracts or as yet structurally uncharacterized marine compounds have been excluded from the present review, although several promising reports were published during 2003-4: a specific inhibitor of a thyrotropin releasing hormone-specific peptidase (Pascual et al., 2004); antimicrobial activity in sub-Arctic marine invertebrates (Lippert et al., 2003); antifilarial activity of the red alga *Botryocladia leptopoda* (Lakshmi et al., 2004); antiviral effects of a sulfated exopolysaccharide from the marine microalga *Gyrodinium impudicum* (Yim et al., 2004) and *Sargassuum patens* (Zhu et al., 2004); a polyhydroxylated fucophlorethol isolated from the marine brown alga *Fucus vesiculosus* shown to be bactericidal towards selected Gram-positive and Gram-negative bacteria *in vitro* (Sandsdalen et al., 2003); and an improvement of "*current cytokine-based therapies*" by sulphated polysaccharides purified from the green alga *Codium fragile*, as well as fucoidan and carrageenan, isolated from brown and red algae, respectively (Nika et al., 2003).

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

Table 1 summarizes new pharmacological findings reported during 2003-4 on the preclinical anthelmintic, antibacterial, anticoagulant, antifungal, antimalarial, antiplatelet, antiprotozoal, antituberculosis, and antiviral pharmacology of the 67 marine natural products shown in Fig. 1.

2.1 Anthelmintic and antibacterial compounds

One study contributed to the search of novel *anthelminthic* marine natural products during 2003-4. The novel acyclic lipids **thiocyanatins (1-4),** were isolated from the Australian sponge *Oceanapia* sp. (Capon et al., 2004b) and were shown to be nematocidal (LD_{99}= 3.1-8.3 μg/mL) to the commercial livestock parasite *Haemonchus contortus*. Although the mechanism of action of these compounds remains undetermined, the investigators noted that both the 2°-alcohol, SCN functionalities and chain length influenced the nematocidal activity.

In view of the fact that resistance to current antibiotics remains a significant challenge for pathogenic bacterial infections, during 2003-4, 19 studies contributed to the search for novel *antibacterial* marine natural products, an increase from 1998-2002 (Mayer and Lehmann, 2000; Mayer and Hamann 2002, 2004, 2005). Four studies reported on the mechanism of action

of novel marine antibacterial agents **(2-6;** Fig. 1**)**. Bugni et al., (Bugni et al., 2004) investigated a series of kalihinols, diterpenes isolated from the Philippine marine sponge *Acanthella cavernosa*, as potential bacterial folate biosynthesis inhibitors. The investigators reported that the pyranyl-type **kalihinols Y (5)** and **X (6)**, although potent antibacterials (MIC=1.56 μg/mL), were however less selective inhibitors of bacterial folate biosynthesis than the furanyl type kalihinols, with the "*C-10 position important for potency*". Isnansetyo and Kamei (Isnansetyo and Kamei, 2003) reported that a bactericidal compound named **MC21-A (7),** a 3,3′,5,5′-tetrabromo-2,2′-biphenyldiol**,** from the new marine bacterium *Pseudoalteromonas phenolica* sp. nov. MC21-A was bactericidal (MIC=1-2 μg/mL) against 10 clinical isolates of methicillin-resistant *Staphylococcus aureus,* and displayed comparable bioactivity to vancomycin (MIC=0.25-2 μg/mL). The mechanism of action of MC21-A involved permeabilizing bacterial cell membranes, and thus "*might be a useful compound*" because of a mode of action that differs from vancomycin. A new dimeric bromopyrrole alkaloid, **nagelamide G (8)** was isolated from the Okinawan marine sponge *Agelas* sp. (Endo et al., 2004). Nagelamide G exhibited antibacterial activity against *M. luteus*, *B. subtilis* and *E. coli,* but weakly inhibited protein phosphatase 2A (IC_{50}=13 μM), thus suggesting that this enzyme may not be the main molecular target responsible for the antibacterial activity of this compound. Tincu et al. (Tincu et al., 2003) reported a new antimicrobial octapeptide **plicatamide (9)** from the hemocytes of the marine tunicate *Styela plicata*. In an extensive and detailed mechanistic study these investigators discovered that despite its small size, the octapeptide plicatamide proved to be a potent, rapidly acting and broad spectrum antimicrobial. The fact that both wild type and methicilin-resistant *S. aureus* responded to plicatamide with a massive and rapid potassium efflux is "*consistent with an antimicrobial mechanism that targets their cell membrane*".

Although additional novel marine antibacterials were reported in 2003-4, no mechanism of action studies were reported for compounds **(10-29)**. Nevertheless, these studies highlight the fact that novel antibiotics are present in marine bacteria, tunicates, sea hares, soft corals, algae, sponges, worms, and fish. Two papers reported on antibacterial activity in compounds isolated from marine sponges: Namikoshi et al. (Namikoshi et al., 2004) reported the isolation of several **manoalide derivatives (10)** from a *Luffariella* sp. sponge collected in Palau, which were active against *S. aureus* at 5-10 μg/disk. The investigators noted that the presence of an "*OH group at the C-25 position (hemiacetal moiety) is important for antibacterial activity.*" Wang et al. (Wang et al., 2003) reported thirteen novel tetramic acids isolated from the marine sponge *Melophlus sarassinorum*. Interestingly, only **melophlin C (11)** displayed "*pronounced antibacterial activity*" against *B. subtilis* and *S. aureus*. One paper reported on new antimicrobial compounds isolated from marine tunicates: Schupp et al. (Schupp et al., 2003) discovered that the β-carboline **eudistomin X (12)**, isolated from the Micronesian ascidian *Eudistoma* sp. was active against *B. subtilis*, *S. aureus* and *E. coli*. One paper reported on a new antimicrobial peptide isolated from sea hares: Iijima et al. (Iijima et al., 2003) reported a novel 33 amino acid antimicrobial peptide **dolabellanin B2 (13)** from the sea hare *Dolabella auricularia*. One hundred percent inhibition of growth of *B. subtilis, H. influenza* and *Vibrio vulnificus* was reported with 2.5-5 μg/mL dolabellanin B2. Two papers reported on new antimicrobial peptides isolated from marine soft corals: Ata et al. (Ata et al., 2004) reported two new diterpenes, **pseudopterosin X** and **Y (14-15)** from the soft coral *Pseudopterogorgia elisabethae* which showed antibacterial activity against Gram-positive bacteria *Streptococcus pyogenes*, *S. aureus*, and *Enterococcus faecalis,* while being inactive against Gram-negative bacteria. Dmitrenok et al. (Dmitrenok et al., 2003) reported several **sphingolipids and glycolipids (16-18)** from soft corals of the Andaman Islands (Indian Ocean). Although the MIC were not reported, "*preliminary tests for antibacterial activity of lipids*" demonstrated that these compounds inhibited the growth of *E. coli, P. aeruginosa, B. subtilis* and *B. pumilus* on solid agar. One paper reported on the presence of antibacterial compounds in marine algae: Xu et al. (Xu et al., 2003) reported that among 5 bromophenols isolated from the marine red alga *Rhodomela confervoides,* the known compound **bis(2,3-dibromo-4,5-**

dihydroxybenzyl) ether (19) showed antibacterial activity against *S. aureus* (MIC=70 μg/mL), *Staphylococcus epidermidis* and *Pseudomonas aeruginosa* (MIC=70 μg/mL). Additional antibacterial marine natural products were isolated from sponges: Pettit et al. (Pettit et al., 2004) reported the antibacterial activity of a novel nitrogen heterocyclic compound **cribrostatin 6 (20)** isolated from the dark-blue marine *Cribochalina* sp. sponge. Cribrostatin 6 showed antibacterial activity against Gram-positive bacteria, and it was most active against *S. pneumoniae* (MIC= 0.5 μg/mL), a leading cause of infection and mortality worldwide. Goud et al. (Goud et al., 2003b) reported a novel **purpuramine L (21)** from the Indian marine sponge *Psammaplysilla purpurea* which was active against *S. aureus, B. subtilis and C. violaceum*. A new nitrogenous sesquiterpene **germacrane (22)** was isolated from an *Axinyssa* n. sp. sponge that demonstrated strong antimicrobial activity against *S. aureus* and *B. subtilis* (Satitpatipan and Suwanborirux, 2004). Yang et al. (Yang et al., 2003c) isolated a new bicyciclic **guanidine alkaloid (23)** from the marine sponge *Ptilocaulis spiculifer*, contributing a new member to the crambescin A class of compounds. Interestingly, 50 μg of the guanidine alkaloid was as potent as 10 μg gentamicin. Two diterpenes **membranolides C and D (24, 25)** derived from an Antarctic cactus sponge, displayed "*modest yet broad spectrum*" Gram-negative antibiotic activity (Ankisetty, S. et al. 2004). Two novel antibacterial peptides were isolated from marine worms: Ovchinnikova et al. (Ovchinnikova et al., 2004) purified and characterized two small 21-residue peptides **arenicin-1 and -2 (26-27)**, from the coelomocytes of the marine lugworm *Arenicola marina*. Both arenicins were active against Gram-positive *L. monocytogenes*, Gram-negative *E. coli* and the fungus *C. albicans*. Pan et al. (Pan et al., 2004) isolated and characterized a 51-amino acid highly basic and hydrophobic peptide **perinerin (28)**, from the marine clamworm *Perinereis aibuhitensis,* an organism that is extensively used as bait in fisheries and aquaculture. Perinerin, a peptide that is constitutively present in the marine worm and whose sequence appears to be novel among all know antimicrobial peptides, was active against Gram-negative and Gram-positive bacteria as well as fungi. Patrzykat et al. (Patrzykat et al., 2003b) reported active novel antimicrobials peptides by screening both genomic and mRNA transcripts from a number of different species of flatfish. The most active peptide coded as **NRC-13 (29)** which was derived from the American plaice *Hippoglossoides platessoides* Frabricius, "*rapidly (5 to 10 min) and efficiently (95-100%)*" killed antibiotic-resistant *P. aeruginosa*, methicillin-resistant *S. aureus* and *C. albicans*.

2.2 Anticoagulant compounds

During 2003-4 three articles reported on the *anticoagulant* properties of marine natural products, an increase from our previous reviews (Mayer and Lehmann, 2000; Mayer and Hamann, 2002, 2004, 2005). Carroll et al. (Carroll et al., 2004) reported three new peptides, **dysinosins B, C (30) and D,** isolated from the sponge *Lamellodysidea chlorea,* that inhibited the blood coagulation cascade serine proteases factor VIIa and thrombin. Furthermore, the study revealed that two structural motifs of the dysinosins contributed to the binding of these compounds to factor VIIa and thrombin proteases. Zancan et al. (Zancan and Mourao, 2004) extended the antithrombotic pharmacology of **fucosylated chondroitin sulfate (31)**, a glycosaminoglycan isolated from the Brazilian sea cucumber *Ludwigothurea grisea*. The researchers noted that it was possible to dissociate the anticoagulant, bleeding and antithrombotic effect of this compound, i.e. the antithrombotic effect varied depending on the *in vivo* experimental model being used, and that it was "*apparently unrelated to its effect on platelet aggregation*". Melo et al. (Melo et al., 2004) extended the pharmacology of anticoagulant **sulfated galactans (32-33)** isolated from the red alga *Botryocladia occidentalis* and the sea urchin *Echinometra lucunter*. The studies demonstrated that the antithrombin-activating conformational change appeared to be of minor significance for the sulfated galactans's anticoagulant activity, and that the antithrombin-sulfated galactan complex differed from the antithrombin-heparin complex, thus leading the researchers to propose that

"*the paradigm of the heparin-antithrombin interaction cannot necessarily be extended to other sulfated polysaccharides*".

2.3 Antifungal compounds

Six studies during 2003-4 reported on the *antifungal* properties of 6 novel marine natural products isolated from marine sponges and ascidians, a slight decrease from 1998-2002 (Mayer and Lehmann, 2000; Mayer and Hamann, 2002, 2004, 2005).

Several novel marine antifungals **(34-38)** were isolated from marine sponges. Yang et al. (Yang et al., 2003b) reported a new **sterol sulfate (34)** isolated from a deep-water marine sponge of the family Astroscleridae, which exhibited antifungal activity against "*supersensitive*" *Saccharomyces cerevisiae* (MIC=15 μg/ml). As part of an ongoing project to discover potential new drugs to treat resistant opportunistic fungal infections, Jacob et al. (Jacob et al., 2003) reinvestigated the antifungal properties of a previously described **sterol (35)** isolated from the marine sponge *Dysidea arenaria*. Interestingly, they observed a reversal of fluconazole resistance from 300 to 8.5 μM when combined with 3.8 μM of the *Dysidea arenaria* sterol, putatively as a result of inhibition of the MDR1-type efflux pump in multidrug-resistant *C. albicans*. With the purpose of finding more selective antifungal agents, Nishimura et al. (Nishimura et al., 2003) focused their research efforts in identifying inhibitors of the pathogenic fungus *C. albicans* geranylgeranyltransferase (GGTase), an enzyme that shares only 30% amino acid sequence homology with the human GGTase. Bioassay-guided fractionation resulted in the isolation of a novel alkaloid **massadine (36)** from the marine sponge *Stylissa aff. massa*, which inhibited fungal GGTase (IC_{50}=3.9 μM). One novel imidazole alkaloid, **naamine G (37)** was reported from the Indonesian marine sponge *Leucetta chagosensis* that exhibited strong antifungal activity against the phytopathogenic fungus *Cladosporium herbarum* (Hassan et al., 2004). It remains to be determined if this compound will also be effective against fungi that infect mammalian hosts. Rifai et al. (Rifai et al., 2004) reported that **untenospongin B (38),** isolated from the Moroccan marine sponge *Hippospongia communis*, was more potent than amphotericin B, a clinically used antifungal agent, against *Candida tropicalis* (MIC=4-8 μg/mL) and *Fusarium oxysporum* (MIC=2-4 μg/mL). Further studies are required to determine the toxicity of untenospongin B *in vivo* as well as its molecular mechanism of action.

Kossuga et al. (Kossuga et al., 2004) reported a new antifungal agent polyketide, **(2*S*, 3*R*)-2-aminododecan-3-ol (39)**, isolated from the Brazilian ascidian *Clavelina oblonga*, which was very active against *C. albicans* (MIC=0.7± 0.05 μg/mL). Although the mechanism of action of this compound remains undetermined its bioactivity was comparable to the clinically used antifungal agents nystatin (MIC=1-4 μg/mL) and ketoconazole (MIC=1.0-4.0 μg/ml).

2.4 Antimalarial, antiprotozoal, antituberculosis and antiplatelet compounds

During 2003-4, and as shown in Table 1, 16 studies were reported in the area of *antimalarial, antiplatelet, antiprotozoal and antituberculosis* pharmacology of structurally characterized marine natural products. Ten compounds **(40-49;** Fig. 1) were shown to possess *antimalarial* activity. Moderate antimalarial activity (IC_{50}=10 μg/mL) against *Plasmodium falciparum* was observed with **bielschowskysin (40)**, a new and highly oxygenated hexacyclic diterpene isolated from the Caribbean gorgonian octocoral *Pseudopterogorgia kallos* (Marrero et al., 2004), as well as the novel diterpenes of the eunicellin class, **briarellins K hydroperoxide (41), D hydroperoxide (42) and L (43),** isolated from the gorgonian *Briareum polyanthes* (IC_{50}=9, 9 and 8 μg/mL, respectively) (Ospina et al., 2003). Wei et al. (Wei et al., 2004) reported moderate cytotoxic activity against the *Plasmodium falciparum* W2 (chloroquine-resistant) strain by the novel **cembradiene (44)** diterpenoids isolated from the Caribbean gorgonian read octocoral *Eunicea* sp., (IC_{50}= 23, 15 and 16 μg/mL, respectively). Fennell et

al. (Fennell et al., 2003) reported the antimalarial activity of **dolastatin 10 (45)**, a peptide microtubule inhibitor isolated from the sea hare *Dolabella auricularia* which is a potent anticancer drug. Although an extensive structure-activity relationship study was described and dolastatin 10 showed potent inhibition of *P. falciparum* (IC_{50}=0.1 nM) by affecting the schizont stage of intraerythrocytic development, which has the highest concentration of tubulin, the investigators concluded that dolastatin 10 was an "*unpromising basis for further antimalarial evaluation*" because of the lack of marked selectivity for parasite over mammalian cells. Rao et al. (Rao et al., 2003) reported structure-activity relationship studies with the manzamine alkaloids as potential antimalarial agents. **Manzamine A (46)** was observed to be particularly active against *P. falciparum* (D6 clone, IC_{50}= 4.5 ng/mL) and *P. falciparum* (chlorine-resistant W2 clone, IC_{50}=8.0 ng/mL), which compared well with artemisinin used as a control in these studies (IC_{50}=10 & 6.3 ng/mL, respectively). As part of an ongoing screening program for novel bioactive compounds from marine Streptomycetes, Maskey et al. (Maskey et al., 2004) reported that the **trioxacarcins A** and **D (48,49)** isolated from the marine *Streptomyces* sp. isolate B8652 BCC 5149 possessed "*extremely high antiplasmodial activity*" against the parasite *Plasmodium falciparum* K1 & NF54 strains (IC_{50}=1.5-1.6 & 2.3-1.7 ng/mL, respectively) which was much higher than the clinically used compound chloroquine (IC_{50}=70 & 3.7 ng/mL, respectively).

Three compounds were shown to possess *antiprotozoal* activity. Nakao et al. (Nakao et al., 2004) reported the isolation of **renieramycin A (50)** a new compound from the Japanese sponge *Neopetrosia* sp. that dose-dependently inhibited recombinant *Leishmania amazonensis* proliferation (IC_{50}=0.2 μg/mL) while showing cytotoxicity at "*ten times higher concentration (IC_{50}=2.2 μg/mL)*". Savoia et al. (Savoia et al., 2004) examined the activity of the sesquiterpene **euplotin C (51)**, isolated from the marine ciliate *Euplotes crassus* on pathogenic protozoa *Leishmania major* and *Leishmania infantum*. Because a significant leishmanicidal activity was noted against both *Leishmania* species (LD_{50}=4.6-8.1 μg/mL), the authors proposed evaluation of this natural product as "*synergistic compound(s) for current antiprotozoon chemotherapeutics*". Roch et al. (Roch et al., 2004) reported that novel non-cytotoxic variant analogues of truncated defensins isolated from the Mediterranean mussel *Mytilus galloprovincialis* were antiprotozoal. Two **defensin** fragments, designated D (Sequence CGGWKRKRC) and P (Sequence CGGYCGGWKRKRCTSYRCG), killed both the African trypanosome *Trypanosoma brucei* (ID_{50}=4-12 μM), which causes sleeping sickness, and the causative agent of cutaneous leishmaniasis, namely *Leishmania major* (ID_{50}=12-45 μM), in a time- and concentration-dependent manner. The mechanism may involve binding of the defensin fragments "*to parasite membranes*", perhaps affecting membrane fluidity.

Seven novel compounds **(47, 52-57;** Fig. 1**)** were contributed to the search for novel *antituberculosis* agents. Rodriguez et al. (Rodriguez and Rodriguez, 2003) reported that a novel diterpene alkaloid **homopseudopteroxazole (52),** isolated from the Caribbean sea plume *Pseudopterogorgia elisabethae,* inhibited growth of *Mycobacterium tuberculosis* $H_{37}Rv$ (MIC=12.5 μg/mL). As part of a manzamine alkaloid structure-activity relationship study, Rao et al. (Rao et al., 2003) noted that **(+)-8-hydroxymanzamine A (47)** was very potent against *M. tuberculosis* ($H_{37}Rv$, MIC=0.91 μg/mL), comparing favorably with rifampin (MIC=0.5 μg/mL). De Oliveira et al. (de Oliveira et al., 2004) reported a new alkaloid **ingenamine G (53)** that demonstrated activity against *Mycobacterium tuberculosis* H37Rv at 8μg/ml. A new scalarane-type bioactive sesterterpene, **12-deacetoxyscalarin 19-acetate (54)**, which was purified from the Thai sponge *Brachiaster* sp (Wonganuchitmeta et al., 2004), inhibited growth of a nonvirulent strain of *Mycobacterium tuberculosis by* 50% at MIC= 4 μM, comparing favorably with kanamycin sulfate (MIC= 3.5-8.5 μM). As a result of a research program designed to identify marine natural products that inhibit the mycothiol-S-conjugate amidase, a mycobacterial detoxification enzyme, Nicholas et al. (Nicholas et al., 2003) reported several

active compounds: a mixture of **1,3 pyridinium polymers (55)** isolated from the marine sponge *Amphimedon* sp., IC_{50}=0.1 μM; an *Oceanapiside* sp.-derived bromotyrosine compound **(56),** IC_{50}=3 μM; and the glycosphingolipid **oceanapiside (57),** IC_{50}=10 μM. Oceanapiside, was observed to be a "*simple non-competitive inhibitor*" of the mycothiol-S-conjugate amidase enzyme.

Two studies contributed to *antiplatelet* pharmacology of marine natural products during 2003-4. Pimentel et al. (Pimentel et al., 2003) using a new microplate assay for Ca^{2+}-induced platelet aggregation, determined that **xestospongin A (58),** isolated from the marine sponge *Xestospongia* sp., inhibited both collagen-and epinephrine-induced platelet aggregation more potently than aspirin. Villar et al. (Villar et al., 2003) evaluated the effects of several zoanthamine-type alkaloids isolated from the zoanthids *Zoanthus numphaeus* and *Zoanthus* sp. on the aggregation of human platelets: 11-**hydroxyzoanthamine (59)** demonstrated strong inhibition of thrombin-, collagen- and arachidonic acid-induced platelet aggregation which appeared related to the hydroxyl group at C-11; in contrast, aromatization in ring A was probably responsible for the selectivity of **zoanthenol (60)** towards collagen- induced aggregation.

2.5 Antiviral Compounds

As shown in Table 1 interest in the *antiviral* pharmacology of marine natural products remained high during 2003-4. During this two-year period 7 novel marine compounds **(61-67)** (Fig. 1) were reported to possess antiviral properties against the human immunodeficiency (HIV) virus by targeting a number of diverse molecular targets. As a result of an effort to identify small molecules that disrupt protein-protein interactions involved in HIV-1 cellular entry, a new polycyclic guanidine alkaloid **crambescidin 826 (61)** was reported from the marine sponge *Monanchora* sp. (Chang et al., 2003). Crambescidin 826 inhibited HIV-1 envelope-mediated fusion *in vitro* (IC_{50}=1-3 μM), thus suggesting that this class of compounds might ultimately aid in "*the rational design... of small molecule HIV-1 fusion inhibitors*". Chill et al. (Chill et al., 2004) isolated a new C_{22} furanoterpene designated **dehydrofurodendin (62)** from a Madagascan *Lendenfeldia* sponge, that was active against HIV-1 reverse transcriptase-associated RNA- and DNA-directed DNA polymerase (IC_{50}=3.2-5.6 μM). As a result of the National Cancer Institute's HIV-inhibitory natural product lead discovery program, a new HIV-inhibitory depsiundecapeptide **neamphamide A (63)** was isolated from the Papua New Guinea marine sponge *Neamphius huxleyi* (Oku et al., 2004). Neamphamide A potently inhibited the cytopathic effect of HIV-1 infection in a cell-based *in vitro* assay (EC_{50}=28 nM). Pereira et al. (Pereira et al., 2004) reported an extensive study on the mechanism of action of two diterpenes, **Da-1 and AcDa-1 (64, 65)**, isolated from the marine alga *Dictyota menstrualis,* that inhibited HIV-1 virus replication in the PM-1 cell line *in vitro*. Although both diterpenes did not affect viral attachment nor internalization of the virus into PM-1 cells, they inhibited the RNA-dependent DNA polymerase activity of the viral reverse transcriptase enzyme (IC_{50}=10 & 35μM, for Da-1 and AcDa-1, respectively) in a cell-free *in vitro* assay. These results strongly suggested that "*inhibition of synthesis of the proviral DNA by the diterpenes*" was the probable mechanism involved in HIV replication inhibition in PM-1 cells. Goud et al. (Goud et al., 2003a) reported inhibition of HIV by two bis-quinolizidine alkaloids **petrosins (66, 67)** isolated from the Indian marine sponge *Petrosia similis*. The extensive investigation determined that both petrosins inhibited HIV-1 replication (IC_{50}=41.3-86.8 μM), formation of giant cells (IC_{50}=21.2-36.1 μM) and recombinant reverse transcriptase *in vitro* (IC_{50}= 10.6-14.8 μM).

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

Table 2 summarizes the preclinical pharmacological research completed during 2003-2004 with the 45 marine chemicals shown in Fig. 2.

3.1 Anti-inflammatory compounds

The anti-inflammatory pharmacology of the marine compounds astaxanthin, bolinaquinone, cacospongionolide B, clathriol B, conicamin, cycloamphilectene 2, elisabethadione, plakohypaphorine, pourewic acid A, methylpourewate B, cadlinolide C, petrocortyne A, petrosaspongiolides M-R, pseudopterosin N, pseudopterosin R, seco-pseudopterosin E was reported during 2003-4, a large increase from our previous reports (Mayer and Lehmann, 2000; Mayer and Hamann, 2002, 2004, 2005).

Ohgami et al. (Ohgami et al., 2003) reported the effect of **astaxanthin (68),** a carotenoid found in crustacean cells, salmon and sea stars on lipopolysaccharide-induced uveitis in rats both *in vitro* and *in vivo*. The investigators observed that astaxanthin, at 100 mg/kg, suppressed development of uveitis and was as potent as 10 mg/kg prednisolone. The mechanism of action determined for astaxanthin probably involved inhibition of nitric oxide, prostaglandin E_2 and TNF-α generation. Lucas et al. (Lucas et al., 2003b) described a detailed mechanistic study on the modulatory effect of **bolinaquinone (69)**, a sesquiterpenoid isolated form a *Dysidea* sp. sponge, in several models of acute and chronic inflammation. The observation that bolinaquinone significantly inhibited cytokine, iNOS expression and eicosanoid (LTB_4, PGE_2) generation *in vitro* and *in vivo* in several models of inflammation through secretory PLA_2 inhibition led the authors to propose that bolinaquinone is a marine compound of "*potential interest in the search for new anti-inflammatory agents*". Posadas et al. (Posadas et al., 2003a) extended the cellular and molecular pharmacology of the sesterterpene **cacospongionolide B (70)** isolated from the Mediterranean sponge *Fasciospongia cavernosa*, and previously shown to be an inhibitor of secretory phospholipase A_2. In mouse peritoneal macrophages *in vitro,* as well as in an *in vivo* model of inflammation, cacospongionolide B decreased nitric oxide, prostaglandin E_2 and TNF-α generation as well as the corresponding gene expression. At the molecular level, cacospongionolide B inhibited nuclear factor-κ-DNA binding activity and enhanced IκB-α expression. Keyzers et al. (Keyzers et al., 2003) contributed a novel anti-inflammatory sterol, **clathriol B (71)** from the New Zealand sponge *Clathria lissosclera*. Clathriol B was shown to moderately inhibit production of superoxide anion from agonist-stimulated human peripheral blood neutrophils. A novel indole alkaloid histamine antagonist, **conicamin (72),** was isolated from the Mediterranean tunicate *Aplidium conicum* (Aiello et al., 2003). *Ex vivo* studies with guinea pig ileum demonstrated a concentration-dependent reduction of histamine-induced contractions, probably by a non-competitive mechanism. Lucas et al. (Lucas et al., 2003a) examined the effects of a series of 6 new cycloamphilectenes isolated from Vanuatu sponge *Axinella* sp. on murine macrophage and human neutrophil functions. All compounds tested reduced nitric oxide (NO) production in the submicromolar range. Interestingly, **cycloamphilectene 2 (73),** which reduced NO production and elastase release without affecting TNF-α release, inhibited the nuclear factor-κB pathway and also exhibited *in vivo* activity. One novel iododinated **plakohypaphorine (74)** with antihistamine activity was isolated from the Caribbean sponge *Plakortis simplex* (Borrelli et al., 2004). The authors noted that the antihistamine activity appeared to be "*connected to the number and nature of the halogen atoms*", because replacement of the iodine atom by chlorine resulted in a loss of the antihistamine property of this compound. Three novel diterpenes, namely **pourewic acid A (75), methylpourewate B (76)** and **cadlinolide C (77),** were purified from the New Zealand sponge *Chelonaplysilla violacea* (Keyzers et al., 2004). The three diterpenes moderately

inhibited production of the inflammatory superoxide anion from human peripheral blood neutrophils stimulated with phorbol myristate acetate or *N*-formyl-methionine-leucine-phenylalanine. Hong et al. (Hong et al., 2003) investigated the anti-inflammatory properties of **petrocortyne A (78)**, a C_{46} polyacetylenic alcohol isolated from the marine sponge *Petrosia* sp.. Petrocortyne A inhibited release of both TNF-α (IC_{50}=2.35 μM) and nitric oxide from macrophages and induced homotypic aggregation of U937 human leukemic monocytes, a process that appears to involve phosphorylation of several intracellular signaling molecules. The molecular pharmacology of **petrosaspongiolide M (79)** was characterized by Posadas et al. (Posadas et al., 2003b), who determined that this marine sesterterpenoid inhibited production of nitrite, prostaglandin E_2 and TNF-α both *in vitro* and *in vivo* while concomitantly inhibiting NF-κB signaling. The authors' results suggested that petrosaspongiolide M had "*potentially (a) wide therapeutic spectrum*" in inflammatory conditions. Monti et al. (Monti et al., 2004) extended the molecular pharmacology of the marine anti-inflammatory **petrosaspongiolides M-R (79-83)**, bioactive sesterterpenes isolated from the marine sponge *Petrosaspongia nigra*. The irreversible inhibition of bee-venom phospholipase A_2 (PLA_2) was investigated by mass spectrometry and molecular modelling approaches and demonstrated that petrosapongiolides N, O, P and R shared the same inhibition mechanism and covalent binding site already reported for petrosaspongiolide M. Ata et al. (Ata et al., 2003) reported two new diterpenes **pseudopterosin N (84)** and **seco-pseudopterosin E (85)** and the hydroxyquinone **elisabethadione (86)** from the marine gorgonian *Pseudopterogorgia elisabethae* with *in vivo* anti-inflammatory activity. Interestingly all three compounds inhibited edema (inflammation) in a mouse ear anti-inflammatory assay more potently than "*the well characterized pseudopterosins A and E*". With the purpose of contributing to the search of novel agents to treat neuroinflammation, several novel diterpene glycoside pseudopterosins and *seco*-pseudopterosins from the Caribbean sea whip *Pseudopterogorgia elisabethae* were evaluated in an *in vitro* anti-neuroinflammatory assay (Rodriguez et al., 2004). **Pseudopterosin R (87)** was observed to be the most promising compound because it significantly inhibited the generation of thromboxane B_2 (IC_{50}=4.7 μM) from activated rat brain macrophages. Although the molecular mechanism of action of pseudopterosin R remains currently undetermined, the authors concluded that it "*could become an anti-inflammatory lead compound*" for anti-neuroinflammatory drug design if its inhibitory effect on thromboxane B_2 release was further enhanced.

3.2 Cardiovascular compounds

Trevisi et al. (2004) reported novel studies on the mechanism of action of **callipeltin A (88)**, a previously described cyclic depsidecapeptide isolated from the marine sponges *Callipelta* sp. and *Latrunculia* sp.. In contrast to the lack of effect on guinea-pig aortic ring contractions, callipeltin A affected resting aorta contraction in a concentration-dependent manner (IC_{50}=0.44 μM) by a mechanism that caused an increase in sodium influx, a phenomenon the authors describe as a "*Na^+-ionophore action*". Thus callipeltin A's cardiovascular effects are probably caused by "*its capacity of mediating Na^+ transport*".

3.3 Compounds affecting the immune system

With the purpose of contributing to the discovery of small molecule agonists and antagonists of chemokine receptors, Yang et al. (Yang et al., 2003d), reported a new sesterterpene **sulfircin (89)** purified from the marine sponge *Ircinia* sp. that inhibited the CCR7 chemokine receptor, a receptor involved in the regulation of T cells and dendritic cell mobilization into lymphoid organs. Anti-adhesive **mucin-type glycoproteins** were characterized from the mucus secretions of starfish *Marthasterias glacialis* and *Porania pulvillus*, and the brittlestar *Ophiocomina nigra* (Bavington et al., 2004). The investigators observed that partially purified mucus glycoproteins from all three species were not cytotoxic and inhibited neutrophil adhesion in a dose-dependent manner, thus suggesting that by blocking adhesion of leukocytes

these mucins might be of therapeutic value to treat inflammatory disorders. Yamada et al. (Yamada et al., 2004) contributed a new series of eremophilane sesquiterpenoids, **peribysins A-D (90-93)**, isolated from a strain of *Periconia byssoides*, a fungus previously isolated from the sea hare *Aplysia kurodai*. Although the molecular mechanism of action of the four peribysins currently remains undetermined, inhibition of the adhesion of HL-60 cells to HUVEC (IC_{50}=0.1-2.7 μM), was significantly more potent than that observed with the control agent herbimycin A (IC_{50}=38μM). A 1,3 β glucan, named **phycarine,** chemically indistinguishable from the known polysaccharide laminarin, was isolated from the alga *Laminaria digitata* (Vetvicka and Yvin, 2004). A detailed pharmacological investigation revealed that phycarine stimulated phagocytic activity in peritoneal macrophages and potentiated the synthesis and release of interleukin-1, 6 and tumor necrosis factor α. Interestingly, phycarine increased NK cell-mediated killing of tumor cells both *in vitro* and *in vivo* by interacting with the CD11b/CD18 receptor (the complement receptor type 3 receptor). Three studies were reported on the pharmacology of a **sulfated polymannurouguluronate (SPMG) (94)** a polysaccharide with an average molecular weight of 8.0 kDa isolated from brown algae, which recently entered Phase II clinical trial in China as the first anti-AIDS drug candidate. While SPMG was initially reported to bind to 28 amino acids located in the HIV viral glycoprotein gp120 V3 loop (Meiyu et al., 2003), more recently, SPMG was shown by flow cytometry and fluorescent microscopy analysis to bind to lymphocyte CD4 receptors, a receptor type known to interact with the HIV virus gp120 envelope glycoprotein, a finding that might contribute to additional mechanistic explanations for the clinical efficacy of SPMG in HIV-infected patients (Miao et al., 2004). Two previous studies by the same research group noted that SPMG upregulated endothelial intercellular adhesion molecule-1 expression in human umbilical vein endothelial cells (Meiyu et al., 2003; Wang et al., 2003).

3.4 Compounds affecting the nervous system

Reports on both central and autonomic nervous system pharmacology of marine natural products during 2003-4 studies involved aplidine, aspermytin A, cribronic acid, dysibetaines, esmodil, jamaicamides, labuanine A, linckosides C-E, acidic oligosaccharide sugar chain, parguerol and isoparguerol, petrosaspongiolide M, sargaquinoic acid, SJG-2 ganglioside, δ-conotoxin, ω-conopeptide MVIIA and χ-conopeptide MrIA.

Perez et al. (Perez et al., 2003) investigated the inhibitory effect of the proline-containing cyclic peptide **aplidine (95)**, isolated from the tunicate *Aplidium albican*, on the *in vitro* aggregation of peptide PrP 106-126, a fraction of the prion protein which has been hypothesized to be involved in fatal neurodegenerative diseases and which can kill neuronal cells in culture. The fact that aplidine was observed to be a strong inhibitor of the aggregation of PrP 106-126 into β-sheet fibrils at a 1:1 molar ratio prompted these investigators to propose that it may be "*a leading compound for drug development efforts*".

Induction of neurite outgrowth *in vitro* was reported for the marine natural compounds aspermytin A, labuanine A, linckosides C-E, parguerol and isoparguerol, ganglioside species SJG-2 and sargaquinoic acid. Tsukamoto et al., (Tsukamoto et al., 2004a) isolated a new polyketide, **aspermytin A (96)** from a cultured marine fungus, *Aspergillus* sp. that induced neurite outgrowth at 50 μM in more than 50% of rat pheochromocytoma (PC-12) cells after two days of *in vitro* treatment, an effect comparable to that of 50 ng/mL of nerve growth factor. Aoki et al. (Aoki et al., 2003) purified a novel pyridoacridine alkaloid **labuanine A (97)** from the Indonesian marine sponge *Biemna fortis* that induced multipolar type neurite outgrowth in Neuro 2A neuroblastoma cells (1-3 μM) by a putative mechanism that "*may relate with inhibition of topoisomerase II*", a hypothesis currently under investigation. Qi et al. (Qi et al., 2004) contributed three new bioactive steroid glycosides **linckosides C-E (98-100)** from the Okinawan marine sea star *Linckia laevigata*, which potently induced neurite outgrowth in rat

PC12 cells, as well as synergistically enhanced the neuritogenic activity of nerve growth factor, a chemical that has been shown to be essential for neuronal outgrowth, survival, function maintenance and prevention of aging in the central and peripheral nervous system. Bioassay-guided fractionation lead to the isolation of **parguerol (101)** and **isoparguerol (102)** from the sea hare *Aplysia kurodai* (Tsukamoto et al., 2004b). Both compounds, the first neurotrophic compounds reported from sea hare metabolites, stimulated neurite outgrowth in PC-12 cells treated with either 25 or 50 μg/mL of the compounds for two days. Further pharmacological research will be required to determine the molecular mechanism leading to morphological changes in PC-12 cells. Two studies were reported on the pharmacology of the low molecular weight quinonic compound **sargaquinoic acid (103)** isolated from the marine brown alga *Sargassum macrocarpum*, and previously noted to possess a novel nerve growth factor-dependent neurite outgrowth promoting activity at the nanogram range. Kamei and Tsang (Kamei and Tsang, 2003) investigated the signaling pathways involved using a pharmacological approach and concluded that sargaquinoic acid enhanced neurite outgrowth in PC12 neuronal cells by involving both TrkA-mitogen-activated protein kinase and adenylate cyclase-protein kinase A signal transduction pathways. In a subsequent study, the neuroprotective effect of sargaquinoic acid was shown to be independent of nerve growth factor and phosphatidylinositol 3-kinase, a key signaling molecule (Tsang and Kamei, 2004). Kaneko et al. (Kaneko et al., 2003) reported the structure of a novel **ganglioside SJG-2 (104)** isolated from the sea cucumber *Stichopus japonicus* which appears to be the "*first ganglioside containing either the branched sugar chain moiety or the N-acetylgalactosamine residue*". While SJG-2 only displayed neuritogenic activity in the presence of nerve growth factor, it was more potent than the GM1 mammalian ganglioside.

Four marine compounds (**105-108**; Fig. 2) were shown to target receptors present in the nervous system. Sakai et al., (Sakai et al., 2003) contributed to the search for novel ionotropic glutamate receptor ligands by reporting the isolation of the novel amino acid **cribronic acid (105)** from the marine sponge *Cribrochalina olemda*. Cribronic acid induced potent convulsive behavior in mice upon intracerebroventricular injection (ED_{50}= 29±3.0 pmol/mouse), as well as inhibited binding of an *N*-methyl-D-aspartic acid (NMDA) receptor ligand (IC_{50}=83±15 nM). In 2004, Sakai et al. (Sakai et al., 2004) isolated two novel cyclopropane amino acids **dysibetaine CPa (106)** and **dysibetaine CPb (107)** from the marine sponge *Dysidea herbacea* collected in Micronesia, that showed weak affinity toward the NMDA-type and the kainic acid-type ionotropic glutamate receptors in a radioligand binding assay. The investigators concluded that the binding of these compounds to the glutamate receptor was of interest because they both lacked "*a glutamate equivalent structure in the molecules*". A screening program for bioactive compounds from marine cyanobacteria led to the isolation of the novel lipopeptides **jamaicamide A (108), B and C** (Edwards et al., 2004), compounds that exhibited sodium channel blocking activity at 5 μM, producing about half the response of saxitoxin applied at 0.15 μM.

During 2003-4, additional marine compounds (**109-112**; Fig. 2) were reported to exhibit pharmacological effects on the nervous system. Bioassay-guided fractionation of the marine sponge *Raspailia* sp. yielded the known synthetic compound **esmodil (109)**, reported in the patent literature in 1935 (Capon et al., 2004a). More than six decades ago, esmodil, an acetylcholine mimic, was shown to be potentially "*useful in treating retention of urine in humans and as influencing the parasympathetic nervous system in cats, rabbits and the Indian buffalo*". Hu et al. (Hu et al., 2004) reported interactions of an acidic **oligosaccharide sugar chain** (AOSC) from the brown alga *Echlonia kurome* with the amyloid beta protein. AOSC was observed to inhibit the toxicity induced by amyloid beta protein in both rat cortical cells as well as human neuroblastoma cells by a mechanism that involved inhibition of apoptosis, reduction of intracellular Ca^{2+} and the generation of reactive oxygen species (ROS). Thus the authors concluded that AOSC "*might be a potentially therapeutic compound for Alzheimer's*

disease". Capasso et al. (Capasso et al., 2003) reported that **petrosaspongiolide M (79)** reduced morphine withdrawal in an *in vitro* model. Although the mechanism underlying petrosaspongiolide M-induced inhibition of morphine withdrawal remains undetermined, one possibility raised by the investigators was the putative inhibition of extracellular type II phospholipase A_2 by this potent anti-inflammatory marine sesterterpene.

Extensive research on the preclinical and clinical pharmacology of conotoxin molecules resulted in the synthetic equivalent of **ω-conopeptide MVIIA (110)**, a 25-amino-acid polybasic peptide derived from the marine snail *Conus magus,* receiving approval from the Food and Drug Administration on December 23, 2004. Currently, Ziconotide (Prialt®), which is marketed by Elan Biopharmaceuticals, Inc., constitutes the third drug in the U.S. Pharmacopeia which has been derived from marine chemicals. Staats et al. (Staats et al., 2004) reported a double-blind, placebo-controlled, randomized trial conducted from 1996-1998 in 32 study centers in the United States, Australia and the Netherlands which assessed the safety and efficacy of intrathecal ziconotide. Ziconotide selectively binds to the N-type voltage-sensitive calcium channels located in neurons thereby blocking neurotransmission and resulting in significant analgesia. In this clinical study, intrathecal ziconotide provided clinically and statistically significant analgesia in 111 patients with pain from cancer or AIDS. As part of a program to explore the diversity of conotoxins produced by *Conus* marine snails found off the Indian coast, Sudarslal et al. (Sudarslal et al., 2003) reported the isolation and characterization of a novel 26 peptide **δ-conotoxin (111)** isolated and purified from the venom of the marine snail *Conus amadis*, collected in the Bay of Bengal. The observation that this novel δ-conotoxin inhibited the inactivation of sodium current in cloned rat brain IIA α-subunit channels led the investigators to conclude that "*conotoxins from some molluscivorous snails may also be active on mammalian* Na^+ *channels*". Sharpe et al. (Sharpe et al., 2003) extended the molecular pharmacology of **χ-conopeptide MrIA (112)**, a 13-residue peptide isolated form the venom of the marine snail *Conus marmoreus*. The investigators reported that the χ-conopeptide MrIA inhibited the norepinephrine transporter by a non-competitive mechanism that possibly involve a binding site "*predicted to be distinct from the substrate binding site but to share some commonality with the antidepressant binding site*".

4. Marine Compounds with Miscellaneous Mechanisms of Action

Table 3 lists marine compounds with miscellaneous pharmacological mechanisms of action, with their respective structures presented in Fig. 3. Interestingly, and in contrast with the 109 chemicals included in Tables 1 and 2, this third group of 54 marine compounds which was isolated from a variety of marine organisms, includes not only nitrogen-containing compounds (i.e. proteins, peptides), but also terpenes and polyketides.

As shown in Table 3, for a limited number of these marine natural products, namely acylspermidine D & E **(113,114),** ageladine A **(115),** alkylpyridinium **(117,118),** *Atriolum robustum* nucleoside **(121),** calyculin A **(123),** Cell-III, meridianin E **(139),** *Psammocinia* spp. diterpenes **(143-147),** punaglandins **(148-152)** and strobilin-felixinin **(163,164)**, both the pharmacological activity and a molecular mechanism of action have been investigated and reported. In contrast, for all the other compounds shown in Table 3, although a pharmacological activity was reported, no additional information was available on the molecular mechanism of action of these chemicals during 2003-2004.

5. Reviews on marine pharmacology

Specific areas of marine pharmacology research benefited from a number of excellent reviews published during 2003-4: (a) *general marine pharmacology*: natural products as sources of new drugs over the period 1981-2002 (Newman et al., 2003); marine natural products from marine invertebrates and sponge-associated fungi (Proksch et al. 2003b; Proksch et al.,

2003a); the biopotential of marine sponges from China oceans (Zhang et al., 2003); marine natural products as therapeutic agents (patents): part 2 (Frenz et al., 2004); natural-product diversity of New Caledonia: a pharmacologically oriented view (Laurent and Pietra, 2004); (b) *antimicrobial marine pharmacology*: genomic screening to identify novel marine antimicrobial peptides (Patrzykat and Douglas, 2003a); marine natural products as anti-infective agents (Donia and Hamann, 2003); mining marine microorganisms as a source of new antimicrobials and antifungals (Bernan et al., 2004); antimicrobial peptides from marine invertebrates (Tincu and Taylor, 2004); bioactive peptides from marine sources: pharmacological properties and isolation procedures (Aneiros and Garateix, 2004); (c) *anticoagulant marine pharmacology*: recent advances in marine algal anticoagulants (Matsubara, 2004); the use of algae and invertebrate sulfated fucans as anticoagulant and antithrombotic agents (Mourao, 2004); (d) *antituberculosis, antimalarial and antifungal marine pharmacology*: antimycobacterial natural products (Copp, 2003); naturally occurring peroxides from marine sponges with antimalarial and antifungal activities (Jung al., 2003); antifungal compounds from marine organisms (Molinski, 2004); (e) *antiviral marine pharmacology*: algae as a potential source of antiviral agents (Luescher-Mattli, 2003); marine natural products as lead anti-HIV agents (Gochfeld et al., 2003); anti-HIV activity from marine organisms (Tziveleka et al., 2003); proteoglycans from sponges as tools to develop new agents for AIDS and Alzheimer's disease (Fernandez-Busquets and Burger, 2003); antiviral marine natural products (Gustafson et al., 2004); (f) *anti-inflammatory marine pharmacology*: anti-inflammatory metabolites from marine sponges (Keyzers and Davies-Coleman, 2005); (g) *nervous system marine pharmacology*: conotoxins as drug leads for neuropathic pain and other neurological conditions (Alonso et al., 2003); conotoxins and structural biology: a prospective paradigm for drug discovery (Grant et al., 2004); drugs from the sea: conopeptides as potential therapeutics (Livett et al., 2004); ziconotide: neuronal calcium channel blocker for treating severe chronic pain (Miljanich, 2004).

6. Conclusion

During 2003-4, and for the first time in many decades, a marine natural product, namely ziconotide (Prialt®) **(110)** was approved for patient care by the U.S. Food and Drug Administration for the management of severe chronic pain in patients for whom intrathecal therapy is necessary, and who appear to be intolerant of or refractory to other treatments, such as systemic analgesics, adjunctive therapies or intrathecal morphine. Although research into the non-antitumor and cytotoxic pharmacology of marine natural products remained concentrated in the specific areas we have highlighted in our present review, this contribution together with our previous ones (Mayer and Lehmann, 2000; Mayer and Hamann, 2002, 2004, 2005), demonstrates that marine pharmacology research continued to proceed at a very active pace in 2003-4, involving natural product chemists and pharmacologists from 28 foreign countries and the United States. Thus, if the rate of preclinical and clinical pharmacological research continues to be sustained over time, additional marine natural products will probably become available as novel therapeutic agents to treat multiple disease categories.

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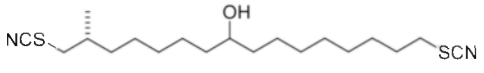
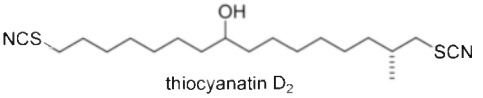
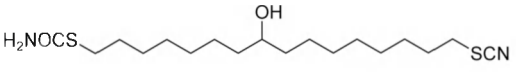


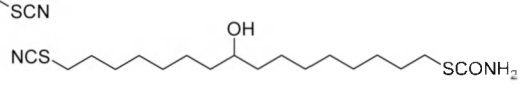
thiocyanatin D_1 (**1**)



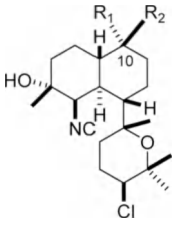
thiocyanatin D_2 (**2**)



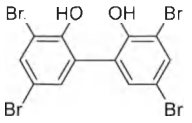
thiocyanatin E_1 (**3**)



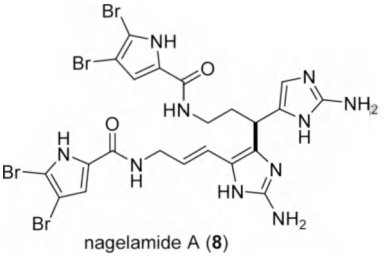
thiocyanatin D (**4**)



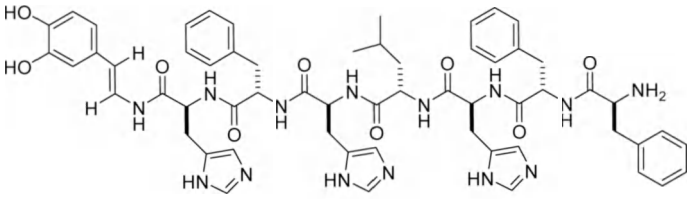
kalihinol Y (**5**) R_1, R_2 = CH_2
kalihinol X (**6**) R_1 = NCS, R_2 = Me



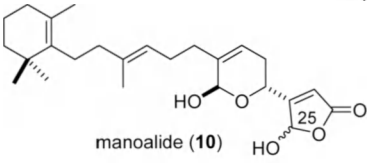
MC21-A (**7**)



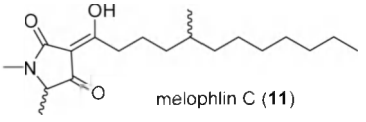
nagelamide A (**8**)



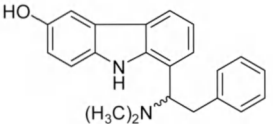
plicatamide (**9**)



manoalide (**10**)



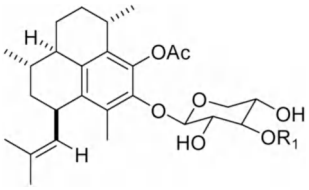
melophlin C (**11**)



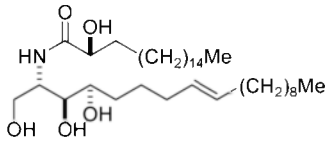
eudistomin X (**12**)

SHQDCYEALHKCMASHSKPFSCSMKFHMCLQQQ

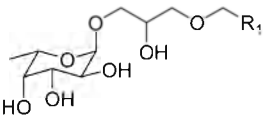
dolabellanin B2 (**13**)



pseudopterosin P (**14**) R_1=H
pseudopterosin Q (**15**) R_2=Ac

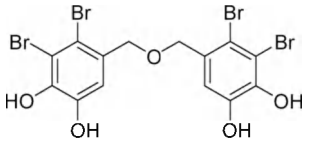


methyl 2-hydroxyoctadecanoate (**16**)

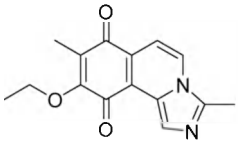


lipid 4a (**17**) R_1= $(CH_2)_{16}Me$

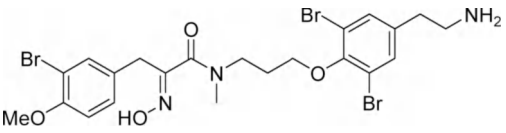
lipid 5a (**18**) R_1= $(CH_2)_{14}Me$



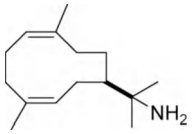
bis(2,3-dibromo-4,5-dihydroxybenzyl) ether (**19**)



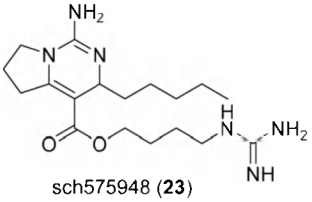
cribrostatin 6 (**20**)



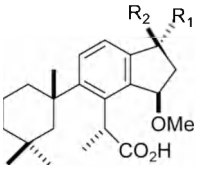
purpuramine L (**21**)



(1*Z*,4*Z*)-7αH-11-aminogermacra-1(10),4-diene (**22**)



sch575948 (**23**)



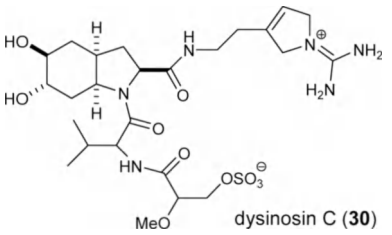
membranolide C (**24**) R_1=OMe, R_2=H
membranolide D (**25**) R_1=H, R_2=OMe

RWCVYAYVRVRGVLVRYRRCW
arenicin-1 (**26**)

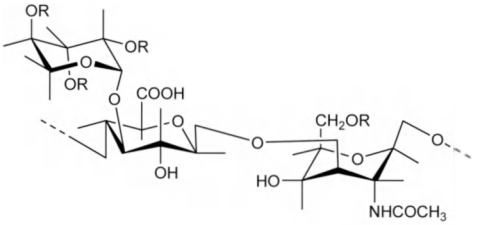
RWCVYAYVRIRGVLVRYRRCW
arenicin-2 (**27**)

FNKLKQGSSKRTCAKCFRKIMPSVHE
LDERRRGANRWAAGFRKCVSSICRY
perinerin (**28**)

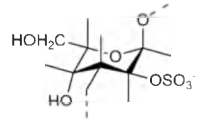
GWRTLLKKAEVKTVGKLALKHYL-NH_2
Hippoglossoides peptide (**29**)



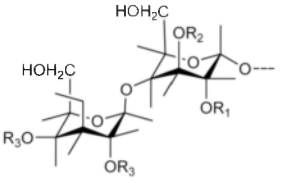
dysinosin C (**30**)



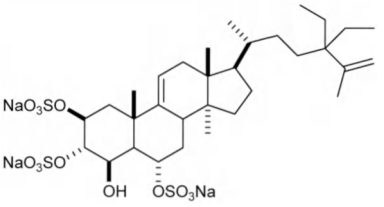
fucosylated chondroitin sulfate (**31**)



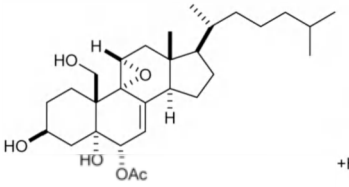
sulfated polysaccharide from *E. lucunter* (**32**)



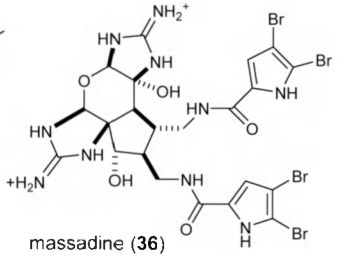
sulfated polysaccharide from *B. occidentalis* (**33**)
R_1, R_2 and R_3=H or SO_3^-



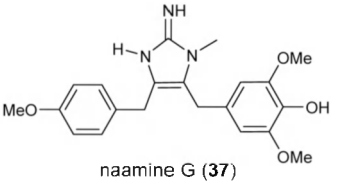
sch 575867 (**34**)



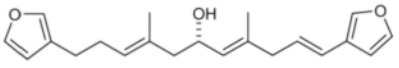
ECTA (**35**)



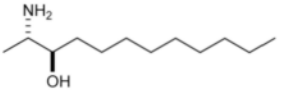
massadine (**36**)



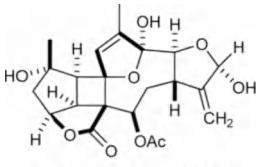
naamine G (**37**)



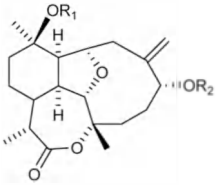
utenospongin B (**38**)



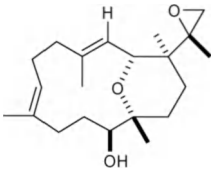
(2S,3R)-2-aminododecan-3-ol (**39**)



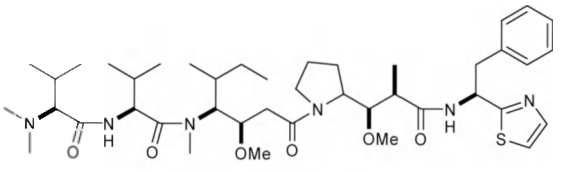
bielschowskysin (**40**)



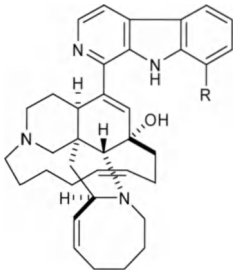
briarellin K hydroperoxide (**41**) R_1 = Ac, R_2 = OH
briarellin D hydroperoxide (**42**) R_1 = COC_3H_7, R_2 = OH
briarellin L (**43**) R_1 = COC_3H_7, R_2 = Ac



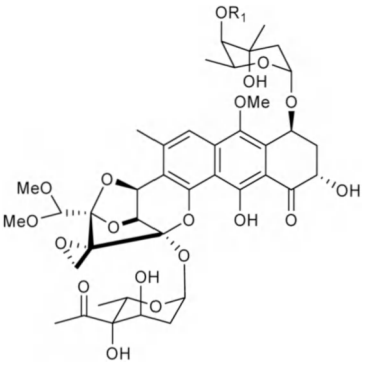
11(S*)-Hydroxy-2(R*),12(R*),15(S*),17-diepoxy-(3E,7E)-1(S*)-cembra-3,7-diene (**44**)



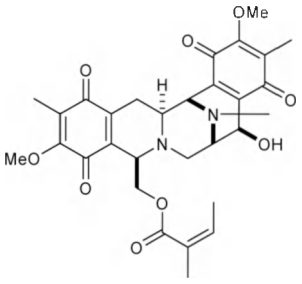
dolastatin 10 (**45**)



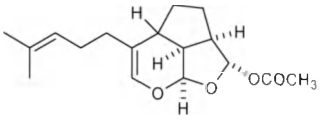
manzamine A (**46**) R = H
8-Hydroxymanzamine A (**47**) R = OH



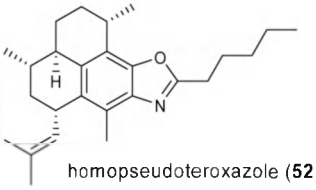
Trioxacarcin A (**48**) R_1=Ac
Trioxacarcin D (**49**) R_1=H



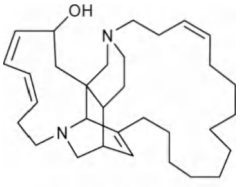
renieramycin A (**50**)



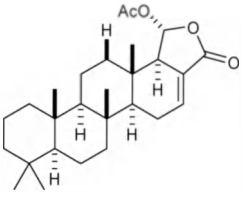
euplotin C (**51**)



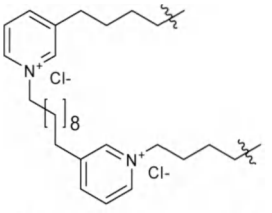
homopseudoteroxazole (**52**)



ingenamine G (**53**)



12-deacetoxyscalarin 19-acetate (**54**)



1,3-pyridinium polymers (**55**)

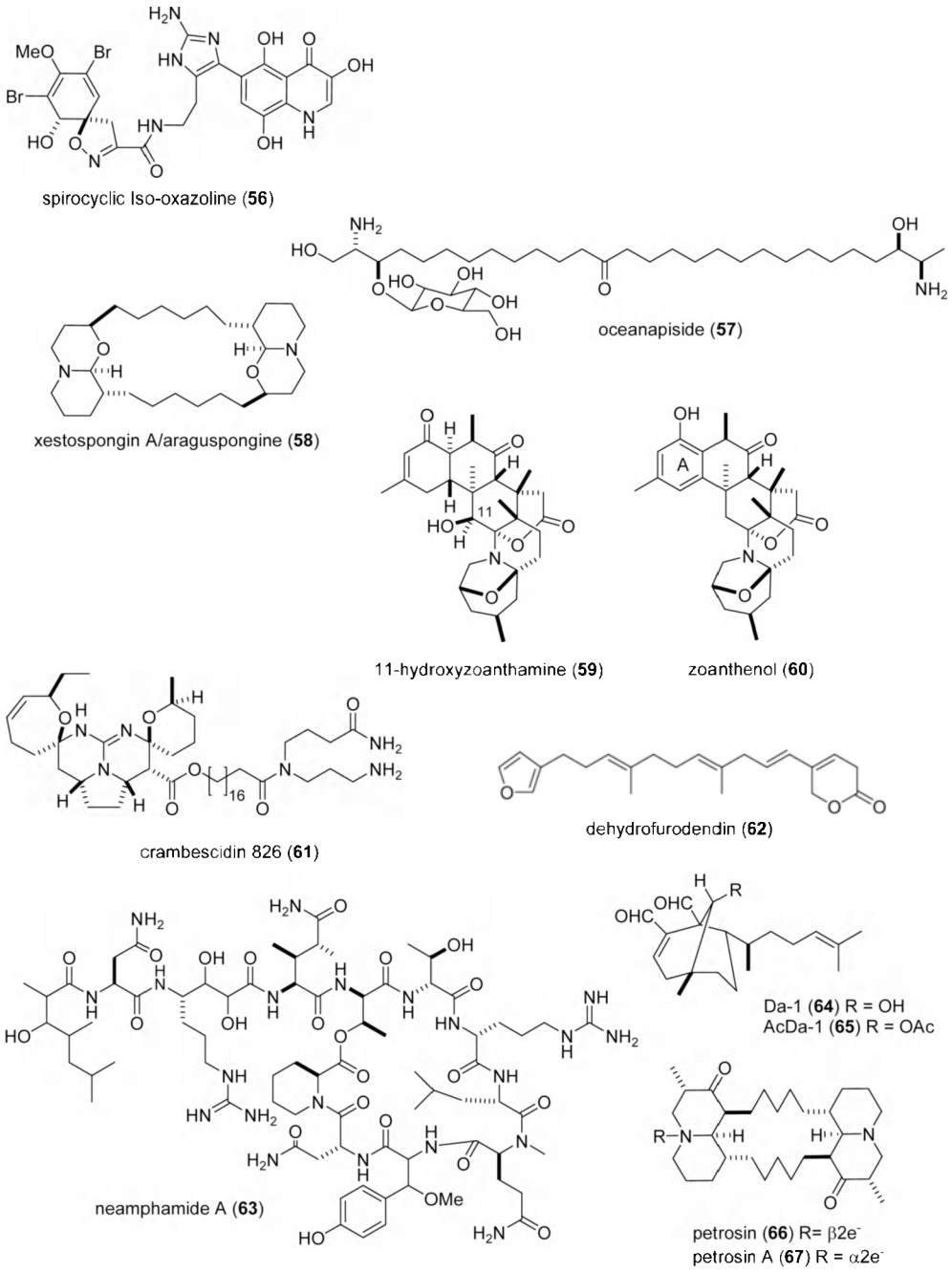
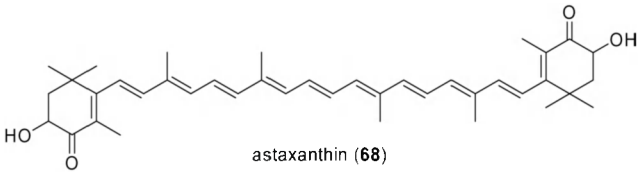
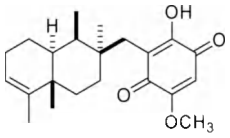


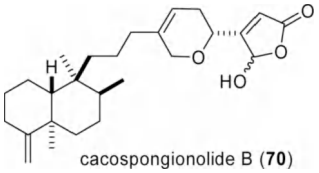
Figure 1.



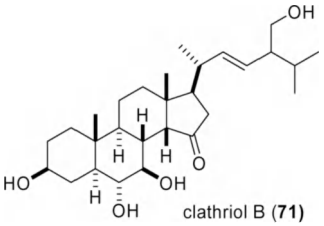
astaxanthin (**68**)



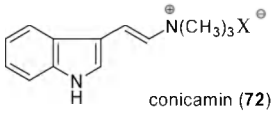
bolinaquinone (**69**)



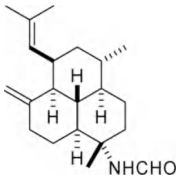
cacospongionolide B (**70**)



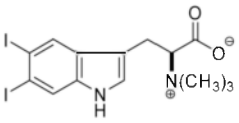
clathriol B (**71**)



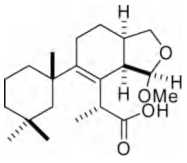
conicamin (**72**)



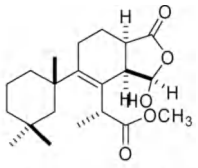
cycloamphilectene 2 (**73**)



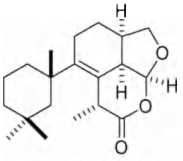
plakohypaphorine D (**74**)



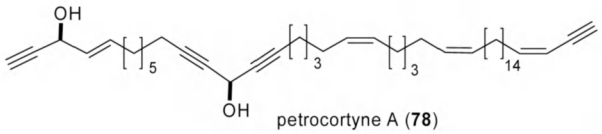
pourewic acid A (**75**)



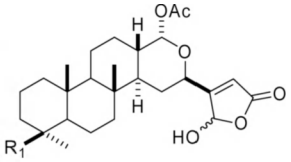
methylpourewate B (**76**)



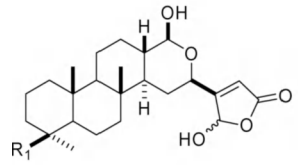
cadlinolide C (**77**)



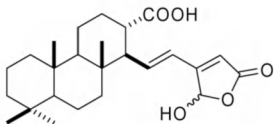
petrocortyne A (**78**)



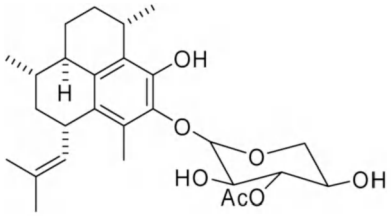
petrosaspongiolide M (**79**) R_1 = Me
petrosaspongiolide N (**80**) R_1 = CH_2OAc



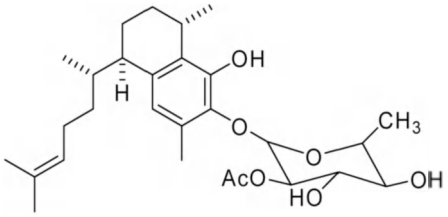
petrosaspongiolide P (**81**) R_1 = Me
petrosaspongiolide Q (**82**) R_1 = CH_2OAc



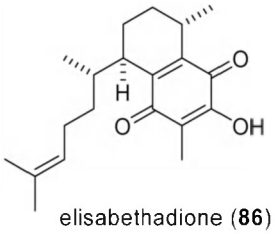
petrosaspongiolide R (**83**)



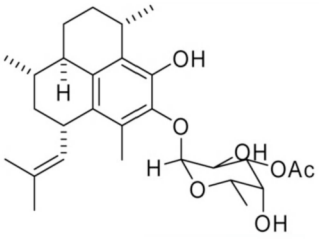
pseudopterosin N (**84**)



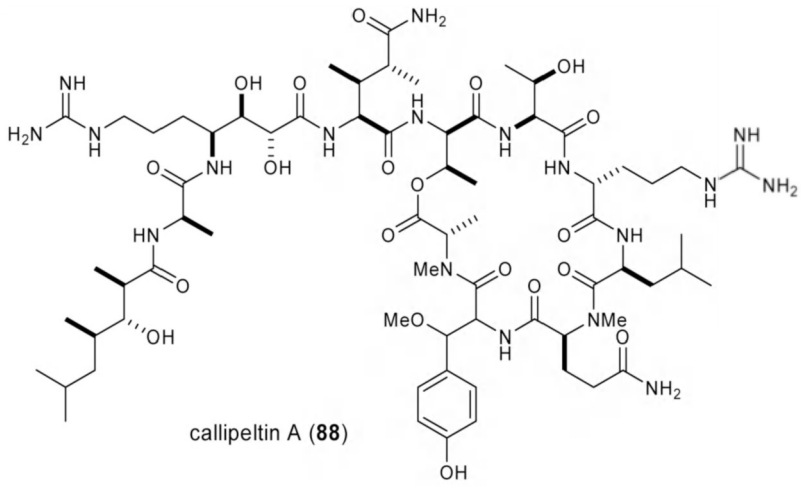
seco-pseudopterosin E (**85**)



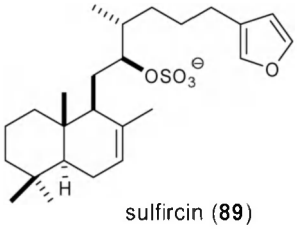
elisabethadione (**86**)



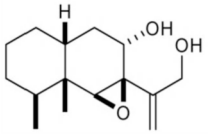
pseudopterosin R (**87**)



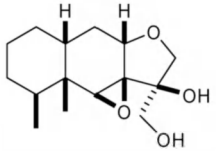
callipeltin A (**88**)



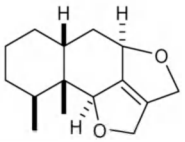
sulfircin (**89**)



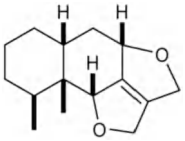
peribysin A (**90**)



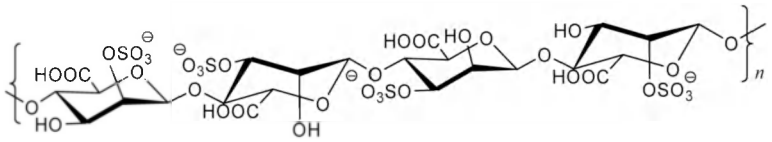
peribysin B (**91**)



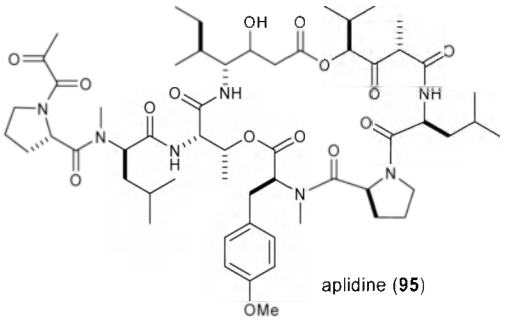
peribysin C (**92**)



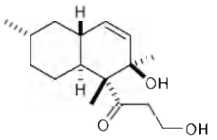
peribysin D (**93**)



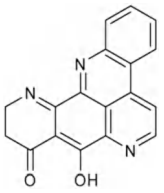
SPMG (**94**)



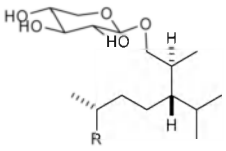
aplidine (**95**)



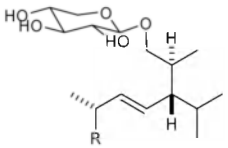
aspermytin A (**96**)



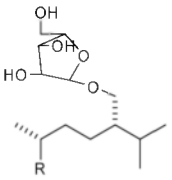
labuanine A (**97**)



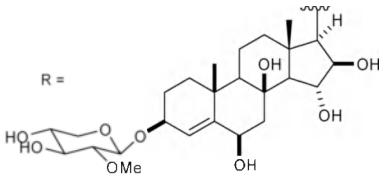
linckoside C (**98**)

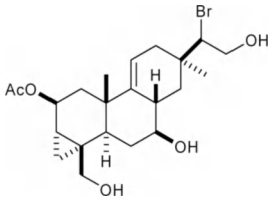


linckoside D (**99**)

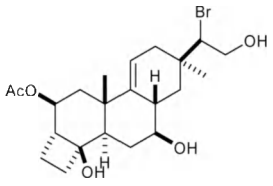


linckoside E (**100**)

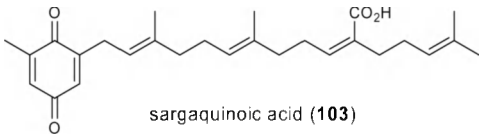




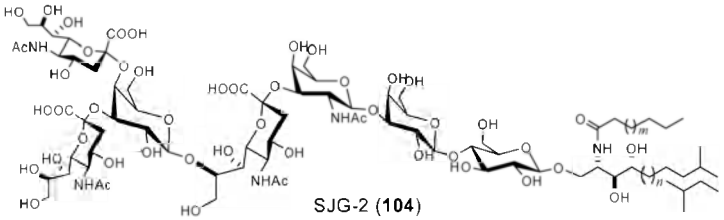
parguerol (**101**)



isoparguerol (**102**)

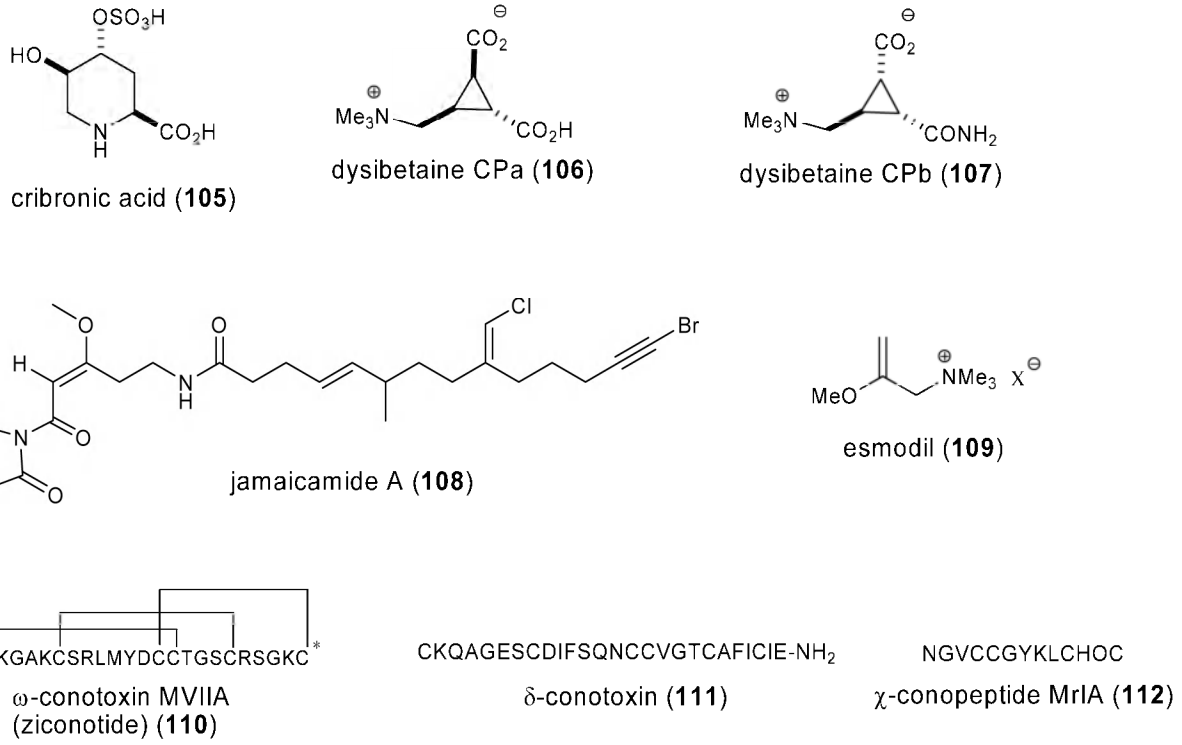


sargaquinoic acid (**103**)



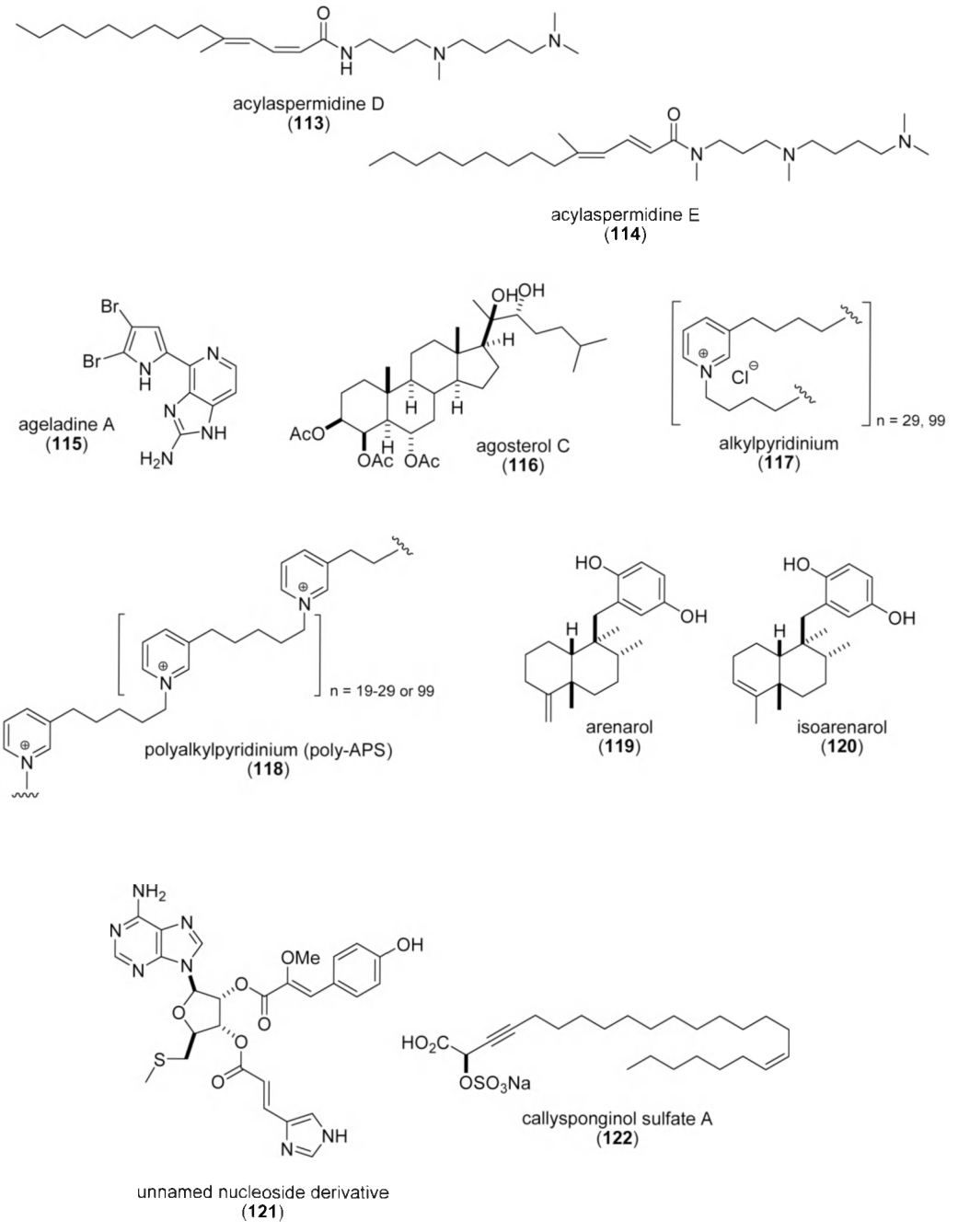
SJG-2 (**104**)

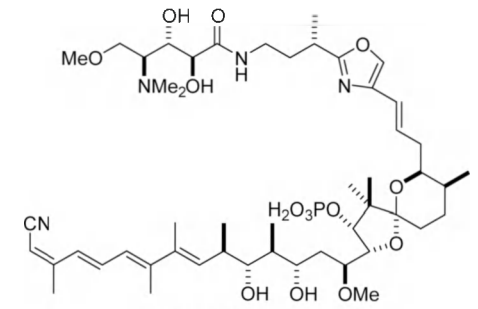
m = 11, 13, 15, 17
n = 8, 9, 10



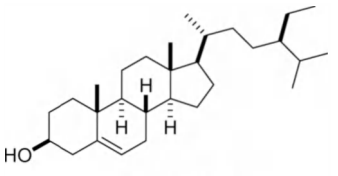
The bars represent the disulfide bonds and the asterisk represents an amidated C-terminus.

Figure 2.

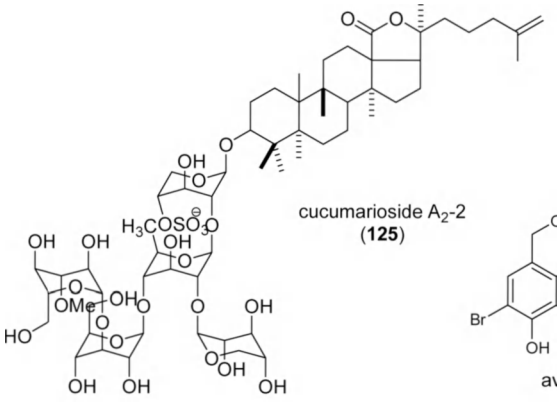




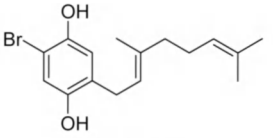
calyculin A
(**123**)



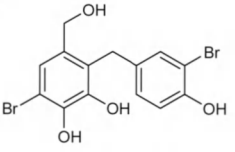
clionasterol
(**124**)



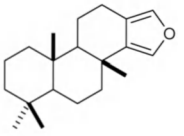
cucumarioside A_2-2
(**125**)



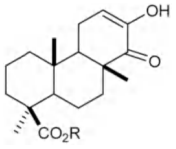
cymopol
(**126**)



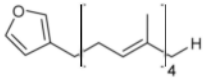
avrainvilleol
(**127**)



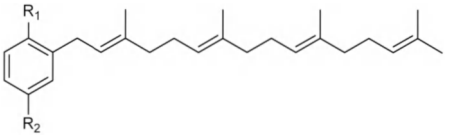
unnamed diterpenoid
(**128**)



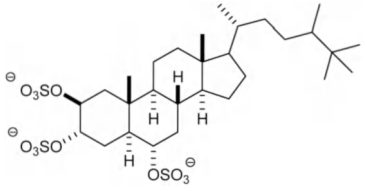
unnamed nor-bisditerpenoids
(**129**) R = H
(**130**) R = Me



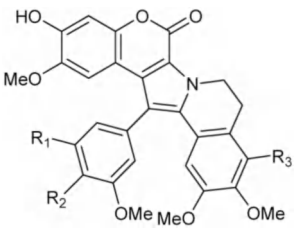
furospinosulin-1
(**131**)



4-OH-3-tetraprenylphenylacetic acid (**132**) R_1 = OH, R_2 = CH_2CO_2H
4-OAc-3-tetraprenyl benzoic acetate (**133**) R_1 = OAc, R_2 = CO_2H

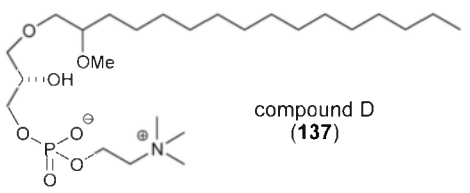


halistanol sulfate
(**134**)

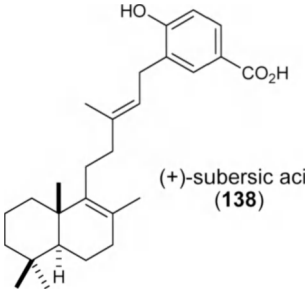


135 R_1 = OMe, R_2 = H, R_3 = OH
136 R_1 = H, R_2 = OMe, R_3 = OMe

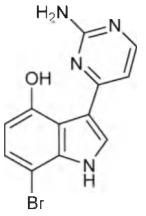
lamellarin G (**135**)
lamellarin I (**136**)



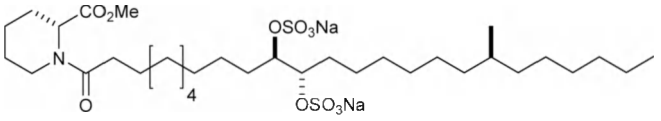
compound D
(**137**)



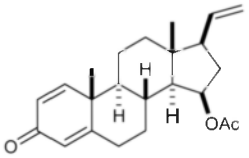
(+)-subersic acid
(**138**)



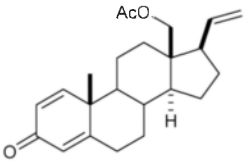
meridianin E
(**139**)



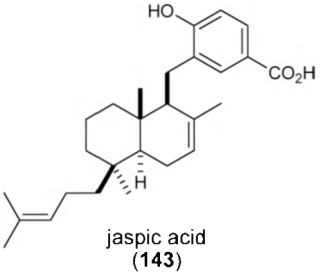
penasulfate A
(**140**)



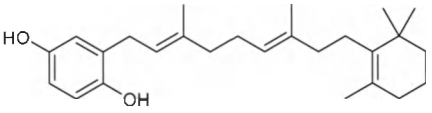
unnamed pregnane
(**141**)



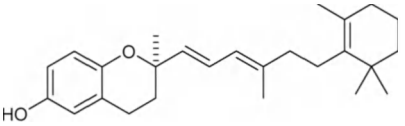
unnamed pregnane
(**142**)



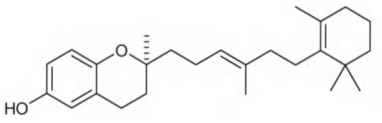
jaspic acid
(**143**)



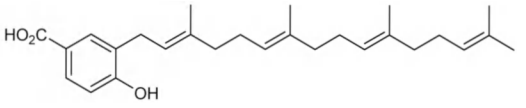
jaspaquinol
(**144**)



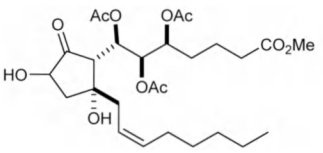
chromarol A
(**145**)



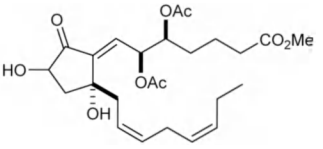
chromarol D
(**146**)



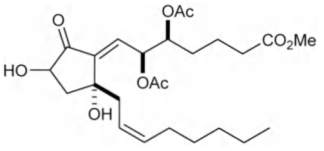
4-hydroxy-3-tetraprenylbenzoic acid
(**147**)



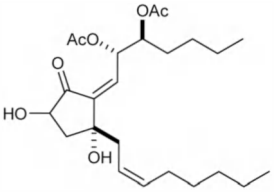
punaglandin 2
(**148**)



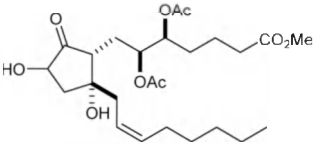
punaglandin 3
(**149**)



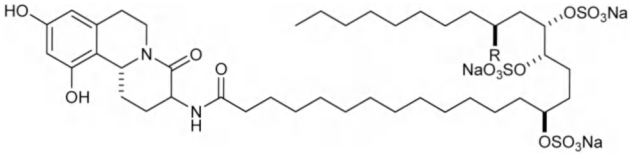
punaglandin 4
(**150**)



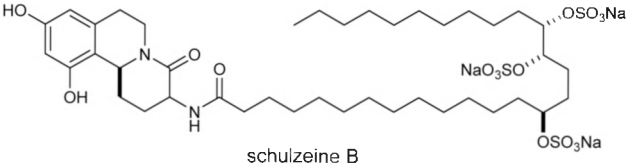
Z-punaglandin 4
(**151**)



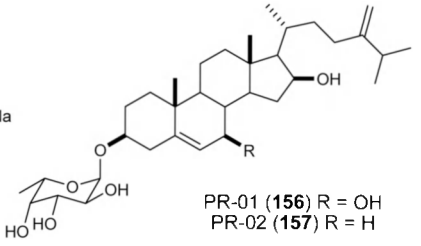
punaglandin 6
(**152**)



schulzeine A (**153**) R = Me
schulzeine C (**155**) R = H



schulzeine B
(**154**)



PR-01 (**156**) R = OH
PR-02 (**157**) R = H

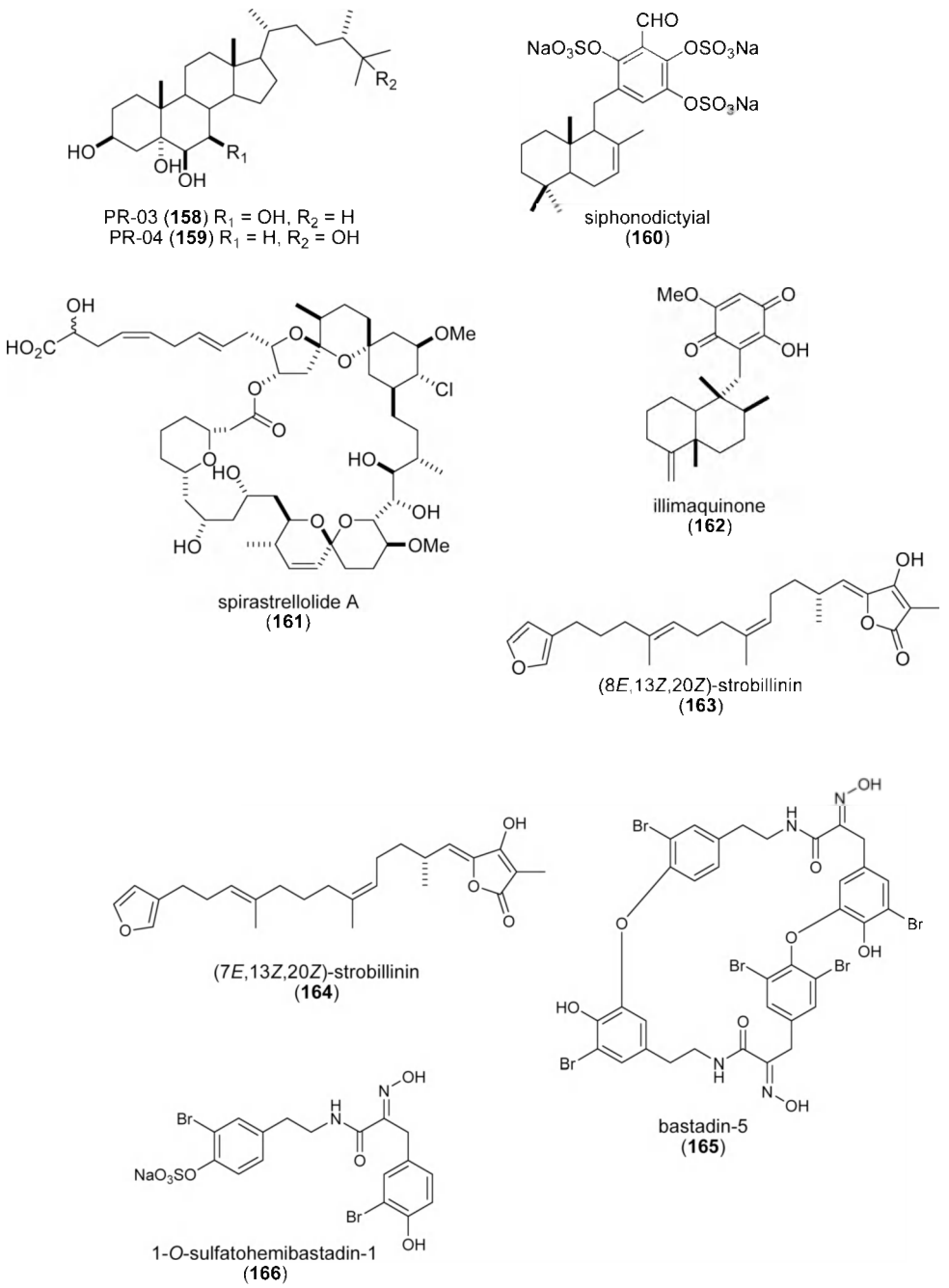


Figure 3.

Table 1

Marine pharmacology in 2003-4: Marine Compounds with Anthelmintic, Antibacterial, Anticoagulant, Antifungal, Antimalarial, Antiplatelet, Antiprotozoal, Antituberculosis, and Antiviral Activities.

Drug Class	Compound/Organism[a]	Chemistry	Pharmacologic Activity	MMOA[b]	Country[c]	References
Anthelminthic	**thiocyanatins (1-4)**/ sponge	Polyketide[d]	Nematocidal activity to *Haemonchus contortus*	Undetermined	AUS	(Capon, R. J. et al. 2004b)
Antibacterial	**kalihinol Y & X (5,6)**/ sponge	Diterpene[e]	*B. subtilis* inhibition	Folate biosynthesis inhibition	PHIL, USA	(Bugni, T. S. et al. 2004)
Antibacterial	**MC21A (7)**/bacterium	Bromophenol	Methicillin-resistant *S. aureus* inhibition comparable to vancomycin	Permeabilization of cell membrane	JAPN	(Isnansetyo, A. et al. 2003)
Antibacterial	**nagelamide A (8)**/sponge	Alkaloid[f]	*M. luteus, B. subtilis* & *E. coli* inhibition	Protein phosphatase 2A inhibition	AUS, JAPN	(Endo, T. et al. 2004)
Antibacterial	**plicatamide (9)**/tunicate	Peptide[f]	Methicillin-resistant *S.aureus, L. monocytogenes, E. coli* & *P. aeruginosa* inhibition	Bind to plasma membrane causing K^+ efflux & depolarization	USA	(Tincu, J. A. et al. 2003)
Antibacterial	**manoalide (10)**/sponge	Sesterterpene[e]	*S. aureus* inhibition	Undetermined	JAPN	(Namikoshi, M. et al. 2004)
Antibacterial	**melophlin C (11)**/sponge	Polyketide[d]	*B. subtilis* & *S. aureus* inhibition	Undetermined	CHI, INDO, GER, NETH	(Wang, C. Y. et al. 2003)
Antibacterial	**eudistomin X (12)**/ tunicate	Alkaloid[f]	*S. aureus, B. subtilis* & *E. coli* inhibition	Undetermined	GER	(Schupp, P. et al. 2003)
Antibacterial	**dolabellanin B2 (13)**/sea hare	Peptide[f]	*B. subtilis, H. influenza* & *V. vulnificus* inhibition	Undetermined	JAPN	(Ijima, R. et al. 2003)
Antibacterial	**pseudopterosin X & Y (14,15)**/soft coral	Diterpene[e]	*S. aureus, S. pyogenes,* & *E. faecalis* inhibition	Undetermined	CAN, USA	(Ata, A. et al. 2004)
Antibacterial	***Simularia* lipids (16-18)**/ soft coral	Polyketide[d]	*B. subtilis, B. pumilus, E. coli* and *P. aeruginosa* inhibition	Undetermined	RUS	(Dmitrenok, A. S. et al. 2003)
Antibacterial	***Rhodomela* bromophenol (19)**/alga	Bromophenol	*S. aureus, S. epidermidis* and *P. aeruginosa* inhibition	Undetermined	CHI	(Xu, N. et al. 2003)
Antibacterial	**cribrostatin 6 (20)**/sponge	Alkaloid[f]	*S. pneumoniae* inhibition	Undetermined	USA	(Pettit, R. K. et al. 2004)
Antibacterial	**purpuramine L (21)**/ sponge	Bromotyrosine Alkaloids[f]	*S. aureus, B. subtilis* & *C. violaceum* inhibition	Undetermined	IND	(Goud, T. V. et al. 2003b)
Antibacterial	**germacrane (22)**/sponge	Sesquiterpene[e]	*S. aureus* & *B. subtilis* inhibition	Undetermined	THAI	(Satitpatipan, V. et al. 2004)
Antibacterial	***Ptilocaulis* guanidine (23)**/ sponge	Alkaloid[f]	*S. aureus* inhibition	Undetermined	USA	(Yang, S. W. et al. 2003c)
Antibacterial	**membranolides C & D (24,25)** /sponge	Diterpene[e]	*S. aureus* & *E. coli* inhibition	Undetermined	USA	(Ankisetty, S. et al. 2004)
Antibacterial	**arenicins 1 & 2 (26,27)**/ polychaeta	Peptide[f]	*E. coli, L. monocytogenes* & *C. albicans* inhibition	Undetermined	RUS	(Ovchinnikova, T. V. et al. 2004)
Antibacterial	**perinerin(28)**/ polychaeta	Peptide[f]	Gram-negative, Gram-positive & fungal inhibition	Undetermined	CHI	(Pan, W. et al. 2004)
Antibacterial	***Hippoglossoides* peptide (29)**/American plaice	Peptide[f]	*P. aeruginosa* & *S. aureus* inhibition	Undetermined	CAN	(Patrzykat, A. et al. 2003b)
Anticoagulant	**dysinosin C (30)**/sponge	Peptide[f]	Factor VIIa and thrombin inhibition	Two structural motifs contribute to protease binding	AUS	(Carroll, A. R. et al. 2004)
Anticoagulant	**fucosylated chondroitin sulfate (31)**/sea cucumber	Polysaccharide[g]	Anticoagulant, bleeding and antithrombotic effects *in vivo*	Accelerated thrombin inhibition	BRA	(Zancan, P. et al. 2004)
Anticoagulant	**sulfated galactans (32,33)**/alga & sea urchin	Polysaccharide[g]	Antithrombin-mediated anticoagulant activity	Interaction holds antithrombin inactive	BRA	(Melo, F. R. et al. 2004)
Antifungal	***Astroscleridae* sterol (34)**/ sponge	Sterol sulfate[d]	*S. cerevisiae* inhibition	Undetermined	USA	(Yang, S. W. et al. 2003b)
Antifungal	***Dysidea arenaria* sterol (35)**/sponge	Terpene[e]	Fluconazole resistance reversal in *C. albicans*	MDR1-type efflux pump inhibition	USA	(Jacob, M. R. et al. 2003)

Drug Class	Compound/Organism[a]	Chemistry	Pharmacologic Activity	MMOA[b]	Country[c]	References
Antifungal	**massadine (36)**/sponge	Alkaloid[f]	Geranylgeranyltransferase I inhibition	Undetermined	JAPN, NETH	(Nishimura, S. et al. 2003)
Antifungal	**naamine G (37)**/sponge	Alkaloid[f]	*C. herbarum* inhibition	Undetermined	GER, NETH	(Hassan, W. et al. 2004)
Antifungal	**utenospongin B (38)**/ sponge	Diterpene[e]	*C. tropicales* & *F. oxysporum* inhibition	Undetermined	NETH, MOR, PORT	(Rifai, S. et al. 2004)
Antifungal	**(2*S*,3*R*)-2-aminododecan-3-ol (39)**/ ascidian	Polyketide[d]	*C. albicans* inhibition	Undetermined	BRA, USA	(Kossuga, M.H. et al. 2004)
Antimalarial	**bielschowskysin (40)**/ coral	Diterpene[e]	*P. falciparum* inhibition	Undetermined	PAN, USA	(Marrero, J. et al. 2004)
Antimalarial	**briarellins (41-43)**/coral	Diterpene[e]	*P. falciparum* inhibition	Undetermined	PAN, USA	(Ospina, C. A. et al. 2003)
Antimalarial	**cembradienes (44)**/sea whip	Diterpene[e]	*P. falciparum* inhibition	Undetermined	PAN, USA	(Wei, X. M. et al. 2004)
Antimalarial	**dolostatin 10 (45)**/sea hare	Peptide[f]	*P. falciparum* FCH5.C2 inhibition	Microtubule & mitotic inhibition	USA	(Fennell, B. J. et al. 2003)
Antimalarial	**manzamine A (46)**/ sponge	Alkaloid[f]	*P. falciparum* D6 & W2 inhibition	Undetermined	USA	(Rao, K. V. et al. 2003)
Antimalarial	**trioxacarcin A & D (48,49)**/bacterium	Glycoside	*P. falciparum* strains NF54 & K1 inhibition	Undetermined	NETH, GER	(Maskey, R. P. et al. 2004)
Antiprotozoal	**renieramycin A (50)**/ sponge	Alkaloid[f]	*Leishmania amazonensis* inhibition	Undetermined	JAPN	(Nakao, Y et al. 2004)
Antiprotozoal	**euplotin C (51)**/ciliate	Sesquiterpene[e]	*Leishmania major & infantum* inhibition	Undetermined	ITA	(Savoia, D. et al. 2004)
Antiprotozoal	**defensins** /mussel	Peptide[f]	*T. brucei & L. major* inhibition	Undetermined	BEL, FRA	(Roch, P. et al. 2004)
Antituberculosis	**(+)-8-hydroxymanzamine A (47)** /sponge	Alkaloid[f]	*M. tuberculosis* inhibition	Undetermined	USA	(Rao, K. V. et al. 2003)
Antituberculosis	**homopseudopteroxazole (52)**/soft coral	Diterpene[e]	*M. tuberculosis* inhibition	Undetermined	USA	(Rodriguez, I. I. et al. 2003)
Antituberculosis	**ingenamine G (53)**/ sponge	Alkaloid[f]	*S. aureus,E. coli & resistant S. aureus* inhibition	Undetermined	BRA, GER	(de Oliveira, J. H. et al. 2004)
Antituberculosis	**12-deacetoscalarin 19-acetate (54)**/sponge	Sesterterpene[e]	*M. tuberculosis* inhibition	Undetermined	THAI	(Wonganuchitmeta, S. N. et al. 2004)
Antituberculosis	***Oceanapiside sp.*** *compounds* **(55-57)**/ sponge	Polyketide[d]	Mycothiol-*S*-conjugate amidase inhibition	Non-competitive inhibition	USA	(Nicholas, G. M. et al. 2003)
Antiplatelet	**xetospongin A (58)** / sponge	Alkaloid[f]	Collagen-induced platelet aggregation inhibition	Undetermined	PHIL, USA	(Pimentel, S. M. et al. 2003)
Antiplatelet	**zoanthamine alkaloids (59-60)**/zoanthids	Alkaloid[f]	Agonist-induced platelet aggregation inhibition	Undetermined	BRA, SPA	(Villar, R. M. et al. 2003)
Antiviral	**crambescidin 826 (61)**/ sponge	Alkaloid[f]	HIV-1 envelope-mediated fusion inhibition *in vitro*	Undetermined	USA	(Chang, L. et al. 2003)
Antiviral	**dehydrofurodendin (62)**/ sponge	Furanoterpene[e]	Reverse transcriptase RNA- and DNA-directed DNA polymerase inhibition	Undetermined	ISRA, FRA	(Chill, L. et al. 2004)
Antiviral	**neamphamide A (63)**/ sponge	Depsipeptide[f]	HIV-growth inhibition	Undetermined	USA	(Oku, N. et al. 2004)
Antiviral	***Dictyota*** **diterpenes (64,65)**/alga	Diterpene[e]	Inhibition of HIV-1 replication in cell line	RNA-dependent DNA-polymerase RT inhibition	BRA	(Pereira, H. S. et al. 2004)
Antiviral	**petrosins (66,67)**/sponge	Alkaloid[f]	HIV-growth inhibition	Giant cell formation & RT inhibition	IND	(Goud, T. V. et al. 2003a)

[a] **Organism**, *Kingdom Animalia*: flounder (American plaice) and tunicates (Phylum Chordata); polychaeta (Phylum Annelida); sea urchins and cucumbers (Phylum Echinodermata), mussels and sea hares (Phylum Mollusca), sponges (Phylum Porifera); corals, sea whips and zoanthids (Phylum Cnidaria); *Kingdom Monera*: bacteria (Phylum Cyanobacteria); *Kingdom Plantae:* algae; *Kingdom Protista*: ciliates (Phylum Ciliophora).

[b] **MMOA**: molecular mechanism of action.

[c] **Country**: AUS: Australia; BEL: Belgium; BRA: Brazil; CAN: Canada; CHI: China; FRA: France; GER: Germany; IND: India; INDO: Indonesia; ISRA: Israel; ITA: Italy; JAPN: Japan; MOR: Morocco; NETH: The Netherlands; NOR: Norway; PAN: Panama; PHIL: The Phillipines; PORT: Portugal; RUS: Russia; SPA: Spain; THAI: Thailand.

[d] Polyketide.

[e] Terpene.

[f] Nitrogen-containing compound.

[g] Polysaccharide.

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Table 2

Marine pharmacology in 2003-4: Marine Compounds with Anti-inflammatory activity, and affecting the Cardiovascular, Immune and Nervous Systems.

Drug Class	Compound/Organism[a]	Chemistry	Pharmacological Activity	MMOA[b]	Country[c]	References
Anti-inflammatory	**astaxanthin (68)**/salmon, sea stars	Tetraterpene[e]	Inhibion of endotoxin-induced uveitis in rats	iNOS, NO, TNF-α & PGE_2 inhibition	JAPN	(Ohgami, K. et al. 2003)
Anti-inflammatory	**bolinaquinone (69)**/sponge	Merosesquiterpene[e]	Inhibition of cytokine, iNOS and eicosanoids	$sPLA_2$ inhibition	SPA, ITA	(Lucas, R. et al. 2003b)
Anti-inflammatory	**cacospongionolide B (70)**/ sponge	Sesterterpene[e]	Nitric oxide, PGE_2 & TNF-α inhibition *in vitro* and *in vivo*	Nuclear factor-κB inhibition	SPA, ITA	(Posadas, I. et al. 2003a)
Anti-inflammatory	**clathriol B (71)**/sponge	Sterol[e]	Neutrophil superoxide inhibition	Undetermined	NZEL	(Keyzers, R. A. et al. 2003)
Anti-inflammatory	**conicamin (72)**/tunicate	Indole alkaloid[f]	Histamine antagonist	Undetermined	ITA	(Aiello, A. et al. 2003)
Anti-inflammatory	**cycloamphilectene 2 (73)**/ sponge	Diterpene[e]	Nitric oxide inhibition	Inhibition of NF-κB pathway	ITA, SPA	(Lucas, R. et al. 2003a)
Anti-inflammatory	**plakohypaphorine D (74)**/ sponge	Indole alkaloid[f]	Histamine antagonist	Undetermined	ITA	(Borrelli, F. et al. 2004)
Anti-inflammatory	**pourewic acid A & methylpourewate B (75,76)**/sponge	Diterpenes[e]	Superoxide inhibition	Undetermined	NZEL	(Keyzers, R. A. et al. 2004)
Anti-inflammatory	**cadlinolide C (77)**/sponge	Diterpene[e]	Superoxide inhibition	Undetermined	NZEL	(Keyzers, R. A. et al. 2004)
Anti-inflammatory	**petrocortyne A (78)**/sponge	Polyacetylene	Macrophage inflammatory mediator inhibition	NO & TNF-α inhibition	SKOR	(Hong, S. et al. 2003)
Anti-inflammatory	**petrosaspongiolide M (79)**/ sponge	Sesterterpene[e]	Nitric oxide, PGE_2 & TNF-α inhibition *in vitro* and *in vivo*	Nuclear factor-κB inhibition	ITA, SPA	(Posadas, I. et al. 2003b)
Anti-inflammatory	**petrosaspongiolides M-R (79-83)**/sponge	Sesterterpenes[e]	Macrophage inflammatory mediator inhibition	PLA_2 inhibition	ITA	(Monti, M. C. et al. 2004)
Anti-inflammatory	**pseudopterosin N (84)**/sea whip	Diterpene[e]	Inhibition of mouse ear inflammation	Undetermined	USA	(Ata, A. et al. 2003)
Anti-inflammatory	**seco-pseudopterosin E (85)**/sea whip	Diterpene[e]	Inhibition of mouse ear inflammation	Undetermined	USA	(Ata, A. et al. 2003)
Anti-inflammatory	**elisabethadione(86)**/sea whip	Diterpene[e]	Inhibition of mouse ear inflammation	Undetermined	USA	(Ata, A. et al. 2003)
Anti-inflammatory	**pseudopterosin R (87)**/sea whip	Diterpene[e]	Microglia thromboxane B_2 inhibition	Undetermined	USA	(Rodriguez, I. I. et al. 2004)
Cardiovascular	**callipeltin A (88)**/sponge	Depsipeptide[f]	Affected resting aorta contraction	Na^+-ionophore action	ITA	(Trevisi, L. et al. 2004)
Immune system	***Codium fragile* polysaccharide**/alga	Polysaccharide[g]	Binding to IL-2, IL-7 and INF-γ	Undetermined	UK	(Nika, K. et al. 2003)
Immune system	**sulfircin (89)**/sponge	Sesterterpene[e]	Mobilization of T cells and dendritic cells	CCR7 chemokine receptor binding	USA	(Yang, S. W. et al. 2003d)
Immune system	**mucins**/sea star	Polysaccharide[g]	Inhibition of neutrophil adhesion	Undetermined	UK	(Bavington, C.D. et al. 2004)
Immune system	**perybysins A-D (90-93)**/ fungus	Sesquiterpenes[e]	Inhibition of human leukemia cell adhesion	Undetermined	JAPN	(Yamada, T. et al. 2004)
Immune system	**phycarine**/alga	Polysaccharide[g]	Stimulation of macrophage phagocytosis	IL-1, IL-6 & TNF-α synthesis	FRA, USA	(Vetvicka, V. et al. 2004)
Immune system	**sulfated PMG (94)**/alga	Polysaccharide[g]	Inhibition of HIV virus infection of lymphocytes	Binding to CD4 receptor on lymphocytes	CHI	(Meiyu, G. et al. 2003)
Immune system	**sulfated PMG (94)**/alga	Polysaccharide[g]	Binding to lymphocytes	Interaction with CD4 receptor	CHI	(Miao, B. et al. 2004)
Nervous system	**petrosaspongiolide M (79)**/ sponge	Sesterterpene[e]	Reduction of morphine withdrawal *in vitro*	Undetermined	ITA	(Capasso, A. et al. 2003)

Drug Class	Compound/Organism[a]	Chemistry	Pharmacological Activity	MMOA[b]	Country[c]	References
Nervous system	**aplidine(95)**/tunicate	Depsipeptide[f]	Inhibition of aggregation of prion petide into β-sheet fibrils	Undetermined	SPA,USA	(Perez, M. et al. 2003)
Nervous system	**aspermytin A (96)**/fungus	Polyketide[d]	Induction of neurite outgrowth	Undetermined	JAPN	(Tsukamoto, S. et al. 2004a)
Nervous system	**labuanine A (97)**/sponge	Pyridoacridine alkaloid[f]	Induction of neuite outgrowth	Undetermined	JAPN, INDO	(Aoki, S. et al. 2003)
Nervous system	**linckosides C-E (98-100)**/ sea star	Steroidal glycoside[e]	Induction of neurite outgrowth	Undetermined	JAPN	(Qi, J. et al. 2004)
Nervous system	**parguerolisoparguerol (101-102)**/sea hare	Diterpene[e]	Induction of neurite outgrowth	Undetermined	JAPN	(Tsukamoto, S. et al. 2004b)
Nervous system	**sargaquinoic acid (103)**/ alga	Meroditerpene[e]	Induction of neurite outgrowth	PI-3 kinase independent; TrKA-MAP kinase and adenylate cyclase-PKA dependent	JAPN	(Tsang, C. K. et al. 2004); (Kamei, Y. et al. 2003)
Nervous system	**SJG-2 ganglioside (104)**/ sea cucumber	Ganglioside	Induction of neurite outgrowth	Undetermined	JAPN	(Kaneko, M. et al. 2003)
Nervous system	**cribronic acid (105)**/sponge	Amino acid[f]	Convulsant activity in mice	Binding to NMDA-type receptor	JAPN	(Sakai, R. et al. 2003)
Nervous system	**dysibetaine CPa-CPb 106,107)**/sponge	Betaine	Binding to ionotropic glutamate receptors	Undetermined	JAPN	(Sakai, R. et al. 2004)
Nervous system	**jamaicamide A (108)**/ cyanobacterium	Lipopeptide[f]	Sodium channel blocking	Undetermined	USA	(Edwards, D. J. et al. 2004)
Nervous system	**esmodil (109)**/sponge	Quaternary amine	Acetylcholine mimetic	Indetermined	AUS	(Capon, R. J. et al. 2004a)
Nervous system	**ω-conopeptide MVIIA (110)**/snail	Peptide[f]	Inhibition of refractory pain in patients with AIDS or Cancer	Binding to N-type Ca^{2+} channels	USA	(Staats, P. S. et al. 2004)
Nervous system	**δ-conotoxin (111)**/snail	Peptide[f]	Na^{+} current inhibition	Undetermined	IND	(Sudarslal, S. et al. 2003)
Nervous system	**χ-conopeptide MrIA (112)**/ snail	Peptide[f]	Norepinephrine transporter inhibition	Non-competitive binding at the antidepressant binding site	AUS	(Sharpe, I. A. et al. 2003)
Nervous system	**Acidic oligosaccharide**/ alga	Polysaccharide[g]	Inhibition of amyloid beta toxicity	Inhibition of apoptosis & intracellular Ca^{2+}	CHI	(Hu, J. et al. 2004)

[a] **Organism**: *Kingdom Animalia*: sea whip (Phylum Cnidaria); tunicate (Phylum Chordata), sea star and cucumber (Phylum Echinodermata); sea hare and snail (Phylum Mollusca); sponge (Phylum Porifera); *Kingdom Fungi*: fungus; *Kingdom Plantae:* alga; *Kingdom Monera*: bacterium (Phylum Cyanobacteria).

[b] **MMOA**: molecular mechanism of action, NO: nitric oxide.

[c] **Country**: AUS: Australia; CHI: China; FRA: France; INDO: Indonesia; ITA: Italy; JAPN: Japan; N. ZEL: New Zealand; SPA: Spain; S.KOR: South Korea; UK: United Kingdom.

[d] Polyketide.

[e] Terpene.

[f] Nitrogen-containing compound.

[g] Polysaccharide.

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Table 3

Marine pharmacology in 2003-4: Marine Compounds with Miscellaneous Mechanisms of Action.

Compound/Organism[a]	Chemistry	Pharmacological Activity	IC_{50}[b]	MMOA[c]	Country[d]	References
acylspermidine D & E (113,114)/ soft coral	polyamine[g]	Vacuolar H+-pyrophosphatase inhibition	0.98 μM	No inhibition of F-P- and V-type H + ATPases and cytosolic pyrophosphatase	JAPN	(Hirono, M. et al. 2003)
ageladine A (115)/sponge	alkaloid[g]	Matrix metalloprotease (MMP) inhibition	0.33-2 μg/mL	Noncompetitive inhibition of MMP-2	NETH, JAPN	(Fujita, M. et al. 2003a)
agosterol C (116)/sponge	sterol[f]	Proteasome inhibition	10 μg/mL	Undetermined	NETH, JAPN	(Tsukamoto, S. et al. 2003)
alkylpyridinium/(117)/ sponge	pyridinium oligomer[g]	Pore-formation on neuronal membranes	ND	Reversible & irreversible increase $[Ca^{2+}]i$; membrane properties attenuated by zinc	TUR, SLO, UK	(McClelland, D. et al. 2003)
alkylpyridinium(poly-APS) (118)/sponge	pyridinium oligomer[g]	Stable DNA transfection	0.5 μg/mL	Transient and reversible pore formation	SLO, UK	(Tucker, S. J. et al. 2003)
arenerol & isoarenarol (119, 120)/sponge	merosesquiter pene[f]	Protein kinases inhibition	4-7 μM	Undetermined	NETH, CAN	(Yoo, H. D. Leung D. et al. 2003)
***Atriolum robustum* nucleoside (121)**/ascidian	Amino acid derived[g]	Partial agonist at rat brain A_1 adenosine receptors	23±0.2 μM	Binding to A_1 & A_3 adenosine receptors	GER	(Kehraus, S. et al. 2004)
callysponginol sulfate A (122)/sponge	Polyketide[e]	MT1-matrix metalloproteinase inhibition	15.0 μg/mL	Undetermined	JAPN, NETH	(Fujita, M. et al. 2003b)
calyculin A (123)/sponge	Polyketide[e]	Histone H1 kinase phosphorylation induction	ND	Type 1 phosphatase inhibition	JAPN	(Tosuji, H. et al. 2003)
CEL-III/sea cucumber	Protein[g]	Erythrocyte hemolysis	ND	Crystal structure suggests lectin domain 3 involved in pore formation	JAPN	(Uchida, T. et al. 2004)
clionasterol (124)/sponge	Sterol[f]	Complement component C1 inhibition	4.1 μM	Undetermined	THAI, NETH, PORT	(Cerqueira, F. et al. 2003)
cucumarioside A_2-2 (125)/ sea cucumber	Triterpene glycoside[f]	Increased $[Ca^{2+}]i$ & lysosomal activity in mouse macrophages	ND	Undetermined	RUS	(Agafonova, I. G. et al. 2003)
cymopol (126) & avrainvilleol (127)/alga	Meromonoter pene/ polyket[f/e]	Antioxidant	4.0-6.1 μM	Undetermined	USA	(Takamatsu, S. et al. 2003)
***Dictyoceratida* diterpenoids (128-130)**/sponge	Diterpene[f]	DNA polymerase B lyase activity inhibition	20.6-26 μg/mL	Undetermined	USA	(Chaturvedula, V. S. P. et al. 2004)
Furano- and aromatic terpenoids (131-133)/sponge	Terpenes[f]	CDC25 phosphatase inhibition	0.4-4 μM	Undetermined	ITA, FRA, SPA, TUR, USA	(Erdogan-Orhan, I. et al. 2004)
halistanol sulfate (134)/ sponge	Sterol[f]	$P2Y_{12}$ purinergic receptor inhibition	0.48 μM	Undetermined	USA	(Yang, S. W. et al. 2003a)
lamellarin G & I (135, 136)/ ascidian	Alkaloids[g]	Free radical scavenging activity	2.96-3.28 mM	Undetermined	IND	(Krishnaiah, P. et al. 2004)
Lysophosphatidylcholine (137)/sponge	Polyketide[e]	Increased Ca^{2+} mobilization in HL-60 cells	ND	Undetermined	S.KOR	(Lee, E. H. et al. 2004)

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(+)-subersic acid (138)/ sponge	Meroterpene[f]	MAPKAP kinase 2 inhibition	9.6-20μM	Undetermined	CAN, INDO, NETH, USA	(Williams, D. E. et al. 2004b)
meridianin E (139)/ascidian	Alkaloids[g]	Cell proliferation and apoptosis inhibition	0.18-0.6 μM	Cyclin B, p25, protein kinase A & G inhibition	ARG, FRA	(Gompel, M. et al. 2004)
penasulfate A (140)/sponge	Aminoacid/polyketide[e]	α-glucosidase inhibition	3.5 μg/mL	Undetermined	JAPN, NETH	(Nakao, Y. et al. 2004)
pregnanes 1 & 2 (141-142)/ coral	Steroids[f]	Mitochondrial respiratory chain inhibition	1.1-1.9 μM	Undetermined	ITA, IND	(Ciavatta, M. L. et al. 2004)
***Psammocinia* spp. diterpenes (143-147)**/sponge	Terpene[f]	Human 15-lipoxygenase inhibition	0.3-0.8 μM	Reduction of lipoxygenase non-heme ferric center	USA	(Cichewicz, R. H. et al. 2004)
punaglandins (148-152)/ coral	Polyketide[e]	Cytotoxicity & apoptosis	0.04-0.37μM	P53 accumulation & ubiquitin isopeptidase activity *in vivo* & *in vitro*	USA	(Verbitski, S. M. et al. 2004)
schulzeienes A-C (153-155)/ sponge	Alkaloid/polyketide[g]	α-glucosidase inhibition	0.048-0.1 μM	Undetermined	JAPN, NETH	(Takada, K. et al. 2004)
***Sinularia* & *Lobophytum* sp. steroids (156-159)**/soft coral	Glycosidic Steroid[f]	5α-reductase inhibition	ND	Undetermined	IND, MEX	(Radhika, P. et al. 2004)
siphonodictyal C (160)/ sponge	Merosesquiterpene[g]	CDK4/cyclin D1 inhibition	9 μg/mL	Undetermined	NZEL, SWI, USA	(Mukku, V. J. et al. 2003)
spirastrellolide A (161)/ sponge	Polyketide[e]	Protein phosphatase 2A inhibition	0.001 μM	Undetermined	CAN, USA	(Williams, D. E. et al. 2004a)
***Spongia* sesquiterpenoid (162)**/sponge	Merosesquiterpene[f]	DNA polymerase B lyase activity inhibition	16.2 μg/mL	Undetermined	USA	(Cao, S. et al. 2004)
strobilin-felixinin (163, 164)/ sponge	Sesterterpene[f]	Antioxidant and radical scavenger	ND	Superoxide scavenging inhibition & H_2O_2 induced DNA strand scission protection	CHI, S.KOR	(Jiang, Y. H. et al. 2004)
sulfatobastadins 1 & 2 (165, 166)/sponge	Bromotyrosine peptides[g]	Inhibition of ryanodine binding	13-29 μM	Undetermined	USA	(Masuno, M. N. et al. 2004)

[a] **Organism**, *Kingdom Animalia*: ascidians (Phylum Chordata), corals (Phylum Cnidaria), sea cucumber (Phylum Echinodermata), sponge (Phylum Porifera); *Kingdom Plantae:* alga.

[b] **IC_{50}**, ND: not determined.

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

[d] **Country**: ARG: Argentina; CAN: Canada; CHI: China; FRA: France; GER: Germany; IND: India; INDO: Indonesia; ITA: Italy; JAPN: Japan; MEX: Mexico; NETH: The Netherlands; NZEL: New Zealand; POR: Portugal; RUS: Russia; S. KOR: South Korea; SLO: Slovenia; SPA: Spain; THAI: Thailand; TUR: Turkey; UK: United Kingdom.

[e] Polyketide.

[f] Terpene.

[g] Nitrogen-containing compound.

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[h] polysaccharide.